Contents

Fluorine-Containing Heterocycles. Part III: Synthesis of Perfluoroalkyl Heterocycles Using Perfluoroolefins Containing a Reactive Group at the Double Bond

GEORGII G.FURIN

Contributors

Numbers in parentheses indicate the pages on which the author's contribution begins.

E.S.H. El Ashry (1), Alexandria University, Chemistry Department, Faculty of Science, Alexandria, Egypt

Georgii G. Furin (239), Novosibirsk Institute of Organic Chemistry, Siberian Division of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation

M. Hagar (1), Alexandria University, Chemistry Department, Faculty of Science, Alexandria, Egypt

A.A. Kassem (1), Alexandria University, Chemistry Department, Faculty of Science, Alexandria, Egypt

E. Ramadan (1), Alexandria University, Chemistry Department, Faculty of Science, Alexandria, Egypt

Alfonz Rybár (181), Institute of Chemistry, Slovak Academy of Science, Bratislava 84538, Slovak Republic

Alexander P. Sadimenko (115), University of Fort Hare, Department of Chemistry, Alice 5701, Republic of South Africa

Preface

Volume 88 of Advance in Heterocyclic Chemistry consists of four contributions, covering a wide range of topics of current interest.

The volume commences with Part I of an overview of the dramatic and beneficial effect on preparative heterocyclic chemistry of the application of microwave methods. The chapter is authored by E. S. H. El Ashry, E. Ramadan, A. A. Kassem, and M. Hagar (Alexandria University, Egypt). This first contribution considers three-, four-, and five-membered heterocyclic rings and their benzo-derivatives. It will be followed by a subsequent chapter covering six-membered and larger heterocyclic rings.

Volume 88 continues with another valuable contribution from A. Sadimenko (University of Fort Hare, South Africa) completing his survey of the organometallic chemistry of pyridine and its derivatives. A previous chapter [04AHC(86)293] in this mini series dealt with all the possible coordination modes of pyridines with metals except the η^2(N,C) class, which is now covered. The η^2(N,C)-coordination compounds are important in the denitrification of fuels and in new materials.

Volume 87 of AHC contained an overview by A. Rybar (Institute of Chemistry, Bratislava) of purines fused to five-membered heterocyclic rings. The third chapter of the present Volume 88 is a sequel by the same author covering purines annulated with six-, seven,- and eight-membered heterocycles.

The final chapter in Volume 88 is entitled ''Fluorine-Containing Heterocycles: Part III. Synthesis of Perfluoroalkyl Heterocycles Using Perfluoroolefins Containing a Reactive Group at the Double Bond''. It is authored by G. G. Furin (Novosibirsk Institute of Organic Chemistry, RAS) and comprises the third part of a mini series by this author of which Part I [03AHC(86)129] covered synthesis by intramolecular cyclization and Part II [04AHC(87)273] dealt with synthesis from carbonyl compounds.

Alan R. Katritzky
Department of Chemistry
University of Florida
Gainesville, Florida

Microwave Irradiation for Accelerating Organic Reactions. Part I: Three-, Four- and Five-Membered Heterocycles

E.S.H. El Ashry,* E. Ramadan, A.A. Kassem, and M. Hagar

Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

I. Introduction

The electromagnetic spectrum has played a decisive role in organic chemistry. From the radio frequency region at the low-energy end of the spectrum to X-rays at the high-energy end and in between the microwave, infrared and ultraviolet have all (except microwave) been used in the structural elucidation of organic compounds.

The microwave (MW) region of the electromagnetic spectrum lies at frequencies from 0.3 to 300 GHz, higher than those associated with radio frequencies but at frequencies lower than those associated with infrared. The energy transitions in the MW region are enough to cause bond rotation, whereas radio frequencies have even lower energy, only enough to cause electronic (ESR) or nuclear (NMR) spin rotations within molecules. More energy causes vibrational (IR) and electronic (UV) transitions, but in the X-ray region the energy may be high enough to break bonds.

Recently, microwave irradiation (MWI) has attracted much attention as a tool of preference in achieving and/or accelerating organic reactions. These reactions may be sometimes carried out in the absence of solvent when coupled with their high yields and short reaction times make these synthetic procedures very attractive.

*Corresponding author. Fax: +20 3 4271360.

E-mail address: eelashry60@link.net, eelashry60@hotmail.com

ADVANCES IN HETEROCYCLIC CHEMISTRY
VOLUME 88 ISSN: 0065-2725 DOI: 10.1016/S0065-2725(04)88001-2

When matter is irradiated with MW, the ability of a molecule to absorb MWI is a function of two main mechanisms: its molecular polarizability which in turn is a function of its dipole moment, and its ionic conduction. Here migration of dissolved ions with their oscillating electric field generate heat as a result of frictional losses in amounts, depending on the size and conductivity of the ions as well as their interactions with the solvent. Thus, molecules rotate to align with the applied field, a rotation similar to the frequency of MWI, and consequently, energy is absorbed by the molecules that sympathetically generate heat. Only polar molecules interact with MW energy. Non-polar solvents and the reaction vessel if made of Teflon, ceramic or even Pyrex does not absorb the energy. In contrast to conventional heating which proceeds from the vessel to the inside, heating under MWI proceeds from inside the vessel and radiates out. The transfer of energy under MWI from the polar molecules to a non-polar solvent is rapid and provides an effective way of using such solvents in organic synthesis. The addition of polar salts to the solvent leads to an increase in heating rates (see Figure 1).

Microwave ovens provide a clean, cheap, and attractive means for heating which is superior to conventional oil baths. Modified ovens which can be adapted with an appropriate condenser may be used conveniently to carry out reactions at atmospheric pressure. Domestic MW ovens may lack sufficient control on reactions and thus may lead to accidents including explosions. However, ovens designed with single-mode cavities have been developed in order to use solvents in MW-assisted organic synthesis without the risk of explosion. Various clays, alumina and silica have been used as a solid support when efficiently mixed with reagents in an appropriate solvent and then evaporated. The adsorbed reagents are then subjected to MWI after which the organic products are simply extracted from the support. For pressure reactions or those in a sealed vessel, thick-walled Teflon screw-capped vessels are common. These may be placed in an insulating material or in a specially designed Parr polyetherimide bomb to absorb any liquid spilled and to prevent damage to the oven. For reactions under pressure in a non-polar solvent, in which the solvent absorbs the thermal energy and transmits it to the reactants, the Pyrex vessel may be embedded in vermiculite (hydrous silicates of iron, aluminum and magnesium) (91CSR1). The vermiculite heats very rapidly because of its water of hydration, which absorbs MW energy, and then transmits the heat rapidly to the

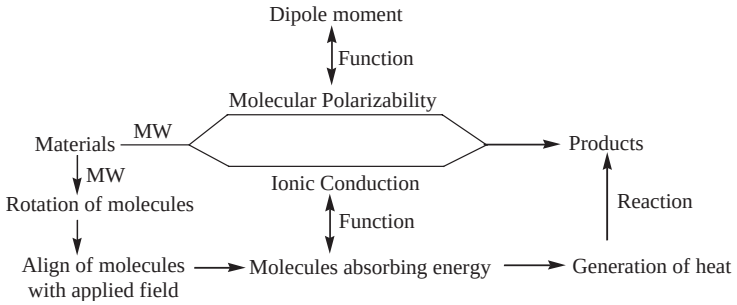


Figure 1

solution. Much higher temperatures are reached rapidly than by using conventional heating methods.

The CSIRO continuous microwave reactor (CMR) was the first system designed for reactions in organic solvents. The reactor consisted of a microwave cavity fitted with a coil fabricated from a microwave transparent inert material. It is operated by passing pressurized liquids or slurries through a microwave zone. The CMR has facilitated a diverse range of reactions at temperatures up to 200 °C (94JOC3408). A significantly more advanced microwave batch reactor (MBR) was developed which had a capacity of 20–100 ml and was capable of operating at up to 260 °C and 100 atm (95JOC2456). Single-mode cavity microwaves are no longer the best choice and multi-mode cavity microwaves should be used. An alternative approach is to use continuous-flow systems in which the reagents are pumped through the microwave cavity, allowing only a portion of sample to be irradiated at a time (94JOC3408).

As a consequence of the advantages of using MWI in organic synthesis, many reviews (91OPP683, 95AJC1665, 95T10403, 97CSR233, 97MI1, 98CSR213, 98CJC525, 98S1213, 99AJC83, 99JHC1565, 99MI1, 99MI2, 99MI3, 99T10851, 00CSR239, 00MI1, 01MI1, 01MI2, 01T4365, 01T9199, 01T9225, 02ACR717, 02MI1, 02MI2, 02MI3, 02T1235, 03MI1, 03MI2, 04H903) have been published. However, owing to the vast increase in the number of publications using microwaves in organic synthesis, it is desirable to review the synthesis and reactions of heterocyclic compounds. A survey of the literature on the synthesis and reactions of three-, four- and five-membered heterocycles constitutes the subject of this review, divided according to the order of increasing size of the heterocycles and the number of heteroatoms. Each type is reviewed according to their methods of preparation of the desired ring and by their reactions. Heterocycles having fused benzene rings then follow.

II. Three-Membered Heterocycles

Examples of three-membered heterocycles, synthesized using MWI, are limited to those with one heteroatom; no examples were found for three-membered heterocycles with more than one heteroatom.

A. Heterocycles with One Heteroatom

These heterocycles may contain nitrogen or sulfur, or especially oxygen. Moreover, most of the interest is concerned with the ring opening of these heterocycles.

1. *Oxiranes*

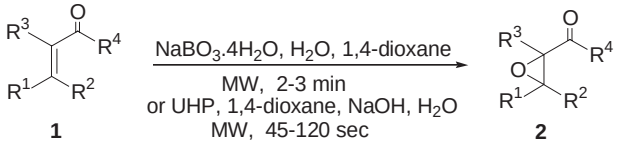
Epoxidation of α,β-unsaturated ketones **1** by sodium perborate in water and 1,4-dioxane as a cosolvent under MWI for 2–3 min produced the corresponding epoxides **2** in good yields (43–93%) (Scheme 1) (98JCR(S)668). The same method without MW activation required a longer period of time (5–26 h) to obtain **2** (89SC3579).

Urea-hydrogen peroxide (UHP) is a relatively stable white crystalline solid formed when urea is recrystallized from aqueous hydrogen peroxide, and it has quite a high hydrogen peroxide content. UHP has been used for epoxidation of α,β-unsaturated ketones, alkenes and allylic alcohols (90SL533, 00MI2), with a dramatic reduction in time, especially for the more sterically hindered compounds, from many hours to few seconds with an improvement in yield was achieved upon applying MWI (04MI1). Thus, the reaction of several α,β-unsaturated ketones **1** with UHP in the presence of aqueous NaOH in 1,4-dioxane occurred within seconds to give the epoxides **2** in 75–95% yields.

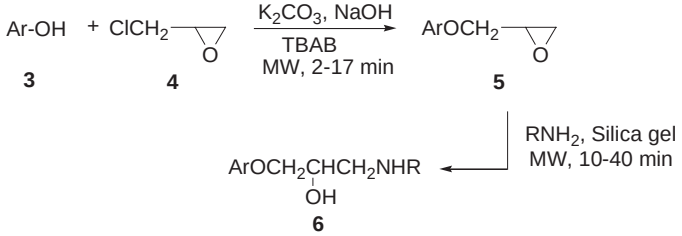
The time required for the reaction between phenol **3** and epichlorohydrin **4** on a solid support with a small amount of tetrabutylammonium bromide (TBAB) as the phase transfer catalyst under MW heating was 100 times shorter than that for the conventional procedure to give arylglycidyl ethers **5** in 67–96% yields (98OPP87) (Scheme 2). The O-alkylation of phenols with **4** has also taken place in aqueous sodium hydroxide under MWI to give a 63–88% yield of **5** (97SC2051). MW has promoted the ring opening of **5** with various amines supported on silica gel to give 3-alkylamino-1-aryloxy-2-propanols **6** in 67–89% yields (98OPP87).

A regioselective ring opening of epoxides **7** with ammonium acetate by MWI in a domestic MW oven under solvent-free conditions gave β-aminoalcohols **8** with a trace of isomer **9**; the regioselectivity was explained by the nucleophilic attack on the less hindered carbon atom of the oxirane ring. The reaction was completed in 40–120 s and the yields ranged between 65 and 85% (Scheme 3) (99MI4). The same reaction conducted in THF required heating for 8 h to afford the β-aminoalcohols in low yield, with recovered starting material.

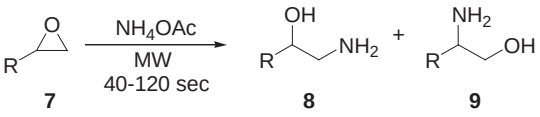
1,2-Disubstituted epoxides can stereospecifically and regioselectively undergo ring opening by ammonia and amines to afford the corresponding aminoalcohols in good



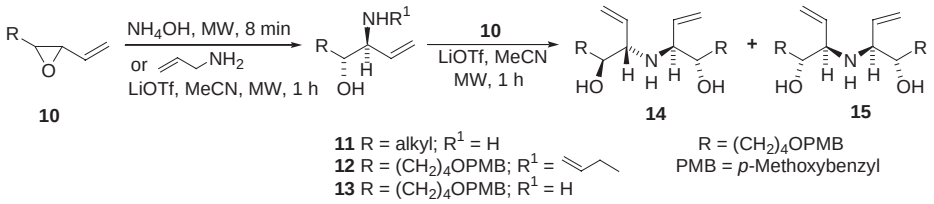
Scheme 1



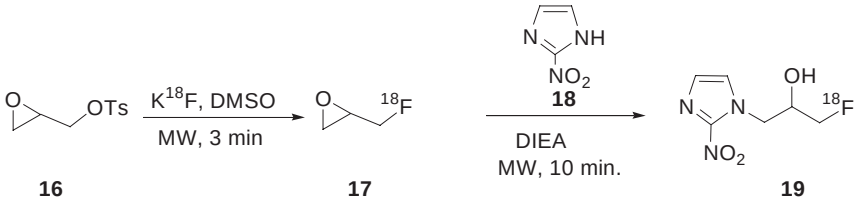
Scheme 2



Scheme 3



Scheme 4



Scheme 5

yields (97TL2027). However, the scope of the reaction is limited as it required prolonged heating in neat ammonia, and when sterically hindered substrates were used, the reaction was almost completely retarded. By contrast, when vinylepoxides **10** in NH_4OH were subjected to MWI at 30 W, complete conversion into aminoalcohols **11** took place in 87–98% yields within 8 min. More sterically hindered substrates were also efficiently converted into aminoalcohols under MWI (99TL9273). Treatment of *rac*-**10** with allylamine in the presence of lithium triflate in acetonitrile under MWI at 120 °C for 1 h gave **12** in 92% yield (Scheme 4). Similarly, **13** was obtained in 98% yield by aminolysis of **10** with NH_4OH under MWI for 20 min. The reaction of *rac*-**13** with *rac*-**10** in the presence of lithium triflate under MWI gave a 1:1 mixture of the diastereomeric amino-diols **14** and **15** in 65% yield (Scheme 4) (02SL731).

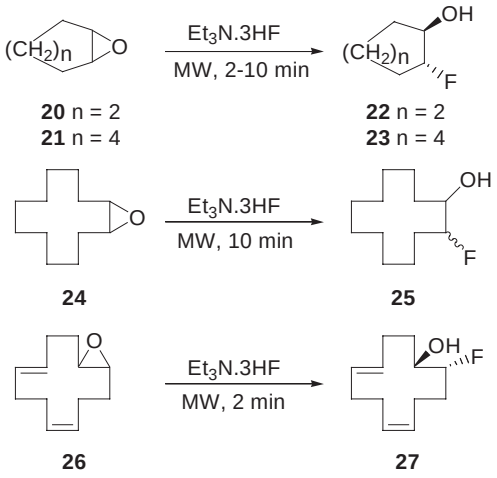
Nucleophilic substitution of the tosylate group in **16** by ^{18}F using $K^{18}F$ in DMSO under MWI gave within 3 min a 70–80% yield of the radiolabeled fluorohydrin **17** whose reaction with 2-nitroimidazole **18** in the presence of *N*,*N*-diisopropylethylamine (DIEA) required 10 min of MWI to give a 65% yield of the imidazole derivative **19** (Scheme 5) (93MI1).

Fluorination reactions using $Et_3N.3HF$ often require high temperature and long reaction time due to low reactivity. Thus, the reaction of $Et_3N.3HF$ with cyclohexene

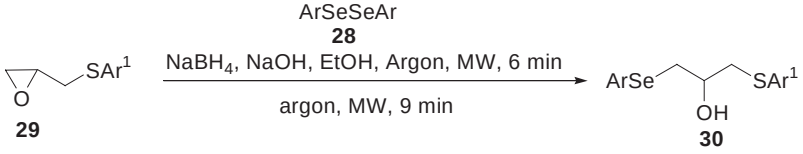
oxide **20** was carried out at 115 °C for 3.5 h to give *trans*-2-fluorocyclohexanol **22** in 69% yield (02JOC3015), and the reaction with cyclooctene oxide **21** took 4 h at 155 °C to give 2-fluorocyclooctanol **23** in 54% yield. However, under the MWI conditions, the fluorination reactions with **20** or **21** were completed in 2 and 10 min, respectively, and the corresponding fluoroalcohols **22** and **23** were obtained in 61 and 60% yield. Similarly, epoxides **24** and **26** were converted into the respective fluoroalcohols **25** and **27** in 2–10 min under MWI in 76 and 71% yield, respectively (Scheme 6) (03S1157).

The reactions of epoxides with organoselenium reagents suffer from poor regioselectivity and required low temperatures (–78 °C) (98CL159). Recently, under MWI substituted glycerol selenide ethers **30** were obtained in high yields (73–87%) and good regioselectivities by reducing dialkyl diselenides **28** with sodium tetrahydroborate in a basic medium, followed by reaction with glycidyl sulfide ether **29**. The reactions under MWI were 40–52 times faster than under conventional heating conditions (Scheme 7) (99JCR(S)688).

The classic oxidation of epoxides **31** by DMSO in the presence of boron trifluoride, trifluoroacetic or flurororboric acid with molecular sieves was reported to give α-hydroxy ketones **32** (61JOC1681, 71BCJ645) but not with such clean, rapid and convenient conditions as that readily obtained by oxidation with DMSO in the



Scheme 6



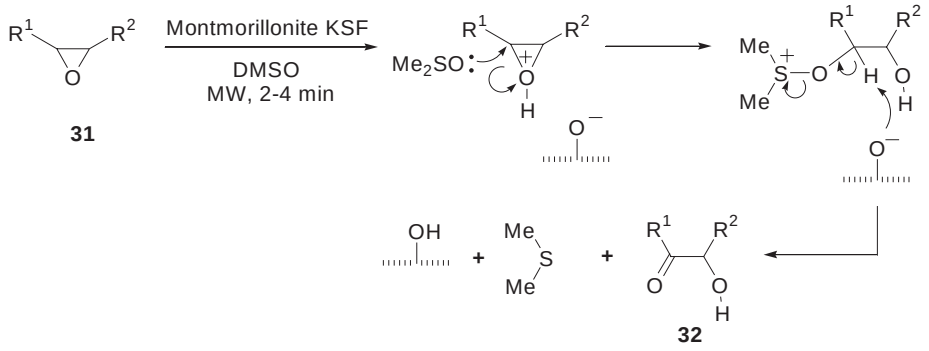
Scheme 7

presence of montmorillonite KSF clay under MWI. The reaction was rapid (2–4 min) and the yields ranged between 55 and 90%. The epoxide was first protonated by the clay and then DMSO attacked the protonated epoxide whereby the ring was opened to give a hydroxysulphoxonium salt adsorbed on the surface of KSF. Then the sulphoxonium salt decomposed to the α-hydroxyketone **32** (Scheme 8) (95SC3141).

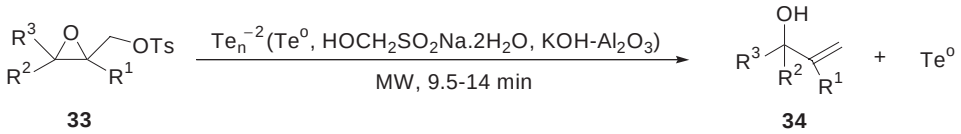
Elemental tellurium (Te°) was reduced under rongalite ($HOCH_2SO_2Na \cdot 2H_2O$) and KOH–Al_2O_3 in the solid phase under MWI for 5–7 min, to give a red–purple mixture containing (Te_n^{-2}); a powerful nucleophile that attacked the electrophilic sites in organic substrates. When this telluride reagent and the glycidyl tosylate **33** were mixed in a mortar and subjected to MWI for 9.5–14 min, the respective allylic alcohol **34** was obtained in high yield (50–83%) (Scheme 9) (97T12131).

2. *Thiiranes*

Most of the synthetic methods available for the synthesis of thiiranes, the simplest sulfur heterocycle, suffer from disadvantages such as poor yields, extended reaction times, and formation of several by-products (69JCS(C)1252, 76JOC1735, 95JOC473, 99OL611). Recently, thiiranes **39** were obtained in excellent yields (81–94%) under MWI from a mixture of α-halo ketones **35** and *O*,*O*-diethyl hydrogen phosphorodithioate **36** on alumina-supported sodium borohydride in a domestic MW oven for 2.5–4 min. The reaction did not even go to 50% completion after 15 h at the same temperature when conventional heating using an oil bath was employed. The formation of **39** was explained by the formation of **37**, the reduction of which followed



Scheme 8



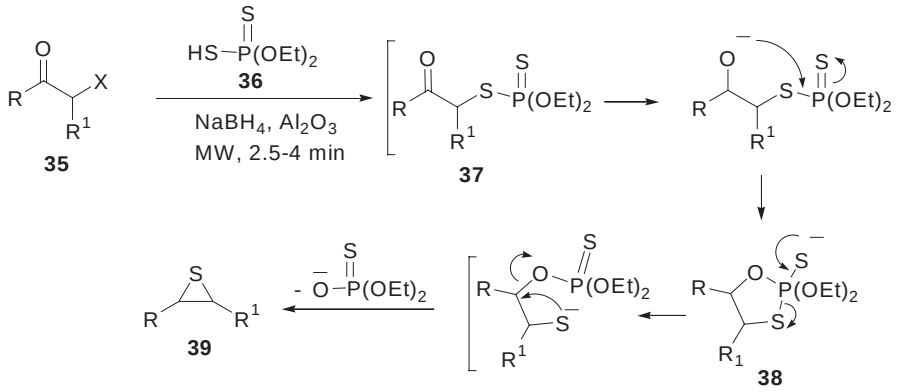
Scheme 9

by intramolecular cyclization of the presumably formed alkoxide ion to **38** which opened and then cyclized to give **39** (Scheme 10) (02SL2344).

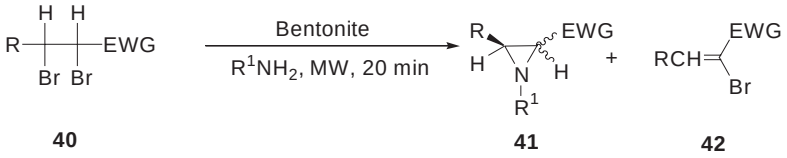
3. *Aziridines*

Activation of the reaction of dibromo compounds **40** with an excess of primary aliphatic amines under MWI over bentonite yielded a mixture of the corresponding *cis* and *trans* aziridines **41** (14–36%) together with alkene **42** (32–42%). The MWI accelerated the process, but the elimination is more efficient to form **42** than the Michael addition to form the aziridines **41** (96JCR(S)429). On the other hand, treatment of **40** with piperidine or Et_3N without solvent under thermal or MW activation led exclusively to α-bromoalkenes **42** (75–100%) in very short times (5–15 min) (Scheme 11) (03S2185).

The cleavage of a variety of N-substituted aziridines **43** with hydroxyl compounds was very facile in the presence of $BF_3.OEt_2$ and $Sn(OTf)_2$, but hindered alcohols took a long time (2 days). However, the cleavage of **43** with hindered alcohols could be achieved under MWI in a very short period (15 min) to give the corresponding 3-amino ethers **44**. Phenols could cleave aziridines only under MWI (Scheme 12) (02T7355).

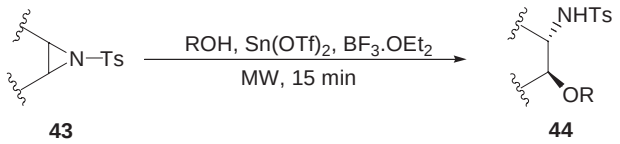


Scheme 10

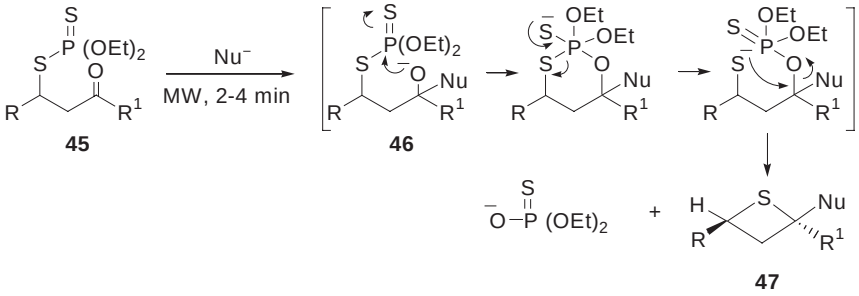


EWG = electron withdrawing group

Scheme 11



Scheme 12



Scheme 13

III. Four-Membered Heterocycles

Again four-membered heterocycles with one heteroatom can only be presented under this title; others with more than one heteroatom are not yet synthesized under MWI.

A. Heterocycles with One Heteroatom

Surprisingly, no examples were found for those heterocycles with oxygen, but there are examples for those with sulfur. On the other hand, much literature has been devoted to those with nitrogen for obvious reasons such as incorporation of the ring in various β-lactam antibiotics.

1. *Thietanes*

Cyclization of Michael adducts **45** by reaction with carbon and sulfur nucleophiles (CN^-, RS^-) under MWI in solvent-free conditions gave (*Z*)-2-alkylsulfenyl(or 2-cyano)-2,4-diarylthietanes **47** in good yields (77–92%) with 93–97% diastereoselectivity. The formation of **47** was explained by the attack of the nucleophile on the carbonyl carbon of **45** to give alkoxide ion **46**, which intramolecularly attacked the phosphorous atom to give a cyclic intermediate that led to the formation of thietanes (Scheme 13). The mechanism was supported by the isolation of the respective cyanohydrin of **46** and its cyclization to thietanes **47** by the action of base (02S1502).

2. *Azetidines (β-Lactams)*

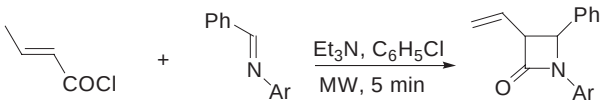
The number of examples under this heading is large due to the incorporation of that ring into a number of β-lactam antibiotics such as penicillins and cephalosporins.

The synthesis of azetidinones **50** can be achieved by the reaction of the α,β-unsaturated acyl chloride **48** with a Schiff base **49** in the presence of triethylamine in chlorobenzene under MWI in 65–70% yield within 5 min, instead of few hours of conventional heating in benzene (Scheme 14) (91JOC6968).

A β-lactam ring can be constructed by placing a mixture of Schiff base **51**, triethylamine and benzyloxyacetyl chloride in ethylene dichloride in an Erlenmeyer flask with a loose cover for a top and a beaker of water by its side. Then the mixture was subjected to irradiation with MW for 3 min in a domestic MW oven. The *cis*-β-lactam **52** was formed in 70–75% yield; few hours were required under traditional reaction conditions. Hydrogenolysis of **52** using ammonium formate and 10% Pd/C was also carried out under MWI in few min to give 3-hydroxy-2-azetidinones **53** in 88–90% yields (Scheme 15) (92TL3603).

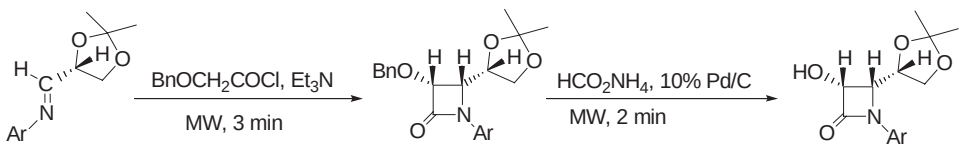
The formation of *trans*-α-acetoxy azetidinones **56** was highly favored by adding the acid chloride **54**, Schiff base **55** and *N*-methylmorpholine (NMM) to preheated chlorobenzene (110 °C) as the reaction medium followed by irradiation with MW; the *trans* to *cis* ratio was 90:10 (Scheme 16) (02S1578).

Reaction of ferrocenylacetic acid **57** with imines **58** in the presence of phenyl dichlorophosphate, triethylamine and a minimum amount of toluene under MWI for 4–6 min provided β-lactams **59** (17–96%) and unreacted starting materials and their decomposition products. In some cases, however, the yields were higher than those obtained by a conventional thermal method. In the case of achiral imines, the *cis*-β-lactams were the only products, while imines derived from *trans*-cinnamaldehyde afforded a mixture of *cis*- and *trans*-isomers, the *cis* being predominant. Chiral imines gave a mixture of diastereoisomeric *cis*-β-lactams with low levels of diastereoselectivity. The ferrocenylimine **60** gave low yield (13%) of the *cis*- and *trans*-β-lactams of **61** in 1:1 ratio, in addition to olefin **62** (Scheme 17) (01SL1092).



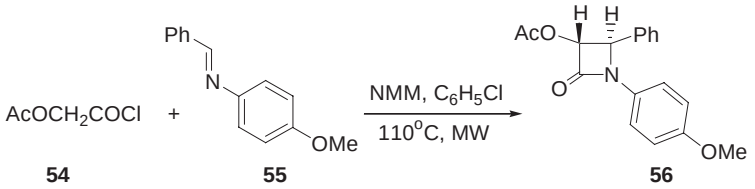
48 **49** **50**

Scheme 14

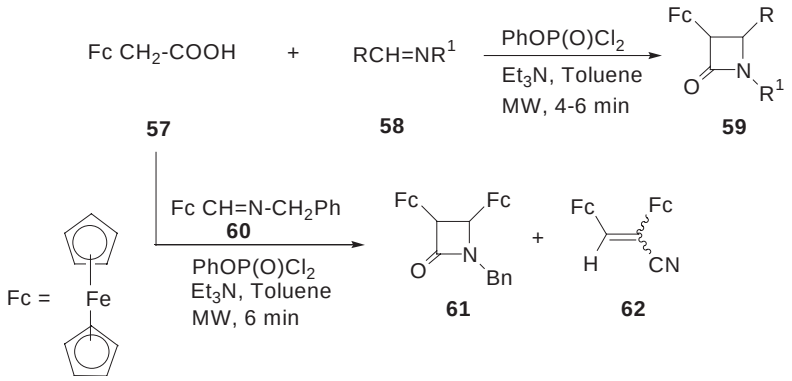


51 **52** **53**

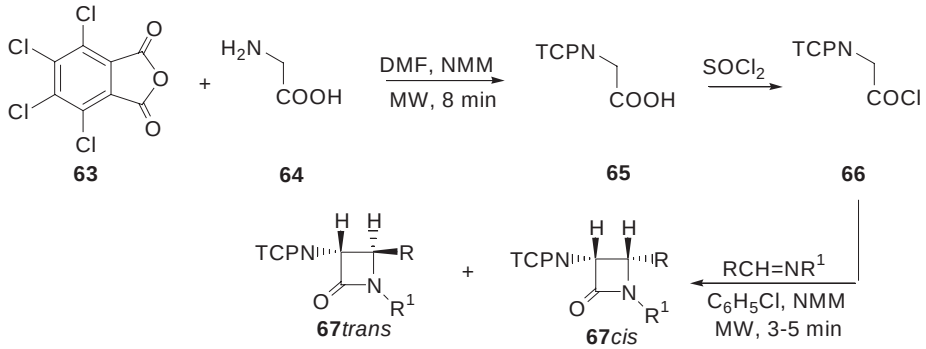
Scheme 15



Scheme 16

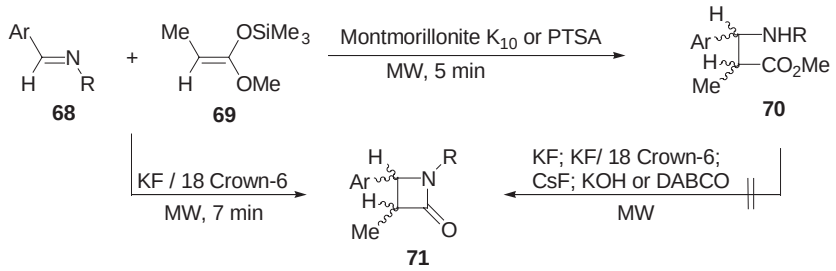


Scheme 17



Scheme 18

The tetrachlorophthaloyl (TCP)-protected glycine **65**, required for the synthesis of β-lactams, was prepared by protection of glycine with commercially available tetrachlorophthalic anhydride **63** in 94% yield after 8 min of MWI. Treatment of **65** with thionyl chloride in refluxing chlorobenzene for 4 h provided the acid chloride **66** in quantitative yield. Reaction of **66** with imines in chlorobenzene in the presence of NMM under MWI provided the corresponding TCP-protected *cis*- and *trans*-β-lactams **67** in 83–99% yields after 3–5 min (Scheme 18). High level of *trans* selectivity, nearly exclusive in some cases, was observed when the reaction was carried out



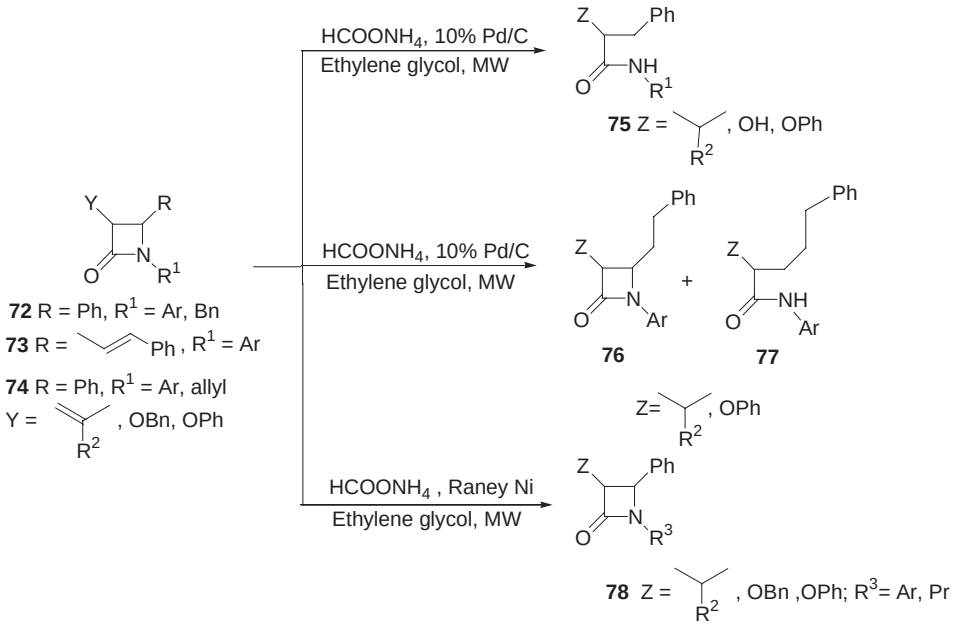
Scheme 19

under MWI. However, only the *cis*-β-lactam was isolated in the case of 4-styryl-2-azetidinone either under MWI or by classical heating (96TL6989).

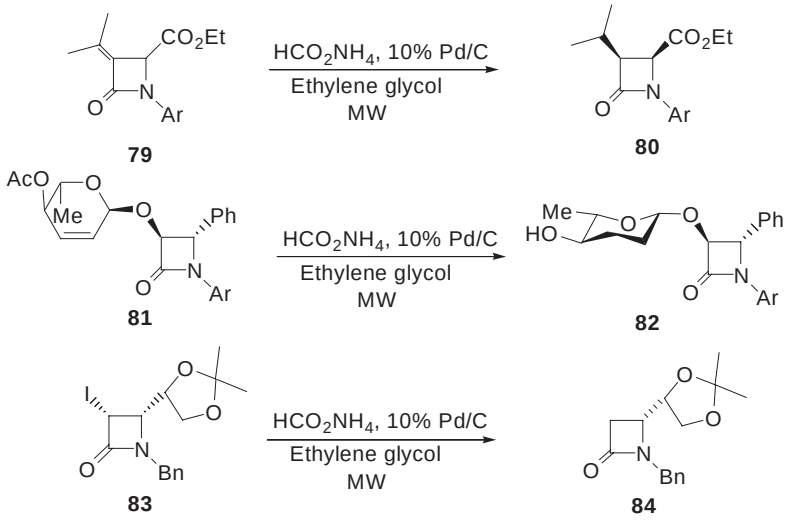
β-Lactams were prepared from the reaction of the silyl ketene acetals with aldimines either by hydrolysis of a preformed metalated intermediate of the formed β-aminoester (77TL3643, 80TL2077, 80TL2081, 84TL2143) or by treatment of the demetalted ester with LDA (77TL3643, 81S545, 83TL4707, 84JCS(CC)883, 84JOC1056, 85JCS(CC)240, 87TL4331, 87TL4335, 87TL227). The synthesis of the β-aminoesters **70** can be achieved under MWI by the reaction of imines **68** with the silyl ketene **69** over dried montmorillonite K_{10} or *p*-toluene sulfonic acid (PTSA) in a few minutes. On the other hand, the cyclization of **70** to the respective β-lactams was unsuccessful under MWI by using a solid base (KF, KF/18 Crown-6, CsF, powdered KOH or DABCO). However, the direct reaction of imine **68** with silyl ketene acetals **69** over basic solids (KF or KF/Al_2O_3) in the presence of CsF gave a mixture of β-aminoesters **70** and β-lactams **71**, although in low yields (30% conversion), but in the presence of KF/18 Crown-6, it was possible to get exclusively the desired β-lactams **71** in 47–93% yields (Scheme 19) (93TL2123).

Hydrogenation of β-lactams possessing various substituents was studied in ethylene glycol as a high boiling solvent and ammonium formate as a hydrogen transfer reagent and in the presence of 10% Pd/C under MWI for 2–5 min. Under these conditions, the 4-aryl-2-azetidinones **72** were easily cleaved to provide 3-arylpropionamides of type **75** in 80–90% yields. The N-benzyl or N-aryl group of **72** was not hydrogenolyzed, but the O-Bn group at C-3 was converted into an OH group (93SL575). Reduction of the vinyl group on C-3 of **72** also took place in addition to the cleavage of the β-lactam ring in less than 45 s under MWI at a temperature of about 110 °C to give the respective amide **75** (91JOC6968). The presence of a styryl group at C-4 as in **73** led to a partial scission of the β-lactam ring whereby the two products **76** and **77** were obtained in a ratio 60:40. In the presence of Raney Ni catalyst, double bonds were reduced without scission of the β-lactam ring. Thus **74** with an N-allyl group were reduced to **78** with an N-propyl group in 80% yield (Scheme 20) (93SL575).

An exo-alkene group at C-3 of β-lactams, such as in **79**, also has been readily reduced to **80** under the similar above conditions using MWI. In addition to the reduction of the double bond in the glycoside **81**, a deacetylation took place to give **82**. Under similar conditions, a smooth dehalogenation of **83** gave **84** in few minutes (Scheme 21) (99JOC5746).

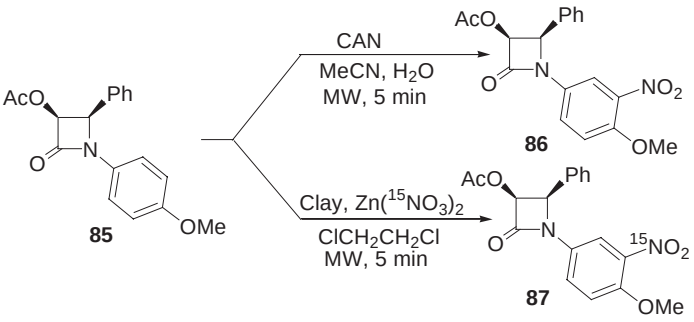


Scheme 20

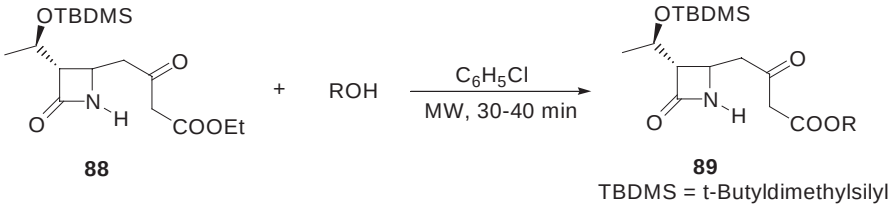


Scheme 21

The nitration of **85** was performed using cerium(IV)ammonium nitrate (CAN) in MeCN-H_2O as the reaction medium under MWI. After about 5 min of irradiation, the nitro compound **86** was obtained in 82% yield. Under similar conditions, the nitration of **85** with $Zn(^{15}NO_3)_2$ adsorbed on clay and using ethylene dichloride as



Scheme 22



Scheme 23

the reaction medium afforded the labeled nitro compound **87** in 85% yield, which showed a high level of ^{15}N by mass spectral examination (Scheme 22) (02S1578).

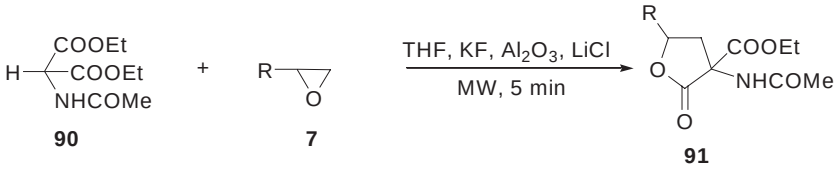
Transesterification of the ester group of azetidinone **88** in chlorobenzene with alcohols in the absence of an acidic or basic catalyst in a normal domestic MW oven gave the azetidinones **89** in good yields (81–95%) without the formation of diastereomers. Moreover, neither deprotection of the TBDMS group nor racemization of the starting alcohols was observed. Transesterification of the ethoxy group took place even in absence of any solvent but in poorer yield (25–40%) (Scheme 23) (00SC1725).

IV. Five-Membered Heterocycles

A. Heterocycles with One Heteroatom

1. *Oxolanes (γ-Lactones and Anhydrides)*

Lactones **91** were obtained as a main product from the epoxide ring opening of a fatty epoxide (tetradecyl-oxirane) **7** with diethyl acetamidomalonate (**90**) and subsequent cyclization. The reaction was performed with or without a solvent on supported reagents of LiCl impregnated together with KF on alumina under MWI



Scheme 24

to give **91** in >90% yield within 5 min (94SC1809). Conventional heating at 120 °C required 18 h to get the lactone **91** (68%) in addition to an unidentified product under phase-transfer catalysis which involved the formation of the anion of **90** *in situ* by the presence of a catalytic amount of base followed by reaction with **7** in the presence of two equivalents of LiCl (Scheme 24) (94SC1809).

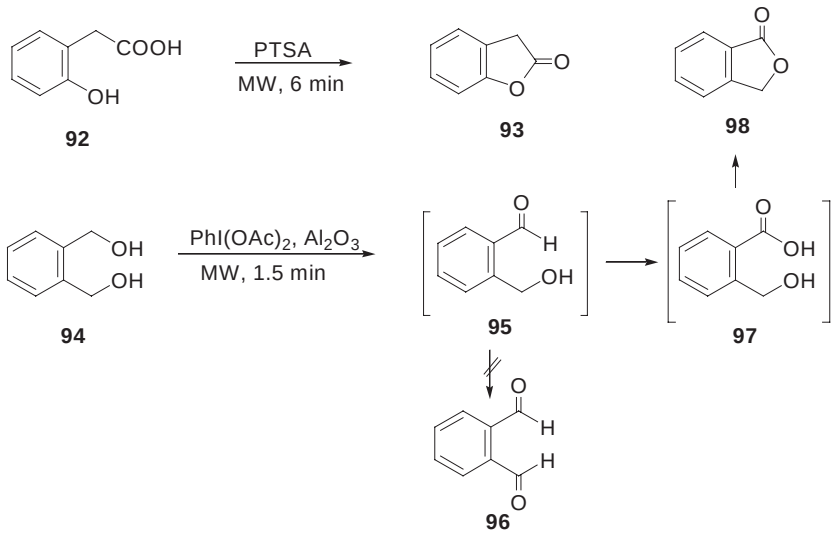
The intramolecular cyclization of 2-hydroxyphenylacetic acid **92** into benzofuran-2(3H)-one (**93**) occurred quickly in 85% yield when promoted by MWI in the presence of catalytic amount of PTSA. The reaction under MW required 6 min compared to the classical heating which required at least 30 min. From an economical point of view, the expenditure of energy was estimated to be 108 kJ under MW for the whole process and 540 kJ by classical heating–magnetic stirring at 1500 W; the latter energy value excluded the preheating required to reach the reaction temperature that was estimated to be at least 3000 kJ (99JCS(P2)2111).

Oxidation of alcoholic groups is an important reaction in organic synthesis and several methods are available to accomplish this conversion under a variety of reaction conditions. Mixing neat 2-hydroxymethylbenzyl alcohol **94** with 2.2 equivalents of iodobenzene diacetate (IBD) doped on neutral alumina and irradiation of the reaction mixture in a MW oven for 1.5 min under solvent-free conditions gave 1(3*H*)-isobenzofuranone **98** (an isomer of **93**) in 86% yield and not the phthalic dicarboxaldehyde **96**. The presumably formed aldehyde **95** was oxidized to acid **97** rather than to dialdehyde **96**; **97** on dehydration gave **98** (Scheme 25) (97TL7029).

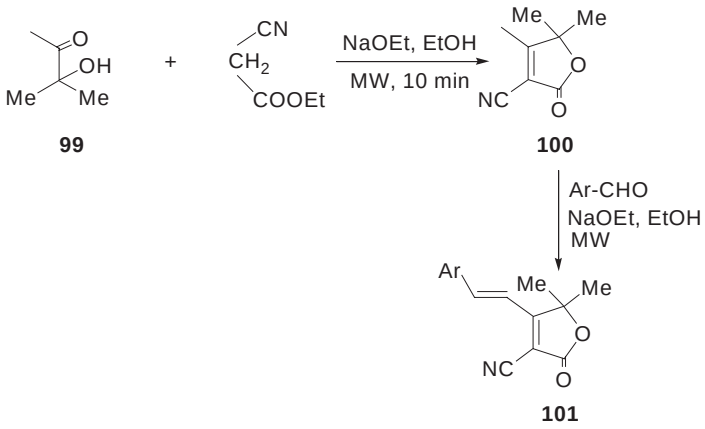
The reaction of 3-hydroxy-3-methyl-2-butanone (**99**) with ethyl cyanoacetate in the presence of sodium ethoxide under focused MWI for 10 min gave 3-cyano-4,5,5-trimethyl-2-(5*H*)-furanone (**100**) in 96% yield (98S1213). Under similar conditions, furanone **100** was condensed with aromatic or heteroaromatic aldehydes to produce 3-cyano-4-(*trans*-aryl-vinyl)-5,5-dimethyl-2-(5*H*)furanones **101** in high yields (71–98%) (Scheme 26). The overall yields in a one-pot synthesis of **101** were 71–88% (00JCR(S)179). The condensation of **100** with thiophen-2-carboxaldehyde in the presence of sodium hydroxide in methanol required 4 h heating under reflux (89CCC1666).

The dry reaction of aromatic aldehydes with furandione **102** supported on acidic montmorillonite KSF under MWI gave efficiently the condensation products as a mixture of isomers **103** in 54–92% yields. The montmorillonite K_{10} gave similar results, but neutral alumina or silica gave lower yields. Basic KF on alumina was unsuitable; obviously the reaction is acid-catalyzed (Scheme 27) (90SC3207).

Condensation of 6-acetoxybenzofuran-3(2H)-one (**104**) with benzaldehyde on alumina under solvent-free conditions in a MW oven takes place with concomitant deacetylation to give **105** in 91% yield (Scheme 27) (93JCS(P1)999).



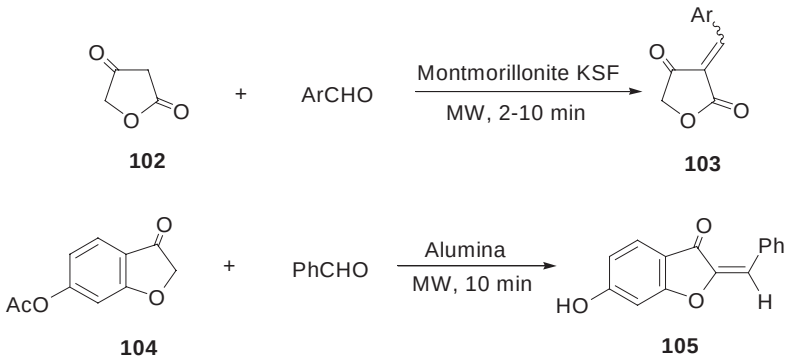
Scheme 25



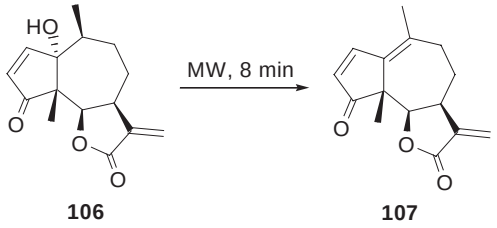
Scheme 26

Parthenin (**106**) is the major sesquiterpenoid lactone of an obnoxious weed. Several transformations of **106** have been carried out to prepare more potent analogs with lower toxicity. Some of the analogs have been synthesized via anhydroparthenin (**107**) that was prepared earlier from **106** by using various reagents, such as formic acid, sulfuric acid, sulfuric acid/acetic anhydride and boron trifluoride-etherate. The MWI of parthenin without any solvent for 8 min was found to be a useful and convenient method for the preparation of **107** in 68% yield (Scheme 28) (99SC863).

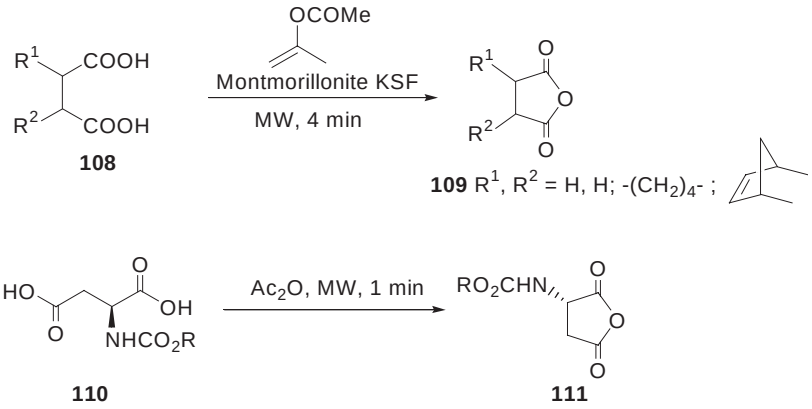
The synthesis of anhydrides **109** was achieved in 90–95% yield by subjecting the respective dicarboxylic acids **108** to MWI for 4 min in the presence of isopropenyl acetate on montmorillonite KSF (Scheme 29) (93SC419).



Scheme 27



Scheme 28



Scheme 29

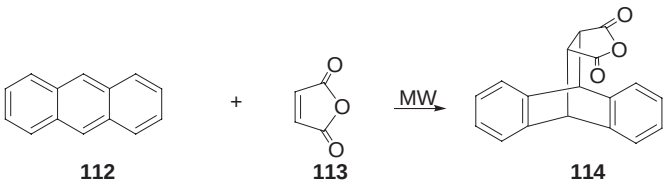
Anhydrides **111** have been obtained in 98% yield by reaction of N-protected L-aspartic acid **110** with acetic anhydride under MWI. The reactions were completed after 1 min in the absence of solvent (Scheme 29) (03SL797).

The Diels–Alder cycloaddition between anthracene (**112**) and maleic anhydride (**113**) in open systems in a MW oven employing chlorobenzene, *o*-dichlorobenzene or

diglyme as the energy transfer medium has been studied. The yield of the adduct **114** was about 40% in the lower boiling solvent chlorobenzene, but it increased to 80–85% in *o*-dichlorobenzene and 90% in diglyme (91JOC6968). The yield of **114** was also high, reaching 92% when the reaction was carried out in *p*-xylene at temperatures between 160 and 187 °C under MW heating for 3 min (86TL4945). However, MW induced the reaction in the absence of solvent and any inorganic catalyst as support. Moreover, the reaction time was dramatically reduced and a good yield was obtained compared with using an organic solvent (Scheme 30) (94SC2417). Supporting the reactants on graphite and using MW irradiation for 3 min gave adduct **114** in 75% yield (96LA739).

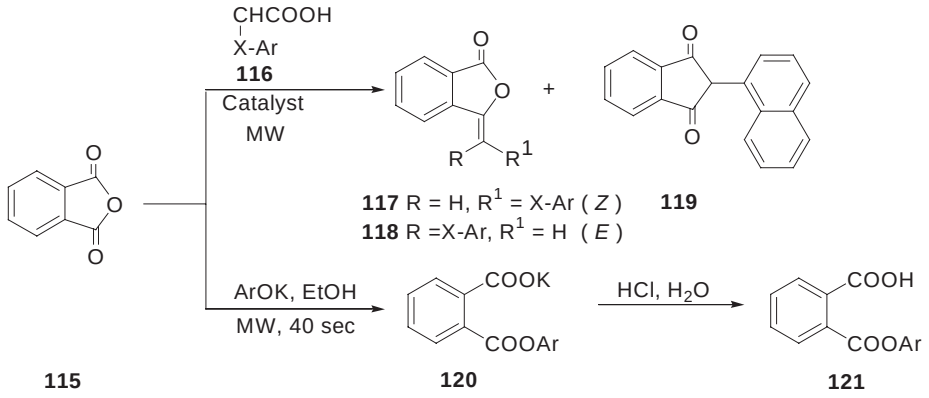
The classical Gabriel synthesis of 3-arylmethylenephthalides consists of prolonged heating of phthalic anhydride, the appropriate acid and a catalyst to 240–260 °C for 2–4 h. When a mixture of phthalic anhydride **115**, arylacetic acid **116** and AcOK as a catalyst was heated in an Erlenmeyer flask in the MW oven for 3–10 min, the *Z* and *E* isomers of arylmethylenephthalides **117** and **118** were isolated in ratios 2–10:1. Under these conditions, 1-naphthylacetic acid and arylthioacetic acid gave good yields (64–89%) of the 3-arylmethylenephthalides, whereas reasonable or poor yields were obtained with 2- or 3-thienylacetic acids and aryloxyacetic acids. Cesium acetate was found to be an efficient catalyst for the synthesis of 3-(2- or 3-thienylmethylene)phthalides in 39–66% yields, but yields of 3-aryloxymethylenephthalides were still very low (4–13%) even when $AcOCs/Al_2O_3$ was used. Using K_2CO_3 or $AcOK/Ac_2O$ as a catalyst, the conversion of 1-naphthylacetic acid into products was less than 50% and a mixture of 3-(1-naphthylmethylene)phthalide and 2-(1-naphthyl)-1,3-indandione (**119**) was formed in 27–54% yields within 1–3 min (Scheme 31) (96T14995).

Direct esterification of phenols with aliphatic or aromatic acids is impossible. However, the reaction can be induced by reacting phenols either in the form of their phenolates or in pyridine with acid chlorides or anhydrides, but this only works with aliphatic acid derivatives (80JCE527, 94MI1, 96MI1). Recently, *o*-phthalic monoesters **121** were synthesized by a reaction between phthalic anhydride **115** and potassium phenoxides under MWI. Ethyl alcohol was used both to homogenize the reaction medium paste and to initiate a chemical reaction generating hot spots in the reaction medium. The initial salt **120** was transformed into **121** by adding hydrochloric acid; the maximum yield (78%) of 2-(phenoxycarbonyl)benzoic acid was obtained after 40 s of MWI. The respective 2-[4-(phenylazo)phenoxycarbonyl]benzoic acid was obtained in high yield (90%) (Scheme 31) (00SC171).

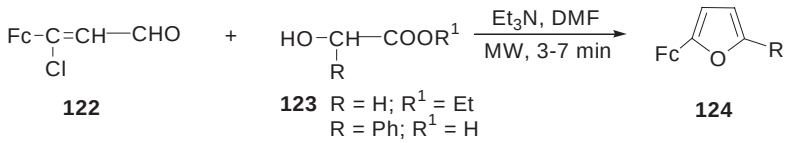


112 **113** **114**

Scheme 30



Scheme 31



Scheme 32

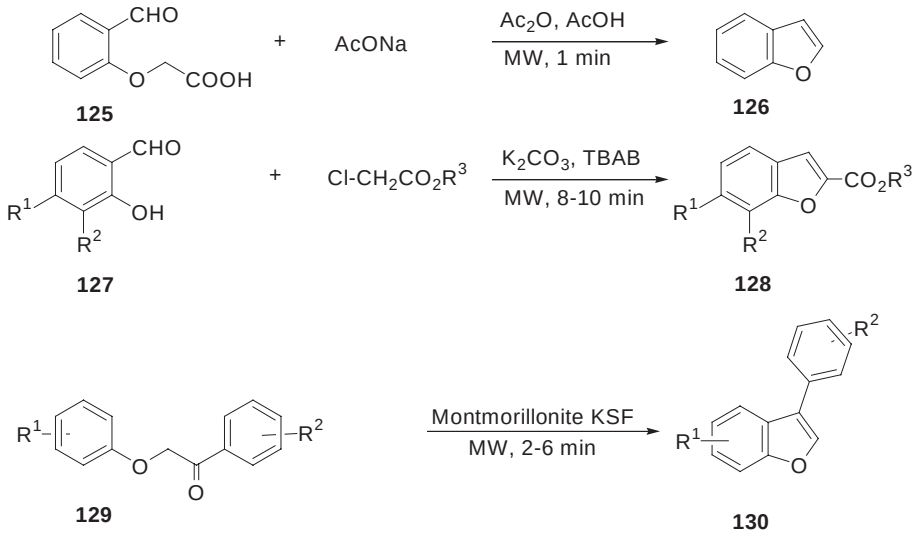
2. *Furans*

The reaction of 3-chloro-3-ferrocenylacrylaldehyde (**122**) with ethyl glycolate or mandelic acid **123** in 1:2 Et_3N/DMF mixture and in a MW oven yielded directly 2-ferrocenylfuran **124** as a red oil in 15–35% yields (Scheme 32). The initially formed ethyl ester of 5-ferrocenyl-2-furancarboxylic acid, produced from the reaction of **122** with ethyl glycolate, was hydrolyzed and decarboxylated during the MWI (94CCC175).

The intramolecular cyclization of 2-formylphenoxyacetic acid (**125**) in the presence of sodium acetate in Ac_2O–AcOH and in a CMR at 180 °C gave benzofuran **126** in 24% yield after only 1 min (Scheme 33) (94JOC3408).

Condensation of salicylaldehyde derivatives **127** with chloroacetic acid esters in the presence of K_2CO_3 and a catalytic amount of TBAB without solvent under MWI led to benzo[*b*]furans **128** in 65–91% yields (Scheme 33). The reactions were carried out in an open vessel bearing a loose cotton cover. Under similar conditions, analogous naphtho[2,1-*b*]furans were prepared from 1-formyl-2-naphthol in 69–94% yields (00T8769).

A convenient synthesis of 3-substituted benzofurans **130** has been accomplished from the cyclization of α-phenoxyacetophenones **129** using zeolite in refluxing xylene (16 h) (91SL121) or Amberlyst 15 as a cyclizing agent in refluxing toluene (7 h) (99JCS(P1)2421). Recently, the α-phenoxyacetophenone **129** in dichloromethane, adsorbed over montmorillonite KSF clay, was subjected to MWI for 2–6 min to give **130** in 76–92% yields (Scheme 33) (00SL1273). The clay brings about the

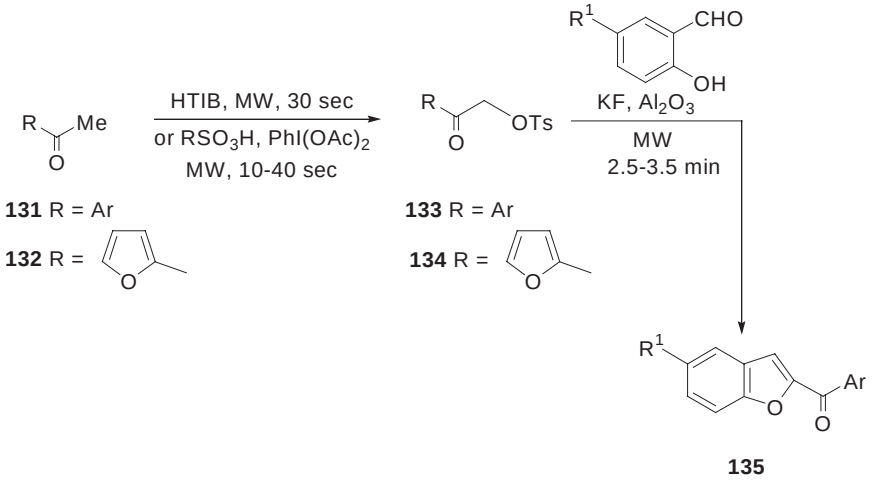


Scheme 33

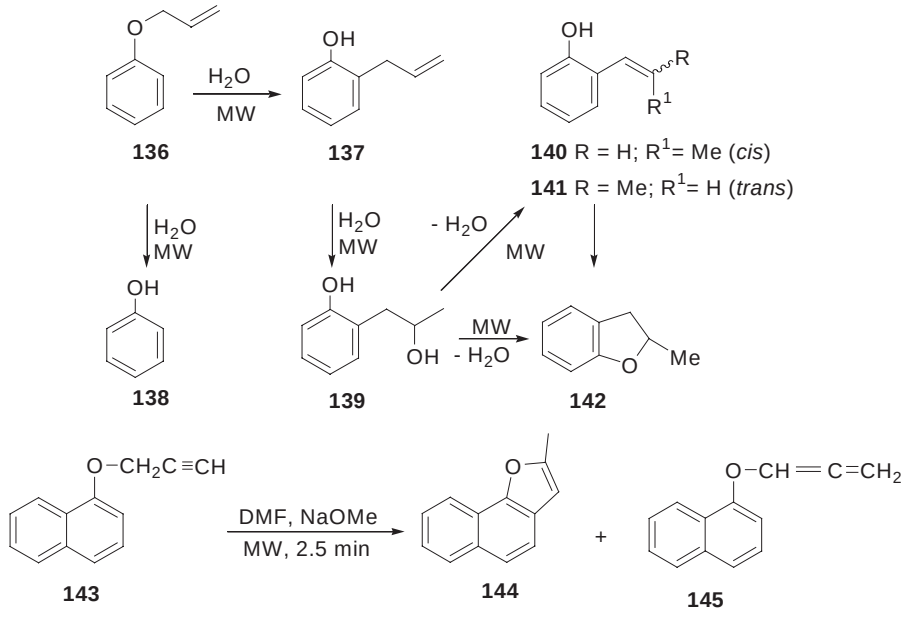
cyclodehydration and the 2:1 ratio of clay to reactant is suitable for cyclization. For a comparative study, the reaction was conducted by using the same ratio of clay and **129** in toluene where it took 10 h for completion (00SL1273).

α-Tosyloxymethylketones **133** and **134** are important precursors for the synthesis of a variety of heterocyclic compounds (94SL221). Conventionally, the preparation of these tosylated carbonyl derivatives from aryl methyl ketones required long reaction time under refluxing conditions in acetonitrile (82JOC2487). However, they can be prepared in high yields (92–96%) by admixing [hydroxy(tosyloxy)iodo]benzene (HTIB) with acetophenones, followed by MW heating (30 s) in an open vessel (98JCS(P1)4093). Recently, the synthesis of **133** and **134** from **131** and **132** was achieved in 80–88% yields under solvent-free MWI using iodobenzene diacetate and organosulfonic acids (01SL234), thus avoiding the preparation of the sulfonylating agent (HTIB) prior the reaction. Admixing salicylaldehydes with **133** on a mineral oxide support such as basic alumina or alumina doped with potassium fluoride, followed by the exposure to MW for 2.5–3.5 min afforded 2-aroylbenzo[*b*]furans **135** in high yields. The basic reaction conditions using Al_2O_3/KF was ideally suited to obtain optimum yields of **135** (89–96%) (Scheme 34) (98JCS(P1)4093).

When the allylphenyl ether **136** was heated in water for 1 h in a MW batch reactor (MBR), five products were detected: 2-allylphenol (**137**), phenol (**138**), *cis*- (**140**) and *trans*-2-(prop-1-enyl)phenol (**141**), 2-(2-hydroxyprop-1-yl)phenol (**139**) and 2-methyl-2,3-dihydrobenzofuran (**142**). Claisen rearrangement of **136** occurred almost exclusively with a maximum conversion to **137**, being 56% at 200 °C. It was suggested that **139** was formed by addition of water to 2-allylphenol **137** above 190 °C, but it also underwent conversion to other products, particularly above 230 °C. Maximum conversion of **136** to **142** (72%) was achieved at 250 °C. The accumulation of **142** at



Scheme 34



Scheme 35

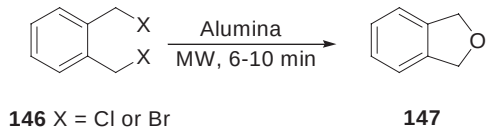
higher temperature, its formation from **136**, **137**, **139**, **140** or **141** and its relative lack of reactivity at 290 °C indicated that it was the most thermodynamically stable product (Scheme 35). These results indicated that water behaved primarily as a medium for the Claisen rearrangement at about 200 °C, but at higher temperature it also played catalytic and participatory roles (96JOC7355, 97JOC2505).

Claisen rearrangement of aryl propargyl ethers under MWI has been reported as a valuable method for selectively preparing naphthofuran in excellent yields (96JCR(S)338). Thus, 1-naphthyl propargyl ether (**143**) was treated with 1.5 equivalents of NaOMe in DMF and subjected to MWI for 2.5 min to give naphthofuran (**144**) (89%) along with naphthyl allenyl ether (**145**) (Scheme 35). The minor product **145** resulted from the isomerization of **143** in the presence of base (97SC4073).

Phthalan **147** is known to be useful as a raw material for preparing resins and a precursor of functionalized compounds such as phthalide. Initially, the intramolecular cyclization of α,α'-dichloro-*o*-xylene **146** with an excess of alumina in hexane at reflux for 1 h gave phthalan **147** in 64% yield. On the other hand, compound **147** was effectively obtained in 59–69% yields from the corresponding dichloro or dibromo compounds **146** supported on alumina under MWI for 6–10 min (Scheme 36). The method eliminates the toxicity and flammability of solvents. The use of alumina in combination with MW accelerated the rate of the reaction. The phthalan was formed by nucleophilic attack of a hydroxy group derived from the surface layer of alumina (02SL1526).

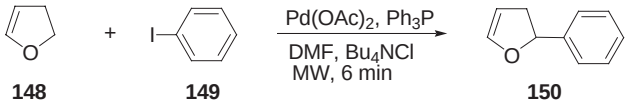
MW assisted palladium catalyzed arylation of 2,3-dihydrofuran (**148**) with iodobenzene (**149**) to afford 2-phenyl-2,3-dihydrofuran (**150**) in fair yield (58%). The reaction was carried out under nitrogen in a sealed Pyrex vessel and in the presence of DMF as a MW-active solvent. The thermal heating procedures produced less than 20% of the expected product (Scheme 37) (96JOC9582).

The coupling reaction of aryliodide or triflate **152** with tris[2-(perfluorohexyl)ethyl](2′-furyl)tin (**151**) bearing 39 fluorine atoms in the presence of lithium chloride and a catalytic amount of $PdCl_2(PPh_3)_2$ in DMF was conducted under MWI to give **153** in 63 and 87% yield within 1.5 or 2 min, respectively (Scheme 37) (97JOC5583, 02ACR717). This required a long reaction time, typically 1 day, by classical heating at 80 °C.

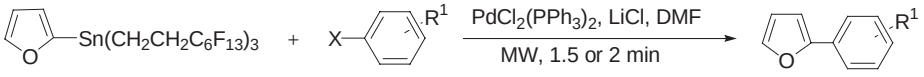


146 X = Cl or Br **147**

Scheme 36



148 **149** **150**



151 **152** X = I, TfO **153**

Scheme 37

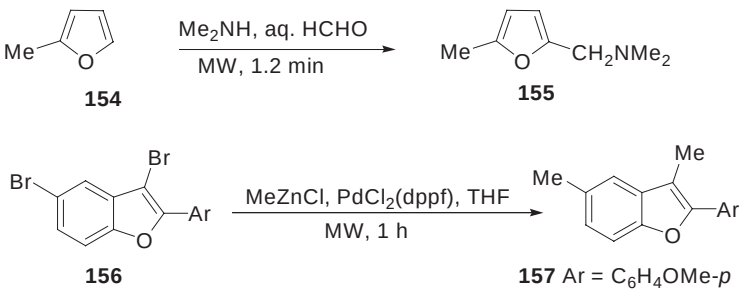
Mannich reaction of 2-methylfuran (**154**) with dimethylamine and aqueous formaldehyde was carried out at 164–165 °C in the CMR to give 5-methylfurfuryldimethylmethylamine (**155**) in 48% yield (Scheme 38) (94JOC3408).

The cross-coupling of 3,5-dibromo-2-(4-methoxyphenyl)benzofuran **156** with methyl zinc chloride in the presence of $PdCl_2$(dppf) as a catalyst required heating for 18 h in THF to give 2-(4-methoxyphenyl)-3,5-dimethyl-benzofuran **157** in 62% yield. However, the same reaction in a MW oven for 1 h gave **157** in 64% yield (Scheme 38) (03S925).

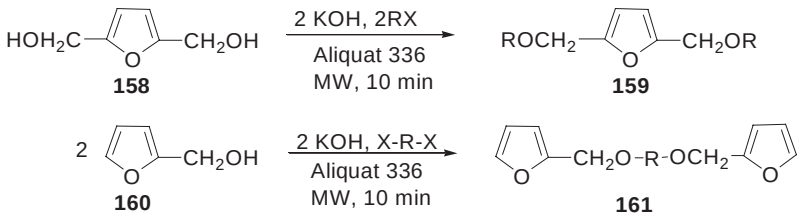
O-Alkylation of 2,5-furandimethanol (**158**) with a slight excess of alkyl halide and potassium hydroxide in the presence of methyl trioctyl ammonium chloride (Aliquat 336) and in the absence of solvent under MWI within 10 min or less gave a high yield of products **159** (74–94%). Under similar conditions, alkylation of furfuryl alcohol (**160**) by alkyl dihalides was achieved within 10 min on irradiation at 60 W to give furanic diethers **161** in 78–96% yields (Scheme 39) (96T617).

The reductive coupling of carbonyl compounds to give pinacols is an important method for the formation of *vicinal* functionalized C–C bonds. By heating TMS-Cl and 2-furaldehyde (**162**) on montmorillonite K_{10} clay in conventional MW oven, the respective coupling product bis(trimethylsilyl)pinacol **163** was synthesized in a very short time with a quantitative conversion of the carbonyl compound by a radical–radical route (Scheme 40) (98SC2017).

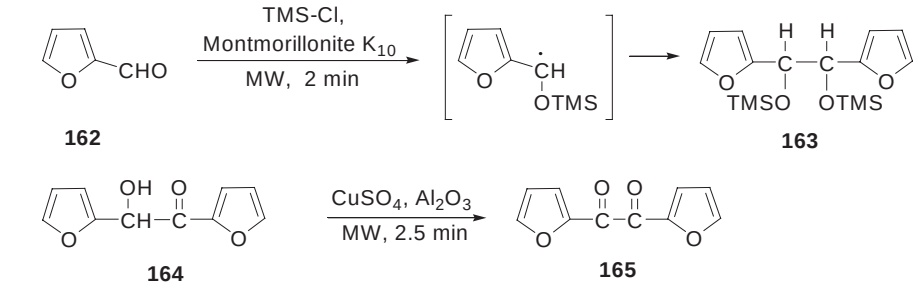
Furoin (**164**) was oxidized with the solid reagent, $CuSO_4/Al_2O_3$, to afford *vicinal* diketone **165** in high yield (82%) within 2.5 min of MWI (Scheme 40) (98JCR(S)324).



Scheme 38

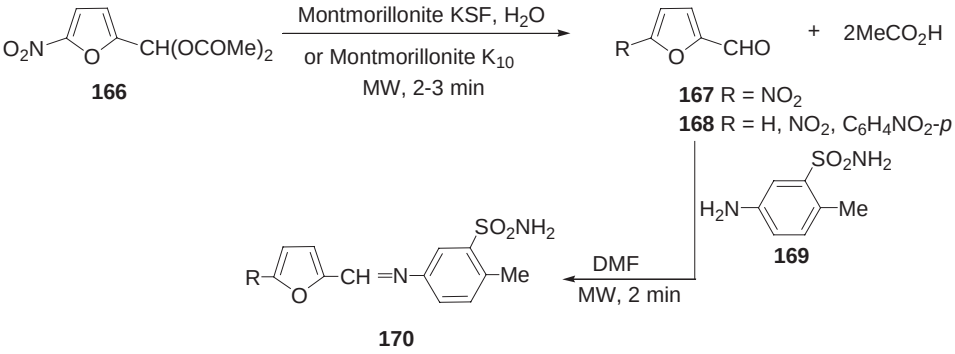


Scheme 39



162 **163** **164** **165**

Scheme 40



166 **167** R = NO_2 **168** R = H, NO_2, $C_6H_4NO_2$-*p* **169** **170**

Scheme 41

Derivatives of 5-nitro-2-furaldehyde (**167**) are very active antifungal and antibacterial compounds. Compound **167** is an expensive product, prepared by hydrolysis of nitrofuraldehyde diacetate (**166**) with sulfuric acid, but the sensitivity of **167** has made it inconvenient. A rapid and reproducible hydrolysis of **166** can be achieved on hydrated KSF clay under MWI in 78% yield (94JCR(S)146). The best method was developed when **166** was dispersed into montmorillonite K_{10} in 1:4 ratio and the mixture was exposed to MWI for 2 min at 355 W in a domestic oven to give 5-nitro-2-furaldehyde (**167**) in almost quantitative yield (99%) and high purity without a need for further purification (Scheme 41) (95TL1779).

Schiff bases **170** were obtained by mixing an equimolar amounts of sulfonamide **169** and furfurals **168** in refluxing ethanol. When the reaction was assisted by MWI using DMF as an energy transfer medium, the imines **170** were obtained in excellent yields (72–96%) (Scheme 41). The preparation of **170** was also performed using montmorillonite K_{10} under MWI, but low yields were obtained compared to those carried out with DMF (97OPP671).

Various catalysts have been known to effect the Knoevenagel condensation of ethyl cyanoacetate and various aldehydes using conventional heating. MWI was used to enhance the reaction rate of a Knoevenagel condensation between ethyl cyanoacetate and 2-furaldehyde (**162**) in the presence of ammonium acetate under a

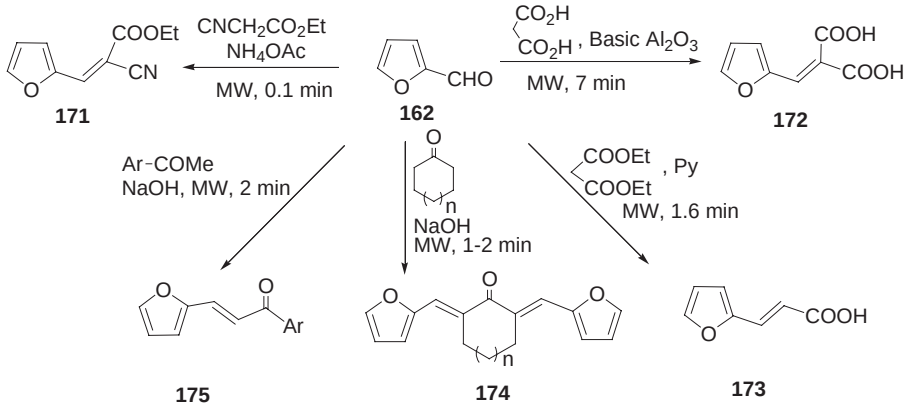
solvent-free condition to give an excellent yield of product **171** (95%) (Scheme 42) (99SC2731). Solid sodium hydroxide was also used to catalyze the condensation of **162** with ethyl cyanoacetate and cyanoacetamide (97SC3677). Montmorillonite K_{10} and $ZnCl_2$ were also useful catalysts for the condensation of 5-nitro-2-furaldehyde with active methylene compounds under MWI (94JCR(S)146).

Successful Knoevenagel condensation between malonic acid and 2-furaldehyde (**162**) under MWI condition over Al_2O_3 support gave 3-(2-furyl)-2-carboxy-2-propenoic acid (**172**). To carry out this condensation, a large vial with a loose cover or an Erlenmeyer flask with a funnel as a loose top was used as the reaction vessel. Basic Al_2O_3 was used in the absence of solvent since bases such as piperidine could lead to decarboxylated products. The reaction was usually completed within 7 min and gave improved yields over conventional methods in a much shorter time (97SC4091).

Bentonite catalyzed the condensation of **162** with malonic acid under MWI in a domestic MW oven for 5 min to give the corresponding diacid **172** in 75% yield. The monoacid **173** was detected as a minor product in the ^{1}H-NMR spectrum. This method offers some advantages in terms of simplicity of performance, non-aqueous work-up, no side products and low cost. In addition, the bentonite can be recycled (01JCS(P1)1220). The reaction of **162** with diethyl malonate in the presence of pyridine in the CMR at 165 °C for 1.6 min gave 3-(2-furyl)acrylic acid (**173**) in 18–44% yields (Scheme 42) (94JOC3408). On the other hand, the monoacid **173** was obtained from **162** and malonic acid under MWI within 4 min in the presence of silica gel (Scheme 42) (00OPP81).

The known Claisen condensation (57JA1482) of **162** with cycloalkanones, catalyzed by solid NaOH, has been carried out under MWI for 1–2 min to give α,α'-bis(substituted furfurylidene)cycloalkanones **174** (80–100%). The reaction of **162** with *p*-substituted acetophenones resulted in excellent yields (85–95%) of chalcones **175** within 2 min (Scheme 42) (97SC3677).

Furan derivatives **176** underwent Diels–Alder reactions with dienophiles **177** in the presence of silica-supported Lewis acids as catalysts under MWI to give 7-oxabicyclo[2.2.1]hept-2-enes **178** as intermediates whose ring opening was promoted by

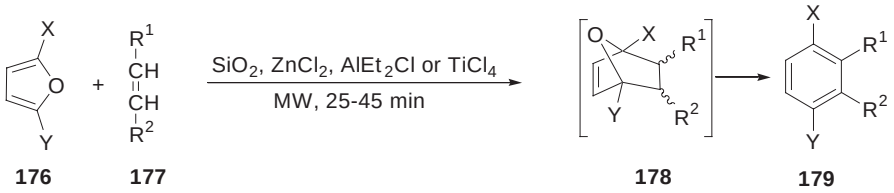


Scheme 42

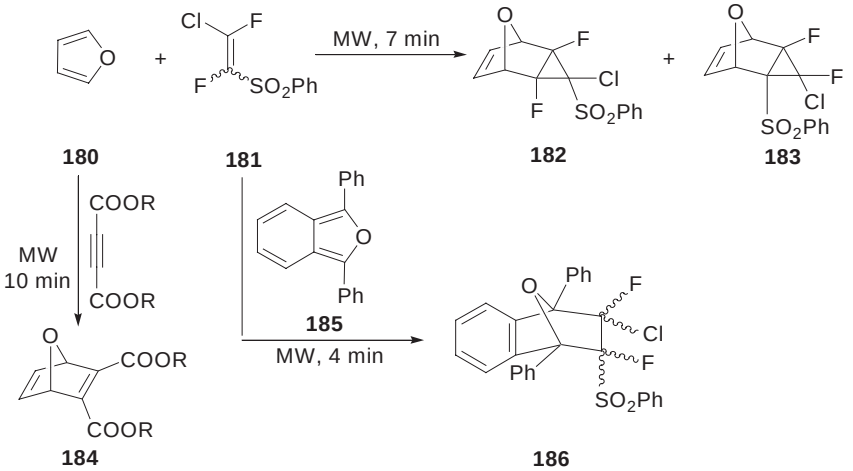
the coordination of the silica-support catalyst with the oxygen bridge leading to the corresponding arenes **179** in a single step. The reactions were performed in sealed Teflon tubes in a domestic MW oven within 25–45 min (Scheme 43). The use of classical heating in an oil bath led to a dramatic decrease in the yield of the aromatic product (01SL753).

Attempted [4 + 2] cycloaddition of 1,2-difluoro-1-chlorovinylphenylsulfone (**181**) with furan (**180**) under conventional heating failed even when reactants were refluxed in chlorobenzene for 3 days. However, the reaction proceeded within 7 min under MWI to form the two isomeric cycloadducts **182** and **183** in 40% yield (98TL6529). On the other hand, dienophile **181** with 1,3-diphenylisobenzofuran (**185**) under both conventional heating and MWI gave almost the same yield of cycloadduct **186**, but within 36 h and 4 min, respectively (Scheme 44) (98TL6529).

The reaction of furan (**180**) with diethyl acetylenedicarboxylate in a commercial MW oven gave a 66% yield of **184** (R = Et) within 10 min; the yield was 68% under conventional conditions (4 h, 100 °C) (Scheme 44) (86TL4945). The comparison of the rate of Diels–Alder reaction of **180** with dimethyl acetylenedicarboxylate to give **184** (R = Me) under conventional or MW heating at the same temperature in dif-



Scheme 43



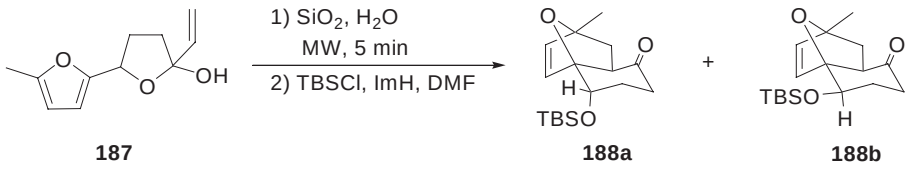
Scheme 44

ferent solvents has provided the first evidence for a specific activating effect of MW under homogeneous conditions (91TL2363).

Initial attempts to perform a Diels–Alder reaction with the hemiacetal **187** led to either decomposition of the starting material or a poor yield of the cycloadduct. However, good yields of the adducts **188** were achieved by adsorbing **187** onto silica gel, saturating the mixture with water and then irradiating it in MW for a total of 5 min, followed by protection of the resulting hydroxyl group. The Diels–Alder adduct **188** was obtained in 64% overall yield as a 1:1 mixture of diastereomers; the adduct **188a** provided a rigid framework upon which stereoselective transformations could be performed (Scheme 45) (92TL7631).

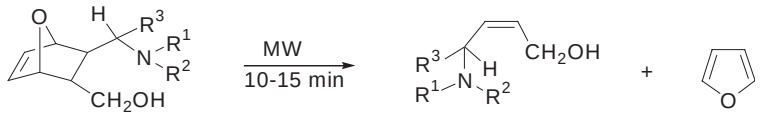
Several reactions were performed under MWI for a variety of neat liquid adducts **189** using a single-mode reactor, where MW activation coupled with solvent-free conditions were shown to be by far the most efficient method for performing retro Diels–Alder reactions. Thus, irradiation of monobenzylated amino compounds **189** under MW gave **190** in near quantitative yield in very short times, in addition to furan **180** (Scheme 46) (98JCR(S)34).

Unusual cleavage of tetrahydrofuran (**191**) by thiophenols on the surface of silica gel impregnated with indium(III)chloride under MWI gave the corresponding dithioethers **192** in 69–82% yields. The presence of a catalytic amount of indium(III)chloride on the silica gel surface was essential for the reaction to proceed. Moreover, no reaction occurred under conventional heating (Scheme 47) (02SL987).



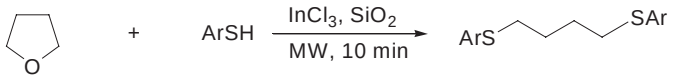
187 **188a** **188b**

Scheme 45



189 $R^1 = CH_2Ar$ **190** **180**

Scheme 46



191 **192**

Scheme 47

3. *Thiophenes*

There are only a few examples incorporating the construction of a thiophene ring under MWI. There are more examples based on chemical modifications of the functional groups linked to a thiophene ring.

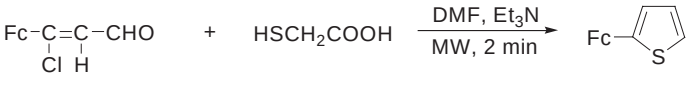
When 3-chloro-3-ferrocenylacrylaldehyde (**122**) was heated under MWI with thioglycolic (**193**) acid in DMF and Et_3N as a catalyst, it gave, after 2 min, the 2-ferrocenylthiophene (**194**) in 79–87% instead of a 20% yield under a conventional method. Similarly, the synthesis of 1,1′-bis(2-thienyl)ferrocene was obtained in high yields (Scheme 48) (94CCC175).

Most known methods for the synthesis of 2-aminothiophene derivatives involve the condensation of aldehydes or ketones, cyanoacetate and elemental sulfur which require long times that vary between 8 and 48 h. The resulting products need laborious purification by chromatography (61AG114, 71IJC1209, 99JHC333, 99TL1597, 01M279, 01TL7181). A number of 2-acyl aminothiophenes have been prepared via a one-pot MW-assisted reaction on solid support. Thus, the commercially available cyanoacetic Wang resin **195**, elemental sulfur, 1,8-diazabicyclo[4.5.0]undeca-7-ene (DBU) and the aldehyde or ketone were suspended together in toluene and heated for 20 min in a MW reactor. Then acyl chloride and diisopropylethylamine (DIEA) were added followed by further heating under MWI for 10 min. Cleavage of the resultant resin by TFA in H_2O/CH_2Cl_2 led to 2-acylaminothiophenes **196** in 81–99% yields (Scheme 49) (03SL63).

MWI as an energy source assisted cyclization of several 2-thienoylbenzoic acids **197** in dry media by using montmorillonite K_{10}, KSF, bentonite or Tonsil as support to give thieno[2,3-*b*]-1,4-naphthoquinones **198** (Scheme 50). The best yields (21–92%) were obtained using a 1:5 ratio of substrate/montmorillonite K_{10} (95TL2165). Low yields were obtained with a thermoregulated sand bath at 320 °C, even after 1 h.

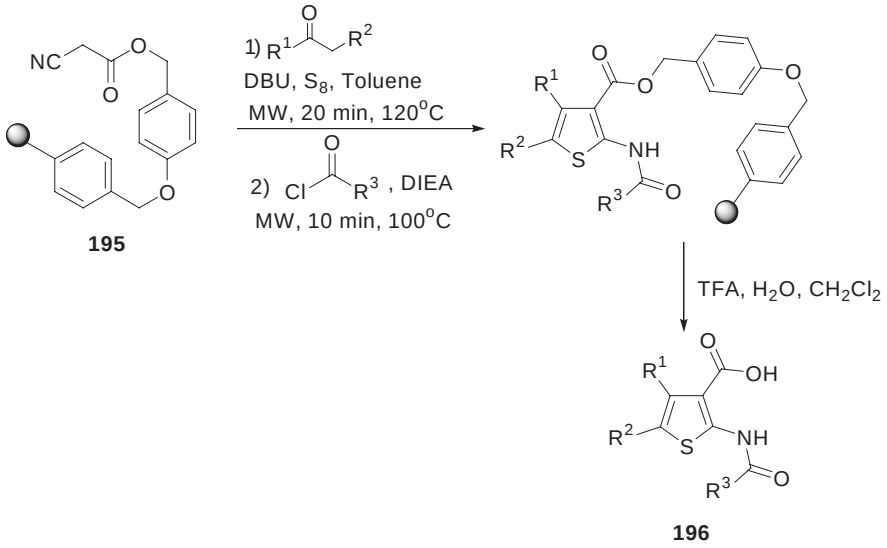
The Suzuki reaction may be the most versatile among cross-coupling reactions. The Suzuki phenylation of **199** containing PEG support with 4-formyl phenyl boronic acid in the presence of $Pd(OAc)_2$ catalyst was performed in aqueous K_2CO_3 under MWI to afford **200** within 2 min, instead of 2 h of classical heating (Scheme 51). The high yield (> 95%) suggested that MW-assisted reactions using PEG as a soluble support led to a potentially powerful transformation (99JOC3885, 02ACR717).

4-Bromo and 4-iodobenzoic acid were coupled to a deprotected resin using 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and DIEA to afford **201**. Suzuki coupling of **201** with thienylboronic acid under MWI gave **202**, in 84–86% yield, after removing the polymer support with trifluroacetic acid (Scheme 52) (02ACR717, 96TL8219).

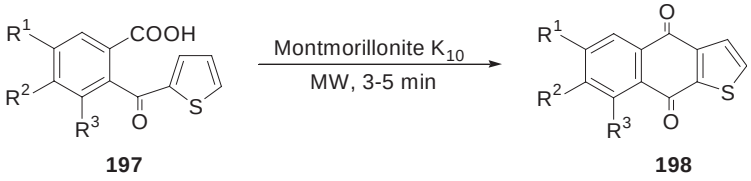


122 **193** **194**

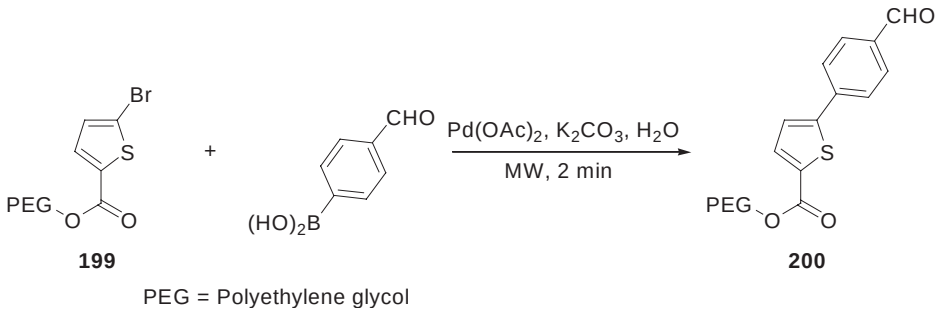
Scheme 48



Scheme 49

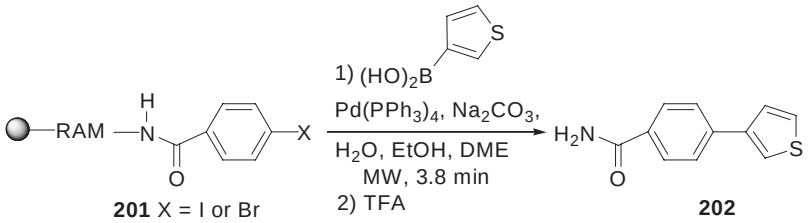


Scheme 50

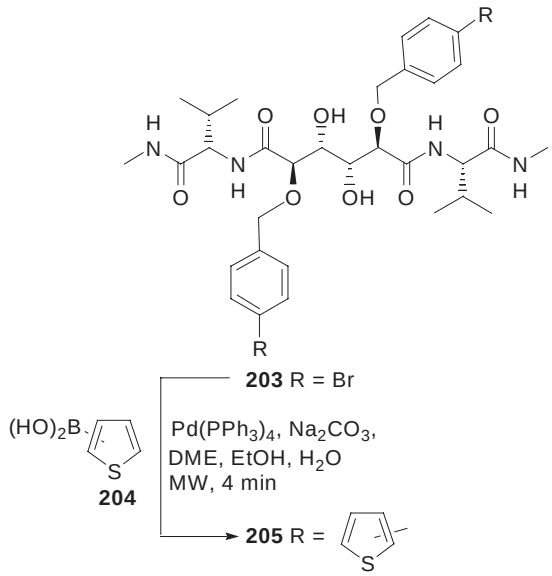


Scheme 51

2- and 3-Thienylboronic acids **204** reacted with peptide **203** in the presence of a catalytic amount of palladium tetrakis(triphenylphosphine) and sodium carbonate base in a mixture of dimethoxyethylene (DME), ethanol and water in a sealed vessel under MWI at 45 W for 4 min to give **205** in 86–96% yields (Scheme 53). The



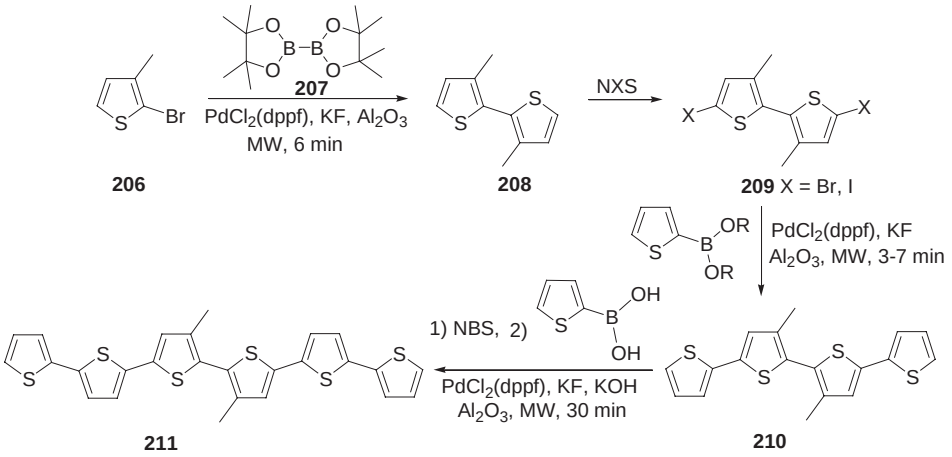
Scheme 52



Scheme 53

3-thienyl compound was selected for cocrystallization with HIV-1 protease and a crystallographic structure was determined (99JMC3835).

Thiophene oligomers are chemically very stable and easy to functionalize (02JOC3961, 02CM1742, 01AGE4680, 01EJO3437, 00CRV2537). Few of these compounds are commercially available. The synthesis of the most appealing is not easy, and the procedures for purification to the high degree useful for applications in electronics or biomedical diagnostics are tedious and time-consuming. However, the solvent-free MW-assisted Suzuki synthesis is a rapid and expedient way to prepare highly pure thiophene oligomers. Thus, the Suzuki coupling of 2-bromo-3-methylthiophene (**206**) with bis(pinacolato)diboron (**207**) in the presence of $PdCl_2$(dppf) catalyst, potassium fluoride base and alumina solid support was achieved under MWI for 6 min to give **208** in 70% yield, then converted into the dibromo or diiodo derivatives **209**. Coupling of the diodo derivative **209** with thiophene boronic derivatives under similar MWI conditions gave **210** in much higher yields (85–90%) than that (18–34%) using the corresponding dibromo derivative. Bromination of **210**



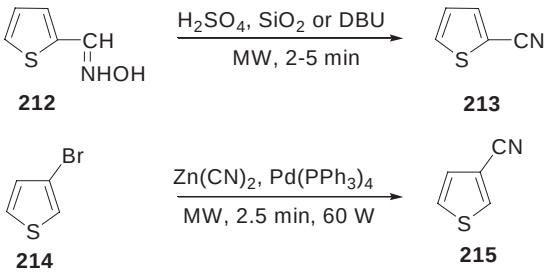
Scheme 54

with NBS, followed by coupling of the dibromo derivative with thiopheneboronic acid by MWI for 30 min gave sexithiophene **211** in 73% yield (02JOC8877). On the other hand, a lower yield (65%) of **211** was obtained from the coupling of the dibromo derivative of **210** with thiopheneboronic acid under MWI for 5 min by using $Pd(OAc)_2$ as the catalyst and K_2CO_3 as the base in H_2O/toluene (Scheme 54) (02T2245).

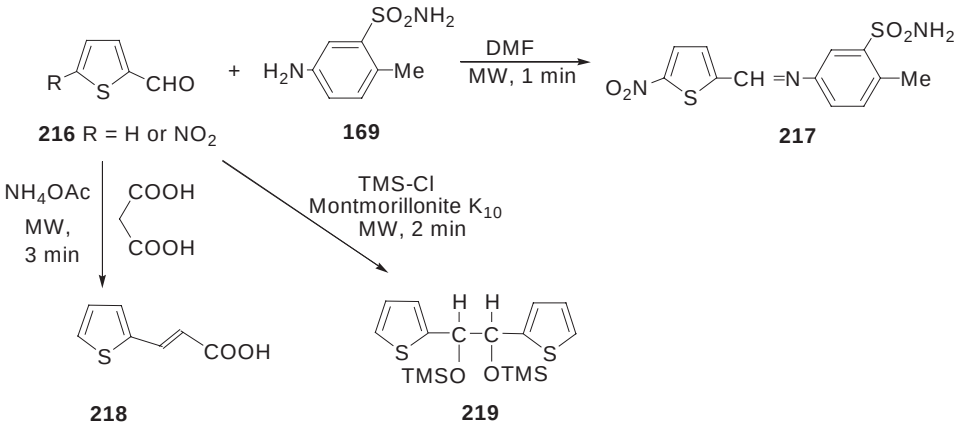
Dehydration of aldoximes to nitriles is an important functional group transformation. However, the methods involving conventional heating using inorganic catalysts generally proceed at a slow rate demanding long reaction times. Dramatic acceleration in the rate of dehydration due to MW heating was established. Conventional heating of aldoximes with the inorganic catalyst formed nitriles only to a minor extent and longer reaction times are required to achieve higher yields. A very quick and simple dehydration of thiophene 2-aldoxime (**212**) on the surface of a H_2SO_4/SiO_2 solid support catalyst was promoted under MWI for 5 min to afford 2-cyanothiophene (**213**) in 64% yield (97SC1327). Aldoxime **212** can be rapidly converted into nitrile **213** in 88% yield with DBU under MWI within 2 min (Scheme 55). However the dehydration of aromatic and heterocyclic aldoximes with DBU by conventional heating in CCl_4, or MeOH, etc. failed to give the nitriles and the starting aldoximes were recovered. This clearly indicates the advantage of carrying out the above reaction under MWI rather than by conventional heating (98SC4577).

Many hours were typically required for the palladium-catalyzed cyanation of aryl and heterocyclic bromides with thermal heating. However, 3-cyanothiophene **215** was prepared in 80% yield from the reaction of 3-bromothiophene (**214**) with $Zn(CN)_2$ using Pd catalyst under MWI in a single-mode cavity for 2.5 min (Scheme 55) (02ACR717).

Condensation of 5-nitrothiophene-2-aldehyde (**216**) with sulfanilamide **169** in the presence of DMF has been carried out under MWI for 1 min to give the Schiff base **217** in 92%, while in the absence of DMF the yield was 30%. When montmorillonite



Scheme 55



Scheme 56

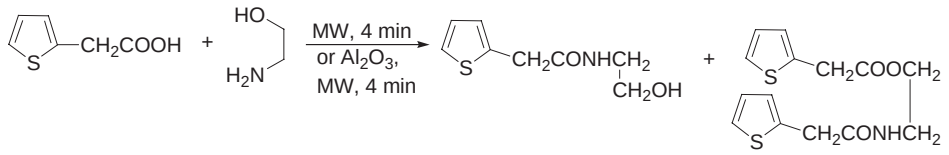
K_{10} was used as an acidic catalyst, a lower yield of **217** was obtained (Scheme 56) (97OPP671).

The α,β-unsaturated acid **218** was formed in almost quantitative yield when a mixture of aldehyde **216** and malonic acid together with ammonium acetate was subjected to MWI for 3 min. The reaction was performed in an open Erlenmeyer flask in the absence of solvent (Scheme 56) (98SC3811).

Reductive coupling of thiophene 2-aldehyde (**216**) with TMS-Cl on montmorillonite K_{10} clay under MWI, in a similar manner to that of furaldehyde, gave the silylated pinacol coupling product **219** in 80% yield (Scheme 56) (98SC2017).

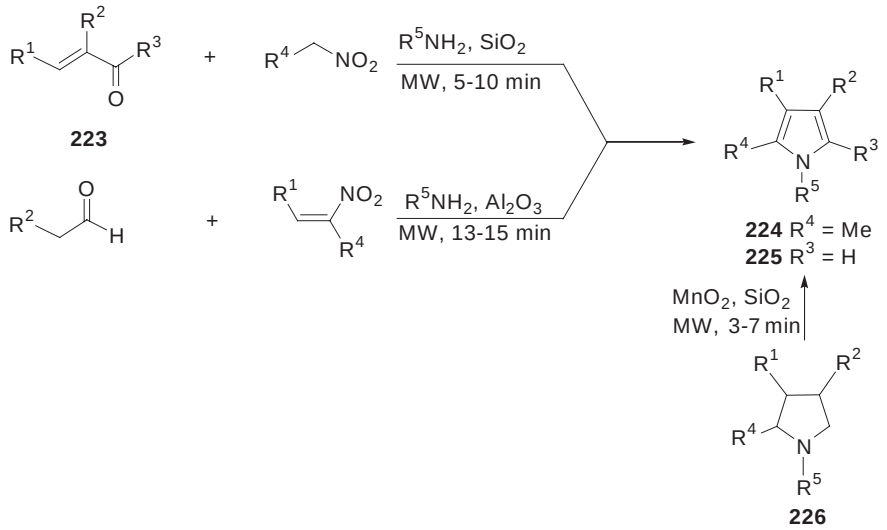
2-Thienylacetic acid (**220**) with ethanolamine in an open vessel in a domestic MW oven gave a mixture of amides **221** and **222** in 40 and 20% yields, respectively. An identical result was obtained using an alumina-supported reagent (Scheme 57) (95SC659).

Sulfoxides are invariably prepared by oxidation of the corresponding sulfides with any of several oxidizing reagents. Most processes suffer from drawbacks, such as the use of corrosive acids, hazardous peracids and toxic metallic compounds that generate waste streams. Tetrahydrothiophene was rapidly oxidized to the corresponding



220 **221** **222**

Scheme 57



223 **226**

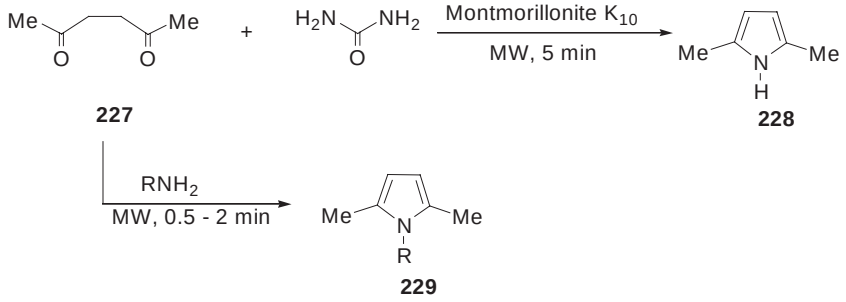
Scheme 58

sulfoxide in high yield (81%) upon MW thermolysis with iron(III)nitrate impregnated on clayfen under solvent-free conditions; longer reaction time was required to achieve the conversion in refluxing methylene chloride (98SC4087).

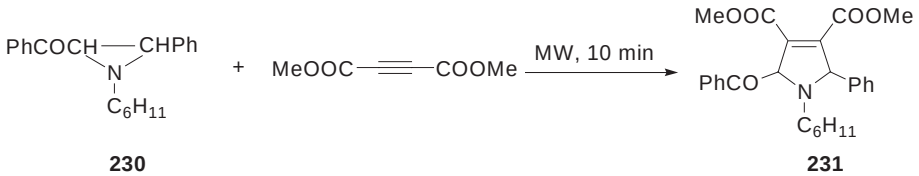
4. *Azolidines and Azoles*

A three component coupling of an α,β-unsaturated carbonyl compound **223**, amine and nitroalkane on the surface of silica gel in one pot under MWI produced the respective substituted pyrroles **224**. The notable advantages of this procedure were the reasonably good yields (60–72%), fast reaction times (5–10 min) and mild reaction conditions (Scheme 58) (00SL75).

Alternatively, the coupling of α,β-unsaturated nitroalkene, aldehyde and amine on the surface of alumina without solvent under MWI for 13–15 min gave **225** in 71–81% yields (01T4767); classical heating required 3–18 h to afford **225** in lower yields (12–65%) (98JOC6234, 99T13957).



Scheme 59



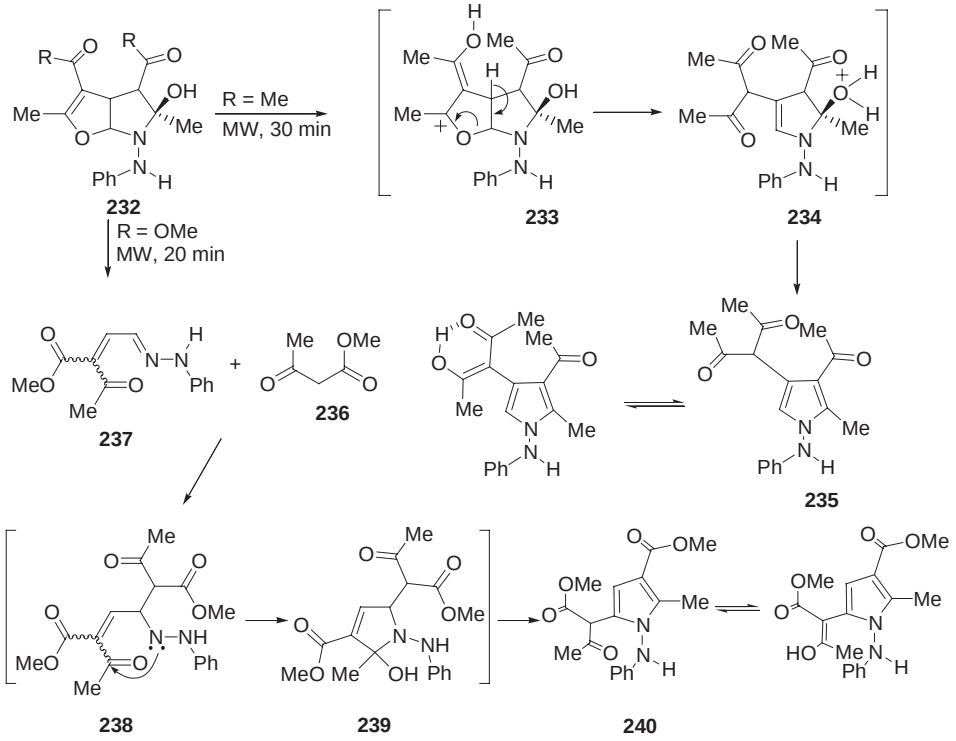
Scheme 60

Substituted pyrroles **225** were prepared in 58–96% yields by the dehydrogenation of pyrrolidines **226** with manganese dioxide in the presence of silica gel by MWI in a domestic MW oven for 3–7 min (Scheme 58) (94CJC2483).

N-unsubstituted pyrrole **228** was formed in 60% yield from urea and acetonylacetone (**227**) adsorbed over montmorillonite K_{10} in a domestic MW oven (94SL935). The respective N-substituted pyrroles **229** were obtained in 75–90% yields by the reaction of primary amines with **227** in less than 2 min under MW activation (Scheme 59). The MW procedure was easily adapted for the synthesis of relatively hindered pyrroles (99TL3957) in a shorter time than the 12 h of heating needed to obtain similar yields (68JHC757, 86T623).

1,3-Dipolar cycloaddition of 2-benzoyl-1-cyclohexyl-3-phenylaziridine (**230**) with dimethyl acetylenedicarboxylate under MWI within 10 min led to the formation of the pyrroline derivative **231** in 70% yield. The reaction involved cleavage of the 2,3-bond of the 2-benzoylaziridine to an azomethine ylide intermediate and subsequent [2,3] cycloaddition to the acetylenic bond (Scheme 60) (96TL4203).

The *N*-anilinopyrrole moiety is present in several natural products that display a wide variety of biological applications (56JAN102, 57JA1265, 64NAT1064). Heterobicycle **232** (R = Me) bearing two acyl groups was transformed to **235** (61%) within 30 min under focused MWI (Scheme 61); 3 months were required at room temperature. The proposed mechanism may involve the generation of cation **233**, which then opens and rearranges to intermediate **234** that upon dehydration gave the *N*-anilinopyrrole **235** (Scheme 61). When heterobicycle **232** (R = OMe) was submitted to similar conditions using focused MWI at 300 W (150 °C) during 20 min,

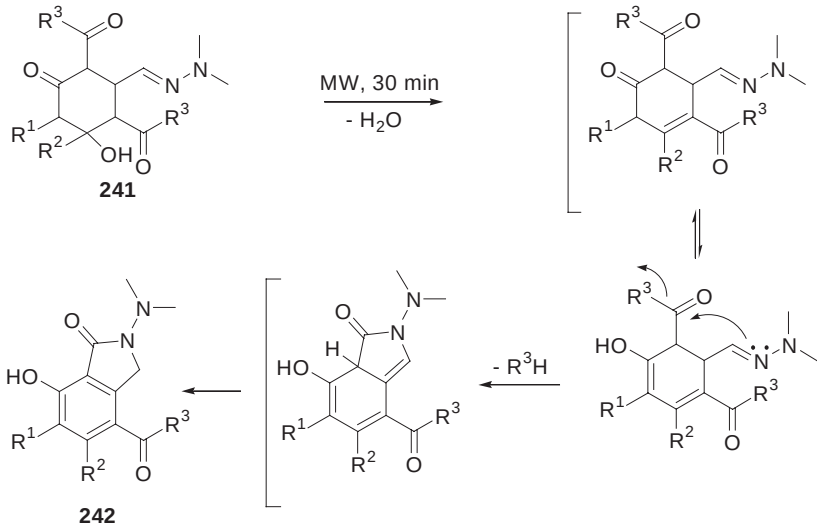


Scheme 61

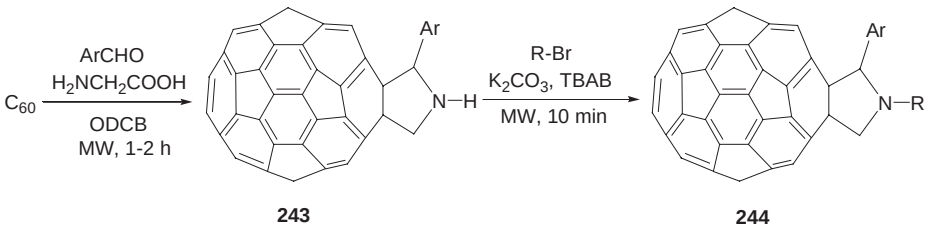
the *N*-anilinopyrrole **240** was obtained in 73% yield. However, several months were necessary for complete conversion at room temperature. The mechanism may involve ring opening of **232** to **236** and alkene **237**, which is then followed by nucleophilic attack of the carbanion of **236** on the hydrazone carbon atom of **237** to give *β*-enone **238**, followed by hydrogen displacement and dehydration to give **240**. ^{1}H-NMR spectroscopy indicated the presence of two forms in a very fast equilibrium at room temperature favored by the involvement of hydrogen bonding which stabilizes the enol (98T4561).

Similarly, the *N*-anilinobenzopyrrolidinones (**242**) were prepared from substituted cyclohexanones **241** when placed in a Pyrex tube without solvent or catalyst and introduced into the MW reactor for 30 min at 300 W (160 °C) to give **242** in 60–87% yields. The structure of **242** has been established by X-ray analysis. The presumed structure is shown in Scheme 62 (98T4561).

1,3-Dipolar cycloadditions provide a powerful tool for functionalizing [60]fullerene that behaves as an electron-deficient olefin with a relatively low lying LUMO. Thus, several fulleropyrrolidines **243** were prepared in 15–37% yields by irradiating a solution of C_{60}, aromatic aldehyde and glycine in dry *o*-dichlorobenzene (ODCB) in a focused MW reactor. The redox potentials of the prepared compounds were determined by cyclic voltammetry (97T2599). Alkylation of **243** has not been described, probably because of the low reactivity of these compounds. However, a



Scheme 62

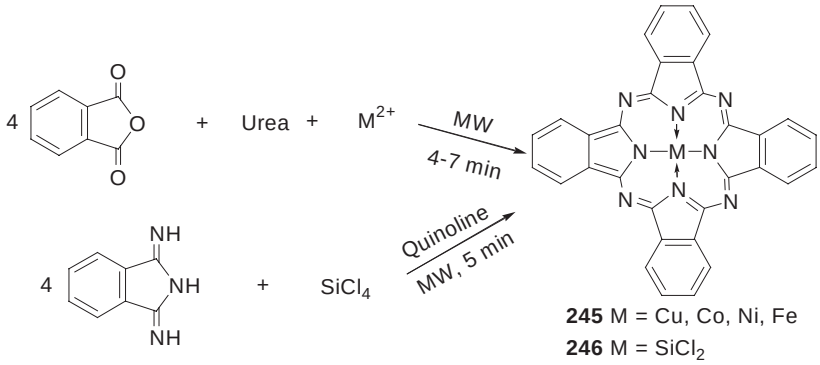


Scheme 63

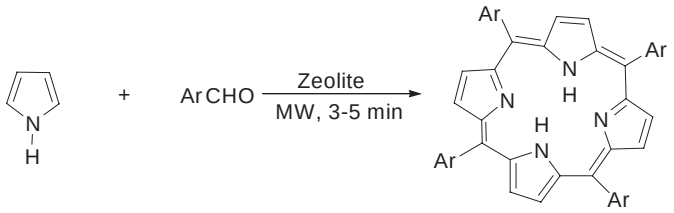
series of *N*-alkylpyrrolidino[60]fullerenes **244** can be prepared in 27–70% yields by alkylating **243** (Ar = Ph) with alkyl or benzyl bromide in the presence of K_2CO_3/TBAB without solvent under MWI in a commercial MW oven using a closed Teflon vessel (Scheme 63) (98TL6053).

The phthalocyanine complexes of Cu, Co, Ni and Fe **245** were easily prepared in high yields (86–91%) upon exposure of the phthalic anhydride, urea and metal ion to MWI within 4–7 min (Scheme 64) (98JCR(S)672). The yield of the copper phthalocyanine reached its maximum under irradiation at high power for 10.5 min at molar ratios of phthalic anhydride/urea/Cu_2Cl_2 of 1: 5: 0.20–0.23 using 3% ammonium molybdate as a catalyst. When Mo oxide was selected as a catalyst, the yield increased with the increasing quality of the catalyst. The yield was higher than that of a conventional heating method with a much shorter reaction time (02MI4).

(Phthalocyaninato)bis(chloro)silicon **246** was prepared in high yield (91%) by MW heating of diiminoisoindolene and silicon tetrachloride in quinoline. The reaction was carried out in a modified MW ashing furnace and required 5 min compared to 30 min with thermal heating (Scheme 64) (01MI3).



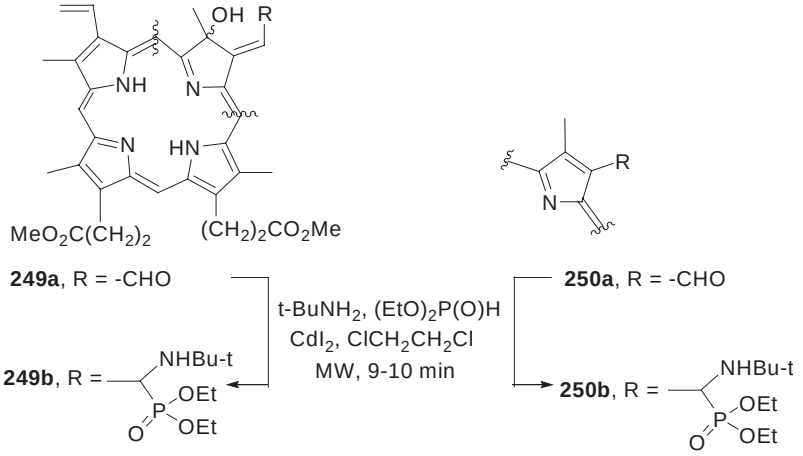
Scheme 64



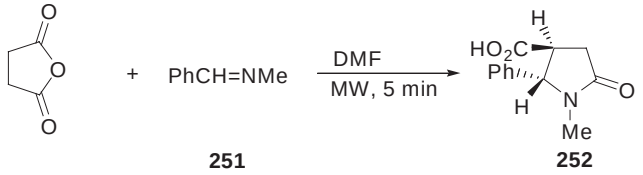
Scheme 65

The MW-assisted cyclocondensation of pyrrole (**247**) and benzaldehyde adsorbed on a solid acidic support, afforded tetraphenyl porphyrin (**248**) within 10 min. Although the products were easily purified, yields were low (0.7–9.5%) and depended on the nature of the support and MWI conditions (92SC1137). On the other hand, the reaction of benzaldehyde and pyrrole in propionic acid for 4 min gave **248** in 41% yield. Similarly, the cyclocondensation was extended to arylaldehydes to give tetraaryl porphyrins under MWI for 3–5 min and gave a remarkably high yield as compared to other high dilution methods (01SC33). When cyclocondensation was catalyzed by zeolite molecular sieve and subjected to 2450 MHz MWI in $CHCl_3$, it formed tetraphenyl porphyrin **248** in 23.5% yield (Scheme 65). The reaction was extended to the preparation of other porphyrin derivatives to provide an eco-friendly, economical, faster and selective heterogeneous method (02MIP1).

Numerous attempts to obtain α-amino phosphonates such as **249b** or **250b** by conventional heating of formylporphyrins **249a** or **250a** with *t*-$BuNH_2$ and $(EtO)_2P(O)H$ in toluene under reflux as well as under milder thermal conditions (30–60 °C/toluene or $ClCH_2CH_2Cl$) led to a complex mixture of unidentified products with no eventual formation of **249b** or **250b**. However, when the reaction was carried out in $ClCH_2CH_2Cl$ under irradiation in a domestic MW oven (102 W), products **249b** and **250b** were obtained in 62–65% yields after 25 min with 15–17% recovery of the starting materials. The reaction preceded faster (9–10 min) in the presence of Lewis acid (CdI_2) with substantially enhanced yields (84 and 85%)



Scheme 66



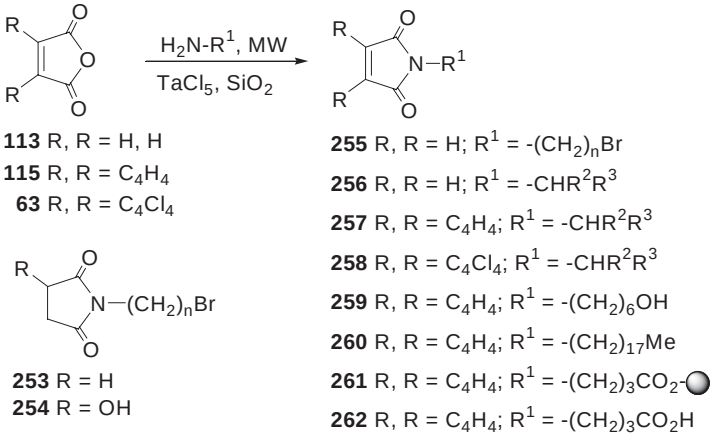
Scheme 67

(Scheme 66). However, the presence of CdI_2 under conventional heating was again unsuccessful. Thus, a synergistic effect of MW and CdI_2 was responsible for the regioselective conversion (03SL2193).

The reaction of succinic anhydride with benzylidenemethylamine (**251**) in refluxing benzene over a period of 36 h led to a mixture of *trans* (major product) and *cis* forms of the substituted 2-pyrrolidinone **252** in 82% yield (69JOC3187). By substituting DMF for benzene and conducting the same reaction in a MW oven for 5 min, the *trans* isomer **252** was obtained in 59% yield (Scheme 67) (90H741).

When succinic acid or maleic acid was heated with amines without solvent in a domestic MW oven for 15–20 min, each gave good yields of the corresponding imides **253** (76–84%) and **254** (59–72%), respectively, together with the corresponding maleimides **255** (14–19%) resulting from the dehydration of **254** (Scheme 68). Heating for a longer time (45 min) did not change the **254**:**255** ratio, indicating that dehydration might occur prior to cyclization (99JCR(S)420).

Maleic and phthalic anhydrides **113** and **115** have been condensed with amino acids and alkylamines under MWI for 2–3 min without a solvent to afford N-substituted maleimides **256** and phthalimides **257** in 89–96% yields (98JCR(S)272). Moreover, the reaction of phthalic anhydride **115** with glycine did not occur in the absence of solvent even after 10 min, but adding a high boiling point solvent (DMF



Scheme 68

or xylenes) caused the reactants to dissolve and the reaction to occur with satisfactory yields to give imide **257** ($R^2 = H$; $R^3 = COOH$) (00T5473). The MWI of a mixture of amino acids or peptides with tetrachlorophthaloyl anhydride **63** in DMF for 4–8 min gave imides **258** in 62–99% yield (01S1313). In the reaction of benzylamine with phthalic anhydride, both reactants are of low polarity and therefore are slightly MW absorbent. The solvent-free reaction showed a rapid rise in temperature to 150 °C in less than 2 min and after 5 min of activation by MWI the respective imide **257** ($R^2 = H$; $R^3 = Ph$) was obtained in 90% yield. Similarly, compounds **259** and **260** were prepared in yields over 90% (Scheme 68) (00T5473). $TaCl_5$–silica gel acted as a very efficient Lewis acid catalyst for the synthesis of *N*-alkyl and *N*-arylimides under MW assistance. When equimolar amounts of phthalic anhydride **115** and benzylamine were adsorbed on silica gel, admixed with 10 mol% of $TaCl_5$–SiO_2 and exposed to MWI for 5 min, *N*-benzyl phthalimide was isolated in 92% yield. Under similar conditions, isobutylamine and *R*(+)-α-methylbenzylamine gave the respective phthalimides in 90 and 88% yields, respectively. For instance, maleic anhydride **113** on treatment with benzylamine yielded *N*-benzyl maleimide in 82% yield. Similar results were observed with aniline and *R*(+)-α-methylbenzylamine; otherwise less reactive succinic anhydride was converted into the corresponding succinimides in 75–80% yields (97TL8089). A disk made of Teflon was designed to hold 28 vials in the highest irradiation area of a domestic MW oven. Consequently, 28 vials containing a mixture of the phthalic anhydride **115** and the corresponding aromatic amine were placed in the MW oven and irradiated for 8.5 min at 550 W to give 28 *N*-aryl phthalimides in 34–97% yields (02SL343). The general method for the synthesis of *N*-aryl phthalimides needed a long heating under reflux (59JOC388). However, a mixture of phthalic anhydride **115** and aromatic amine in an open container in a MW oven and irradiated for 2–10 min gave *N*-aryl phthalimides in 91–95% yields (02SC927).

A preparation of *N*-alkyl imides under microwave assistance on polymer support in the solid state has been developed. Thus, γ-aminobutyric acid was esterified with

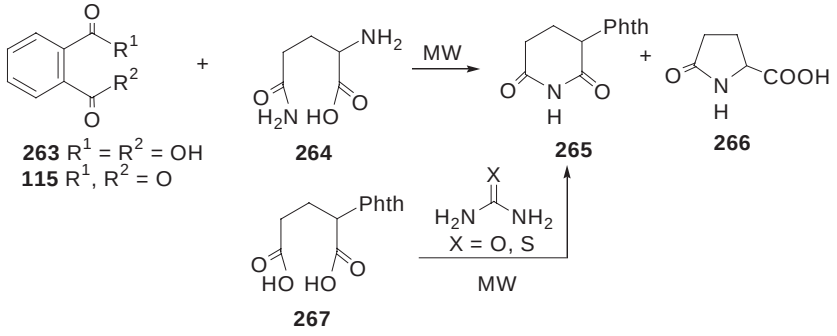
Merrifield resin, treated with phthalic anhydride and $TaCl_5/SiO_2$, and subjected to MWI for 5 min to furnish polymer bound imide **261** whose cleavage from resin by treatment with trifluoroacetic acid in CH_2Cl_2 gave **262** in 65% yield. Maleic anhydride and succinic anhydride also gave the respective imides in 65 and 60% yields (Scheme 68). Similar results were observed by the use of polymer-supported alanine with phthalic anhydride, maleic anhydride or succinic anhydride (99SL1597).

Several strategies have been employed for the synthesis of thalidomide **265**; a drug achieving great therapeutic importance in the treatment of several diseases. It was synthesized in 91% yield by cyclization of *N*-phthaloylglutamine (99MI5). However, irradiation of L-glutamine **264** in the presence of phthalic acid **263** in a domestic MW oven gave pyroglutamic acid **266** as the only product. When phthalic anhydride **115** was irradiated with L-glutamine **264** for 19 min, (±)-thalidomide **265** was obtained in low yield together with **266**. However, thalidomide **265** was obtained in 63% yield by MWI (10 min) of *N*-phthaloyl-L-glutamic acid **267** and urea and the yield of **265** was increased to 85% when thiourea was used instead of urea after 15 min of MWI (Scheme 69). Thus, when L-glutamic acid, phthalic anhydride and thiourea were irradiated for 20 min, thalidomide was formed in 60% yield without significant formation of pyroglutamic acid (01S999).

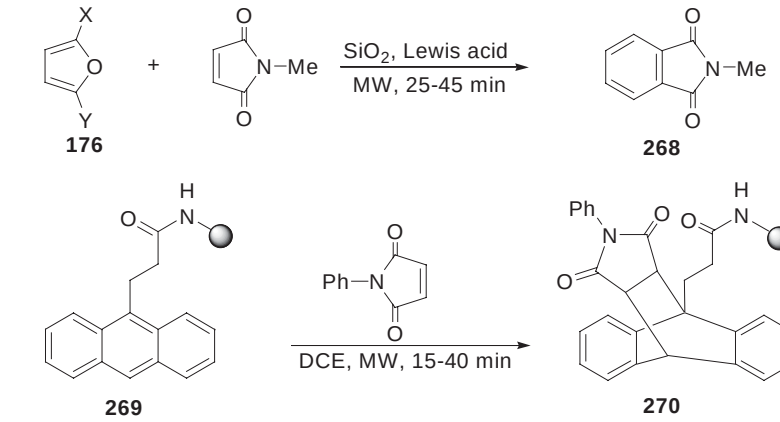
Treatment of furan derivatives **176** with N-methylmaleimide in the presence of silica-supported Lewis acids as catalysts under MWI gave N-methylphthalimide derivatives **268** (28–100%) yield (Scheme 70). Reactions were performed in the absence of solvent within 25–45 min and the best results were obtained using Si(Ti). The advantage MWI was not exclusively in the acceleration of the reaction, but in increasing the yield, since low yields were obtained on classical heating in an oil bath under comparable conditions (01SL753).

Under MWI a thermally stable polymer-supported anthracene derivatives **269** was successfully used for scavenging dienophiles such as *N*-phenylmaleimide to give the cycloadduct **270** within 15–40 min (04OL795).

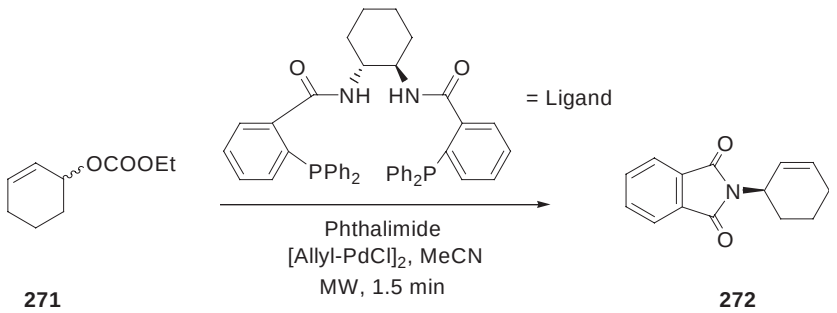
The Pd-catalyzed substitution of *racemic* ethyl 3-cyclohexenyl carbonate (**271**) with phthalimide as the nucleophile in the presence of a chelating ligand occurred at 140 °C to give **271** (87%). Much higher yields of **271** were obtained using MW rather than classical heating, but the enantiomeric excesses were the same (95–96%) from both methods (Scheme 71) (00S1004, 02ACR717).



Scheme 69



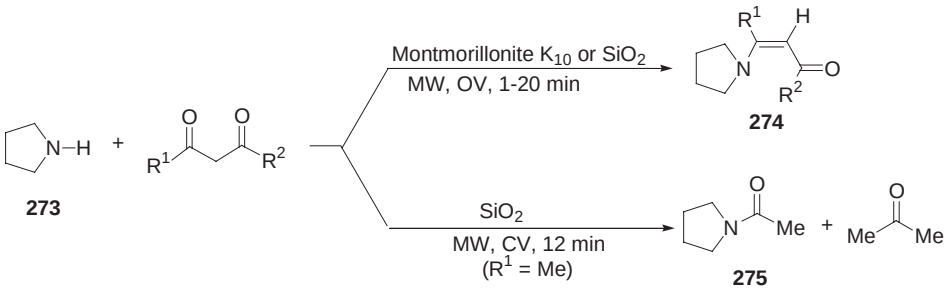
Scheme 70



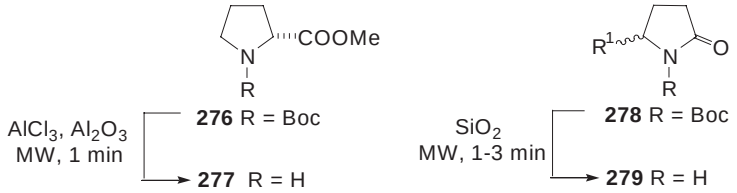
Scheme 71

The Gabriel synthesis of amines by N-alkylation of heterocyclic compounds bearing an acidic hydrogen atom attached to nitrogen can generally be accomplished by treatment with an appropriate base followed by the alkylating reagent. Although the reaction could be accelerated using protic solvents such as DMF, a remarkably fast method of synthesis of N-alkylazaheterocycles in dry media under MWI was reported (96SL873, 97H715). The reactions were carried out by mixing an azaheterocycle like pyrrole with a 50% excess of an alkyl halide and a catalytic amount of tetrabutylammonium bromide (TBAB). The reactants were adsorbed either on a mixture of K_2CO_3 and KOH or K_2CO_3 and then irradiated in an open vessel in a domestic MW oven for 34–60 s to give 58–77% yields of the N-alkylated pyrrole. Similarly, phthalimide was alkylated to give products in 50–93% yields after MWI for 4–10 min.

β-Diketones with pyrrolidine (**273**) adsorbed over montmorillonite K_{10} or silica gel under MWI in an open vessel (OV) gave within few minutes the corresponding enaminoketones **274** in 79–95% yields. Acetylacetone also reacted with **273** in the absence of a solid support to give **274** ($R^1 = R^2 = Me$) in 98% yield. However, when the same reaction was carried out in a closed Teflon vessel (CV) in the presence of silica gel, the *N*-acetyl pyrrolidine (**275**) was obtained in 90% yield (Scheme 72). The



Scheme 72



Scheme 73

acyl group in the β-position of the initially formed enaminoketone favored the cleavage of the C–C bond and stabilized the resulting carbanion leading to acetone elimination (93TL5071).

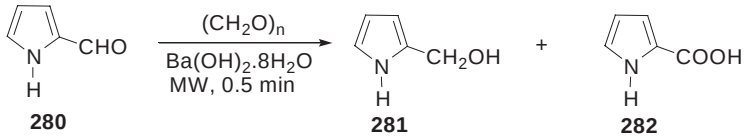
Several reagents have been documented for *t*-Boc cleavage such as $BF_3 \cdot OEt_2$ (83JA1697), CF_3COOH (63HCA870) and bromocatechol borane (85TL1411). The use of the Lewis acid $AlCl_3$ doped on neutral alumina under MWI was found to be highly favorable for this purpose. Under these conditions, *t*-Boc proline ester **276** gave the corresponding proline ester **277** in 88% yield. The reaction proceeded efficiently in 1 min and the ester linkage survived under the reaction conditions (Scheme 73) (98TL5631).

Another efficient method for the *t*-Boc deprotection of nitrogen atoms has been developed by coupling **278** with silica gel and MWI for 1–3 min to give the pyrrolidin-2-ones **279** in 91–96% yield (Scheme 73) (98SL147).

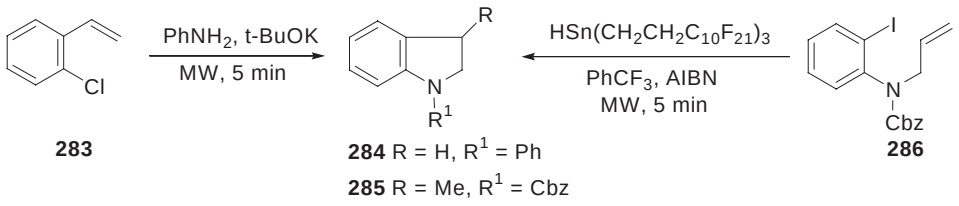
Reduction of pyrrole-2-aldehyde (**280**) to alcohol **281** (97%) was achieved by using $Ba(OH)_2 \cdot 8H_2O/(CH_2O)_n$ under MWI for 0.5 min. The acid **282** was produced as a minor by-product (3%) (Scheme 74) (98TL8437).

5. *Indoles and Carbazoles*

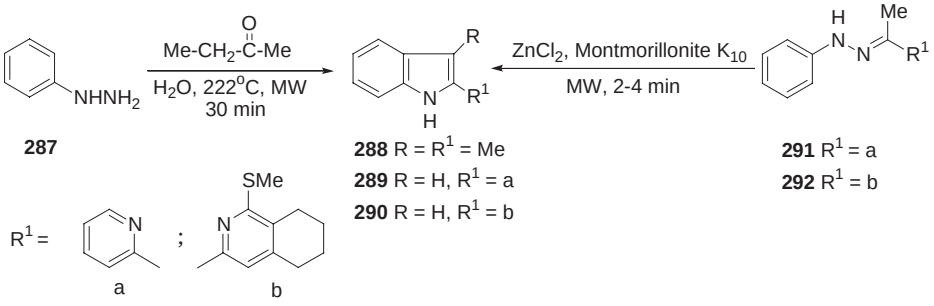
Domino hydroamination-cyclization of 2-chlorostyrene (**283**) with aniline in the presence of potassium *tert*-butoxide in 1:1:2 ratio under MWI in a domestic MW oven gave *N*-phenylindoline (**284**). The product formed in a very good yield (96%) after 5 min of irradiation (Scheme 75) (01SL875).



Scheme 74



Scheme 75

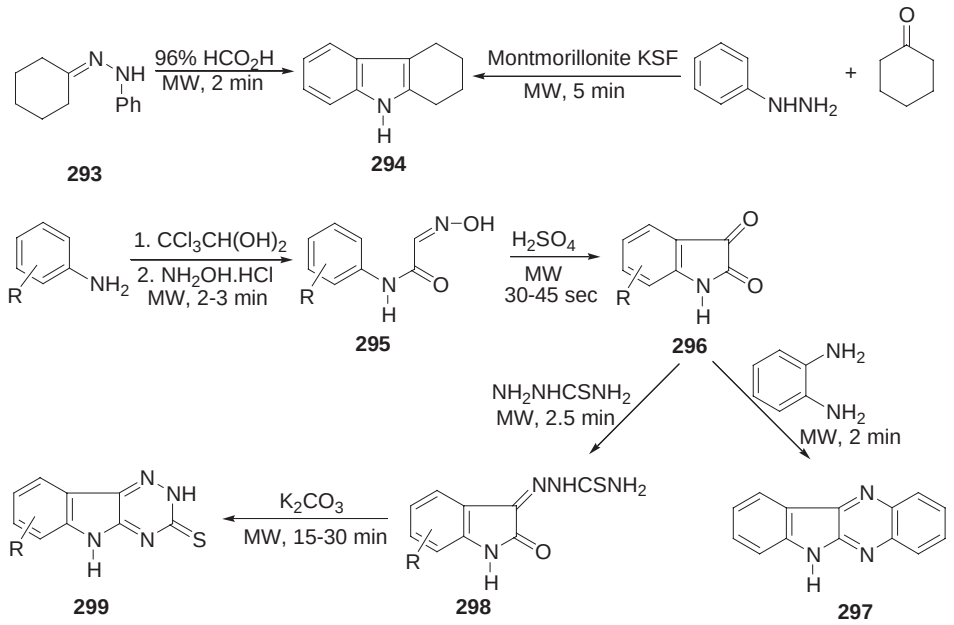


Scheme 76

Flash-heating by MWI promoted a rapid radical-mediated cyclization of **286** to **285** in high yield (93%) after 5 min, the fluorous tin hydride containing $CH_2CH_2C_{10}F_{21}$ groups had a sufficient fluorine content to permit a convenient liquid–liquid extraction into fluorinated phase (three phase water, dichloromethane, perfluoroheptane) and subsequent chromatography (Scheme 75) (99JOC4539).

A one-step Fischer indole synthesis of 2,3-dimethylindole (**288**) was achieved by heating phenylhydrazine (**287**) and 2-butanone in water at 222 °C for 30 min in a MW batch reactor (Scheme 76). The product was isolated in 67% compared to 27% yield by conventional heating (97JOC2505). On the other hand, a number of 2,3-disubstituted indoles were prepared in 50–68% yields by irradiating a mixture of phenylhydrazine hydrochloride and ketones in acetic acid in a MW oven for 28 s (97IJC(B)86).

The 2-(2-pyridyl)indole **289**, a basic structural element of many natural products, was synthesized by heating an intimate mixture of 2-acetylpyridine phenylhydrazone (**291**) and zinc chloride in 1-methylnaphthalene at 220 °C for 3 h, but in low yields (30–40%) due to substrate decomposition under these conditions. Furthermore, methylnaphthalene is toxic and difficult to remove. These difficulties were overcome when the reaction was conducted under MW activation in a dry medium. A monomode



Scheme 77

reactor, Synthewave 402, was used to take advantage of both its focused MW and temperature control. A satisfactory yield (60%) was obtained within 4 min. The best conditions were extended to the synthesis of **290** from **292** in 50% yield, after irradiation for 2 min at 110–120 °C (Scheme 76) (99SC1349).

Tetrahydrocarbazole **294** was obtained in quantitative yield when cyclohexanone phenylhydrazone **293** was heated in a MW oven with 96% formic acid in a Parr bomb for 2 min using a domestic MW oven. However, only a trace of **294** was obtained and most of **293** was recovered unchanged upon heating **293** with montmorillonite KSF in a MW oven (Scheme 77) (92SL795). However, irradiation of a mixture of phenylhydrazine and cyclohexanone supported on montmorillonite KSF in an open pyrex flask in a MW oven gave **294** in 85% yield (Scheme 77) (89CIL607).

The Sandmeyer method for the synthesis of isatins involved heating a mixture of aromatic amine, chloral and hydroxylamine hydrochloride to give the intermediate isonitrosoacetanilide **295**, which then can be cyclized to isatin **296** under acidic conditions. This procedure often results in the formation of resinous material with loss of yields. However, when the above reactants were exposed to MWI in a domestic MW oven, the isonitrosoacetanilide **295** was obtained in 50–94% yields after 2–3 min. This intermediate was smoothly cyclized to isatin **296** (61–85%) with 86% H_2SO_4 also under MW conditions (Scheme 77). 3,5-Dibromoaniline was also converted into 3,5-dibromoisonitrosoacetanilide and then to 4,6-dibromoisatin utilizing the same procedure (99SC3627). Reaction of **296** with thiosemicarbazide under MWI gave **298** (92–93%) within 2.5 min, which can be cyclized into the triazine **299** (64–87%) within 15–30 min (04SL723). Condensation of **296** with

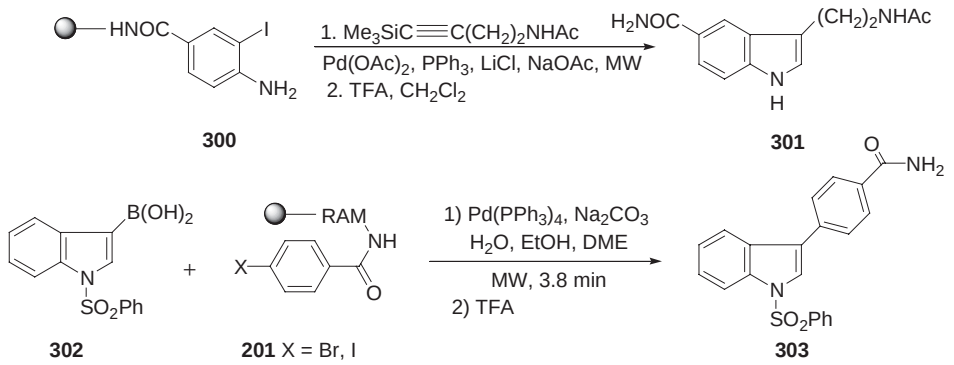
o-phenylenediamine under MWI gave exclusively the indoloquinoxaline **297** and no spiral derivatives on C-3 could be isolated; spiral compounds were isolated as by-products under conventional heating (Scheme 77) (05UP1).

Coupling of **300** with a trimethyl silyl acetylenic compound under MWI, followed by treatment with trifluoroacetic acid in dichloromethane afforded the indole derivative **301** in 90% yield instead of the 73% yield obtained by classical heating (Scheme 78) (02OL2613).

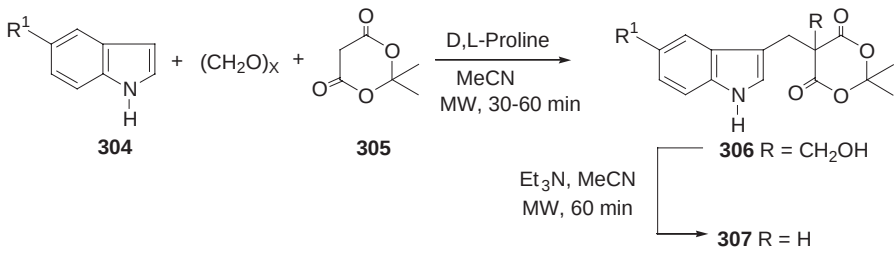
Suzuki coupling of **201** with indole boronic acid **302** under MWI and subsequent removal of the polymer support afforded **303** in 88–89% yield within 3.8 min (Scheme 78) (96TL8219, 02ACR717).

The reaction of indoles **304** with Meldrum's acid (**305**) and paraformaldehyde in acetonitrile in the presence of D,L-proline catalyst was investigated both by conventional heating and MW irradiation. In all cases, adducts **307** were formed along with their hydroxymethylated derivatives **306** in good yields; the MW irradiation reduced the reaction time and gave cleaner reaction mixtures (Scheme 79) (99S254). When the product **306** (R^1 = Br) in a mixture of acetonitrile and triethylamine was exposed to MWI at 85 °C for 60 min, it afforded **307** (R^1 = Br) in quantitative yield (Scheme 79).

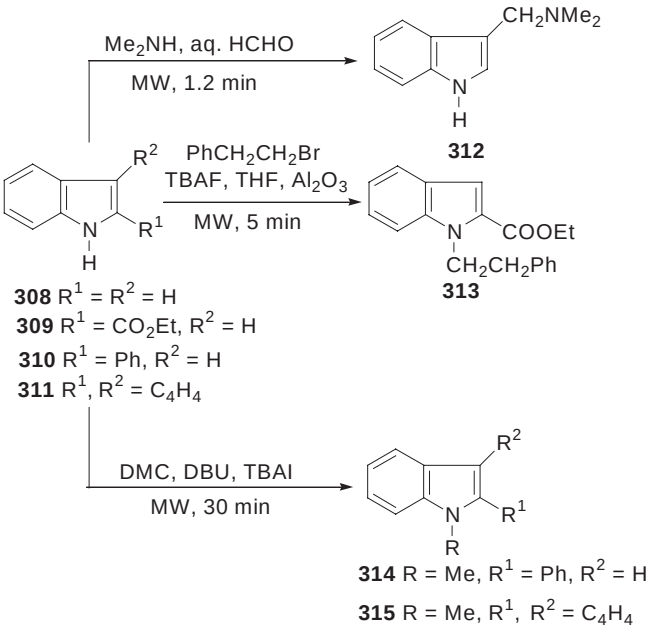
Gramine was obtained by the Mannich reaction of indole **308** with dimethylamine and aqueous formaldehyde. When the reaction was carried out in the CMR, the



Scheme 78



Scheme 79



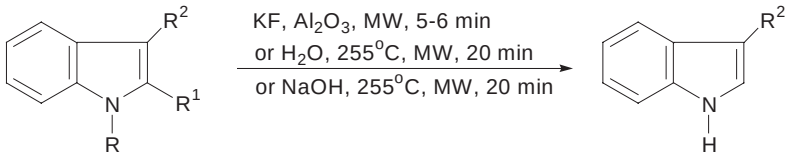
Scheme 80

reaction temperature was 160–170 °C and the purified Gramine (**312**) was obtained in 97% yield after a reaction time of 1.2 min (Scheme 80) (94JOC3408).

The dry MW induced alkylation of ethyl indole-2-carboxylate (**309**) with 2-phenethyl bromide on tetrabutylammonium fluoride (TBAF) and Al_2O_3 gave the N-alkylated product **313** in only 19% yield (Scheme 80), while C-alkylation of ethyl *N*-methylindole-2-carboxylate was unsuccessful under any of the tried MW conditions (TBAF/Al_2O_3, TBAF/SiO_2, CsF, Al_2O_3). Thus, dry MW-induced alkylation of indoles was unsatisfactory (95SC1).

The use of dimethyl carbonate (DMC) as a methylating agent in the presence of DBU catalyst and tetrabutylammonium iodide (TBAI) utilizing MWI accelerated the methylation of 2-phenylindole (**310**) to give N-methyl derivative **314** in 30 min in about 91% yield. The rate of acceleration is up to 50-fold more than in conventional thermal heating, which required a high temperature and a long time. Similarly, methylation of carbazole **311** under MWI gave N-methylcarbazole **315** in 30 min and 97% yield (Scheme 80) (01OL4279). Under MWI carbazole **311** also reacted remarkably fast with a number of alkyl halides by mixing carbazole with a 50% excess of an alkyl halide and a catalytic amount of TBAB. The mixtures were adsorbed on K_2CO_3 and irradiated in an open vessel in a domestic MW oven for 1–10 min to give the corresponding N-alkyl derivatives in 32–95% yields (97SC1553, 97H715).

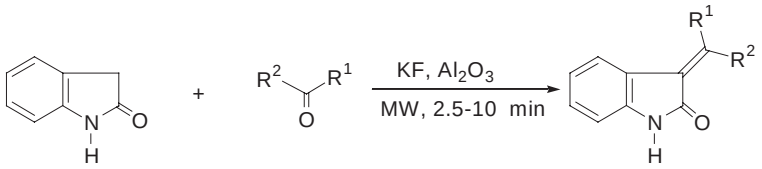
Reductive cleavage of sulfonamides with Pd/C, SmI_2, Mg/MeOH, Na in liquid NH_3 or sodium naphthanilide results in the reduction of other functional groups as well. Moreover, acid-sensitive functionalities like Boc and Cbz do not survive under



309 R = R^2 = H, R^1 = COOEt
316 R = Ts, R^1 = H, R^2 = H or Ac
317 R = R^2 = H, R^1 = COOH

318 R^2 = H, Ac

Scheme 81



319 **320**

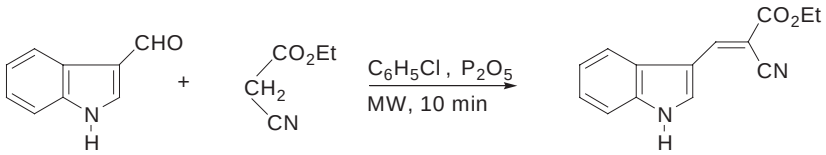
Scheme 82

the conditions of cleavage with HBr/AcOH. However, the cleavage of sulfonamides **316** was carried out using KF/Al_2O_3 under MWI within 5–6 min to give indoles **318** in 76–80% yields. The cleavage of the N-Ts group of carbazole under similar condition by MWI took place within 6 min to give carbazole in 78% yield (Scheme 81) (99SL1745).

Indole-2-carboxylic acid (**317**) was quantitatively decarboxylated to indole after 20 min at 255 °C in water in a MW batch reactor (MBR). 2-Carbethoxyindole (**309**) underwent low conversion into indole under these conditions. However, in aqueous NaOH, ester **309** underwent hydrolysis at 200 °C in MBR to afford acid **317** within 10 min, while at 255 °C ester **309** was hydrolyzed within 20 min to give **317** that underwent decarboxylation to produce indole in 93% yield (Scheme 81) (97JOC2505). MW thermolysis of a quinoline solution of **317** in a sealed tube in the presence of copper chromite (5%) gave a low yield (3%) of indole whereas CuCl proved to be an efficient catalyst, giving 83% of indole (**318**, $R^2 = H$) within only 12 min of thermolysis. However, using the copper(II) salt of **317** in quinoline led to a 4% yield of the decarboxylated indole, but thermolysis using copper powder as a catalyst produced a 94% yield of indole (93JOC5558).

The dry condensation of oxindole (**319**) with carbonyl compounds supported on KF/alumina without solvent under MWI occurred without difficulty. The reaction was successful with a number of aromatic and heterocyclic aldehydes as well as aliphatic and aromatic ketones to afford **320** in 35–94% yields. Ketones required a more prolonged MWI than the aldehydes (Scheme 82) (98SC3201).

Efficient Knoevenagel reaction between indole-3-carboxaldehyde (**321**) and ethyl cyanoacetate under MW conditions gave the desired product **322** in 76% yield; a large vial with a loose cap or an Erlenmeyer flask with a funnel as loose top was used



321 322

Scheme 83

as the reaction vessel. Monochlorobenzene was used as the energy-transfer medium since its boiling point (131–133 °C) is about 30 °C higher than that of water, required to be eliminated in the process; P_2O_5 was also used to remove the water produced in the reaction (Scheme 83). Although the required irradiation time was 10 min, the presence of the C-2 methyl substituent reduced the yield significantly (5%) even after 30 min of MW irradiation (97SC533).

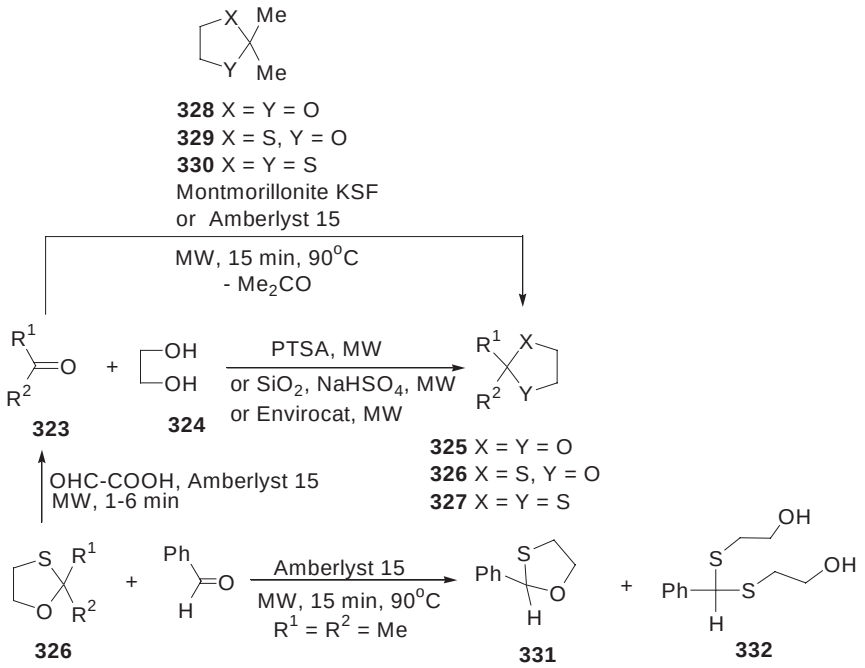
B. Heterocycles with Two Heteroatoms

1. *Dioxolanes, Oxathiolanes, and Oxadithiolanes*

Dioxalanes ketals are usually formed reversibly in the process of protecting aldehydes and ketones **323** by reaction with 1,2-ethanediol **324**. Thus, the reaction of **323** with **324** without solvent in the presence of an acid catalyst such as PTSA under MWI gave 9–98% yields of the corresponding dioxolanes **325**. Depending on the nature of the carbonyl compound, yields may be good or poor, especially for the less reactive or polymerizable compounds (Scheme 84) (97TL7867). An efficient method for the chemoselective acetalization of aldehydes involves acid catalysis by metallic sulfates such as $NaHSO_4$ supported on silica gel under MWI under solvent-free conditions for 3–6 min to give dioxolanes **325** in 71–98% yields. Rate enhancement of these reactions under MWI has been realized avoiding the low yields of products obtained, even after long reaction times (8–12 h) under conventional heating (00SL701).

Envirocats are new types of unique and environmentally friendly supported catalysts consisting of reagents on inert supports that are designed to carry out electrophilic reactions and oxidations. Envirocat EPZG catalyst efficiently promotes tetrahydropyranylation, dehydration, condensation, thioacetalization and methoxymethylation. This catalyst has efficiently catalyzed the acetalization of carbonyl compounds with 1,2-ethanediol under MWI and solvent-free conditions; without MWI, benzene was used for azeotropic water removal to shift the equilibrium to achieve a satisfactory yield (97SC3705).

A transacetalation process takes place upon reaction of **323** with 2,2-dimethyl-1,3-dioxolane (**328**) in good yields within very short time by using montmorillonite KSF clay (97TL7867). Similarly, protection of aldehydes and ketones **323** as hemithioacetals or dithioacetals by an exchange reaction with 2,2-dimethyl-1,3-oxathiolane (**329**) or 2,2-dimethyl-1,3-dithiolane (**330**) catalyzed by solid acidic catalysts was

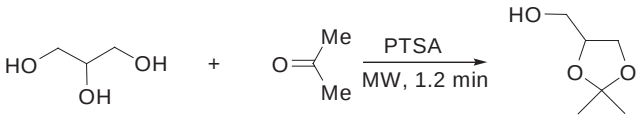


Scheme 84

readily achieved without solvent under MWI. Starting from 2-phenylacetaldehyde **323** ($R^1 = H$; $R^2 = PhCH_2$) and **329**, the best yield of the respective 1,3-oxathiolane **326** (86%) was obtained after 15 min of MWI at 90 °C in presence of montmorillonite KSF. The same reaction for **330** was completed using 10% Amberlyst 15 as acidic catalyst to give **327** ($R^1 = H$; $R^2 = PhCH_2$) in 78% yield. These two procedures were extended to other aldehydes and ketones leading to their oxathiolanes and dithiolanes with good to excellent yields. The oxathiolane exchange with benzaldehyde led to the formation of 2-phenyl-1,3-oxathiolane (**331**) in 63% yield, in addition to benzaldehyde-bis(2-hydroxyethyl)dithioacetal (**332**) as a side product (Scheme 84) (00MI3).

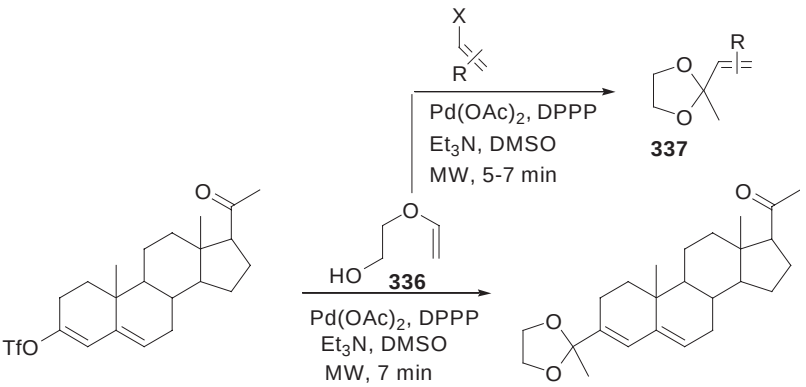
Carbonyl compounds **323** can be regenerated in 78–94% yields from the corresponding 1,3-oxathiolanes **326** via equilibrium exchange with glyoxylic acid and Amberlyst 15 as the heterogeneous catalyst at room temperature within 3–10 h. Under MWI and the same conditions, the deprotection has been completed in 1–6 min (Scheme 84). Thioacetals of aromatic ketones were deprotected faster than other ketones. 1,3-Oxathiolanes of aromatic aldehydes were deprotected with equal ease, while those of aliphatic aldehydes were more resistant to the reagent and the reaction took place only at a high temperature (01SL1251).

2,2-Dimethyl-1,3-dioxolane-4-methanol (**334**) was prepared in 84% yield by heating a solution of glycerol (**333**) in acetone containing PTSA catalyst in the CMR for 1.2 min. A conventional method took 21–36 h to give **334** in 87–90% yield (Scheme 85) (94JOC3408).



333 334

Scheme 85



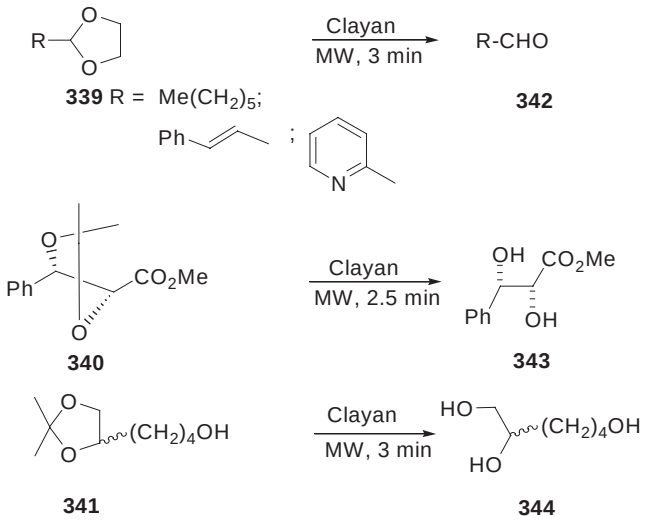
Scheme 86

A mild chemo- and regioselective procedure for the direct synthesis of 2-alkene-2-methyl-1,3-dioxolanes **337** (45–89%) uses Heck vinylation of 2-hydroxyethyl vinyl ether **336** with a vinyl triflate or bromide in the presence of palladium acetate catalyst, 1,3-bis(diphenylphosphino)propane (DPPP) a chelating ligand and triethylamine by flash heating under MWI (00JOC4537).

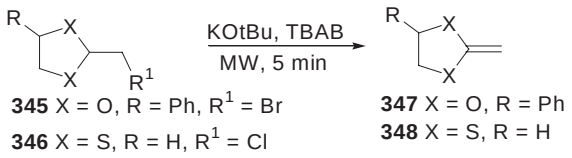
Similarly, the preparation of masked α,β-unsaturated methyl ketone **338** (53%) was also accomplished in 7 min under MWI by the reaction of the triflate **335** with **336** (Scheme 86). This complements the standard thermal heating to drastically reduce reaction times (02ACR717).

The general methods employed for the cleavage of acetals involve aqueous media containing mineral acids or non-aqueous media containing organic acids. Other methods utilizing wet silica gel, phosphorous triiodide, titanium(IV)chloride, borane triflouride-iodide ion or cerium(III)chloride have been also reported. Most of these procedures often suffer from a lack of selectivity, unsatisfactory yields, toxic and expensive reagents and the formation of considerable amounts of side products. The cleavage of THP ethers, acetonides and acetals using clayan under activation with MWI under solvent-free conditions has been achieved for the cleavage of compounds **339**–**341** to give **342**–**344**, respectively, in 70–90% yields (Scheme 87). The reactions proceed efficiently within a few minutes, whereas other groups like ester, benzyl ether, olefin or acetylene functionality remained unaffected (99SC2807).

Ketene *O*,*O*-acetal **347** was prepared in 87% yield from the corresponding bromo derivative **345** when subjected to KOtBu in the presence of TBAB in a focused MW



Scheme 87



Scheme 88

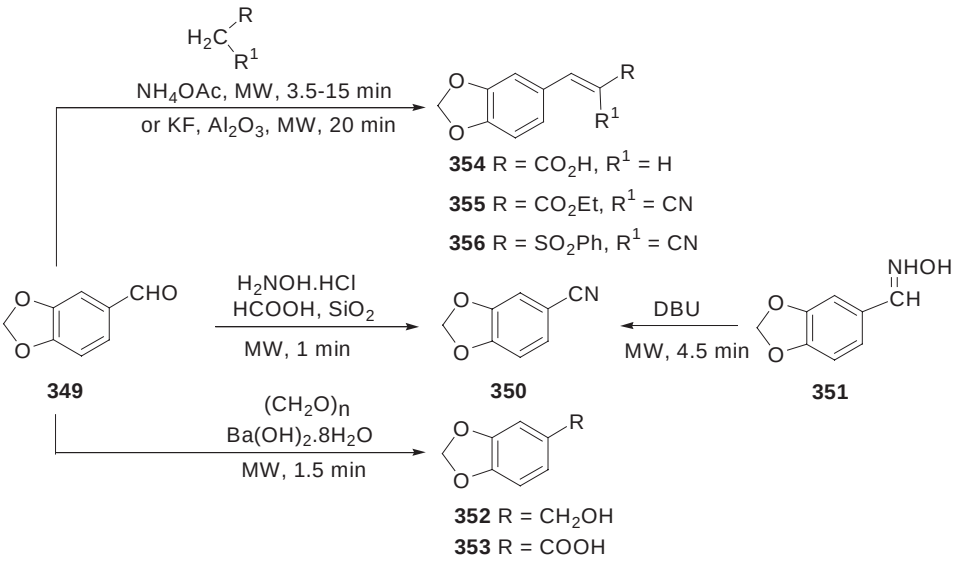
reactor under solvent-free conditions which caused a β-elimination reaction to take place (Scheme 88). Similarly, the ketene *S*,*S*-acetal **348** was obtained from **346** in 92% instead of 71% yield on using classical heating (96TL1695).

Rapid reaction of **349** with hydroxylamine hydrochloride using $HCOOH/SiO_2$ as a solid support catalyst under MWI without solvent afforded nitrile **350** in 92% yield (98SC3765). The same nitrile could also be prepared in 73% yield from the aldoxime **351** by the action of DBU for 4.5 min (Scheme 89) (98SC4577).

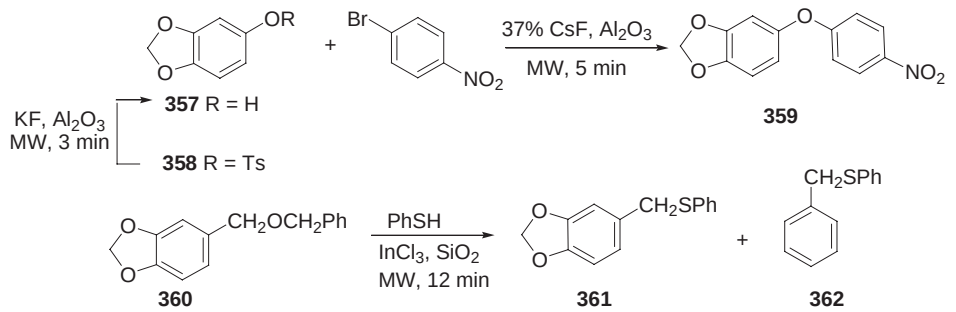
Reduction of aldehyde **349** to alcohol **352** (82%) made use of barium hydroxide and paraformaldehyde under MWI within 1.5 min; acid **353** was obtained as a by-product (15%) (Scheme 89) (98TL8437).

Condensation of **349** with malonic acid or ethyl cyanoacetate in the presence of ammonium acetate was carried out under MWI for 3.5 and 15 min to yield **354** (93%) (98SC3811) and **355** (90%) (99SC2731), respectively. Dry reaction of **349** and benzenesulphonyl acetonitrile adsorbed onto KF/Al_2O_3 at room temperature gave with MWI a 95% yield of the condensation product **356**, but without MWI the yield was 2% (Scheme 89) (89JCS(CC)386).

Phenolic compound **357** with *p*-nitrobromobenzene under MWI in the presence of 37% CsF on Al_2O_3 afforded within 5 min biaryl ether **359** in 88% yield (Scheme 90). Different inorganic fluorides like LiF, NaF and KF doped on an Al_2O_3 matrix were



Scheme 89

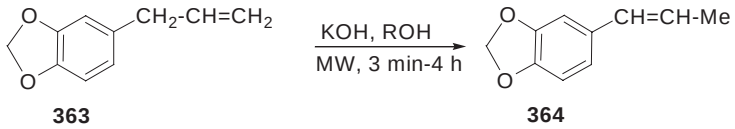


Scheme 90

used, but CsF/Al_2O_3 was found to be the most efficient in terms of degree of conversion and reaction times (00MI4).

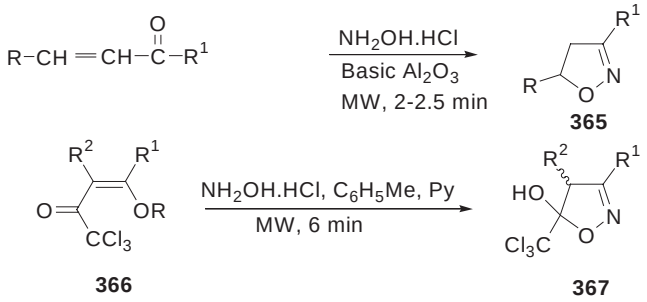
A simple and efficient cleavage of sulfonate **258** using KF/Al_2O_3 in dry media under MW was reported. A strong MW effect on the rate of the reaction was observed as the yield was 80% under MWI instead of 40–50% under conventional conditions (Scheme 90). Sulfonates were selectively cleaved in the presence of benzyl, *N*-Boc or allyl groups indicating the tolerance of other functionalities in the substrate (99SL1745).

Benzyl ether **360** underwent cleavage by thiophenol on the surface of silica gel impregnated with a Lewis acid ($InCl_3$) under MWI to produce the corresponding monothioethers **361** and **362** in a 3:1 ratio and 81% yield. Preferential cleavage at the C–O bond adjacent to the substituted phenyl ring occurred providing the thioether



363 **364**

Scheme 91



Scheme 92

361 as a major product (Scheme 90). Compound **362** was formed due to the electronic influence of the phenyl group on the adjacent C–O bond (02SL987).

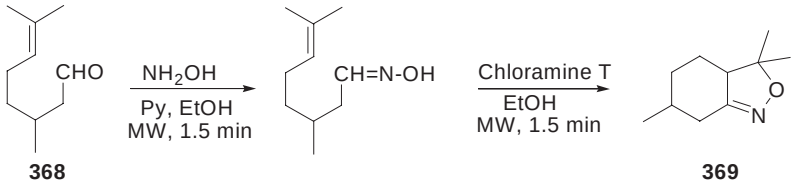
The isomerization of safrole (**363**) is of great interest since the product isosafrole **364** is used industrially in the process of manufacturing pharmaceuticals and fragrances. Attempts to isomerize **363** to the more stable alkene **364** by conventional methods were inconvenient for large-scale preparations. However, the reaction was carried out under MWI at atmospheric pressure and homogeneous medium in various alcoholic solvents and different basic concentrations to give **364** in 90–99% yield (Scheme 91). The reaction rate was 2.7–13.2 times faster than by conventional heating (97SC4335).

2. *Isoxazoles*

Adsorption of chalcones on basic alumina with hydroxylamine hydrochloride in CH_2Cl_2, followed by MWI for 2–2.5 min afforded 3,5-diaryldihydroisoxazoles (**365**) in 63–67% (Scheme 92) (99SC3237, 97IJC(B)175).

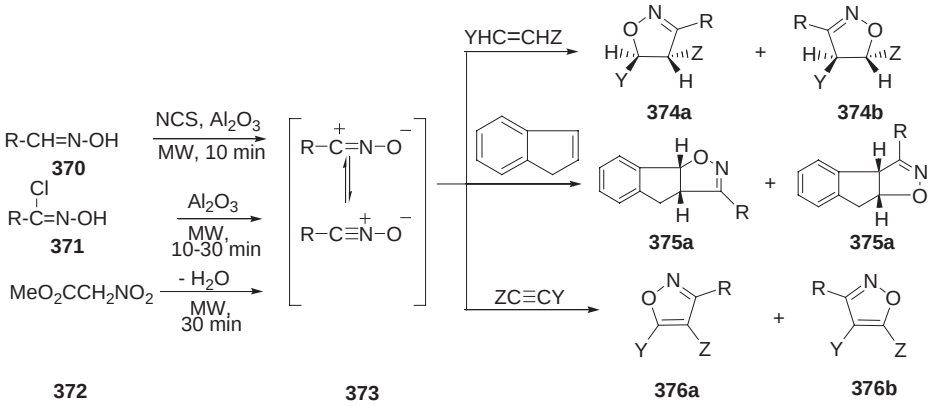
5-Hydroxy-5-trichloromethyl-4,5-dihydroisoxazoles **367** have been prepared in 78–96% yields by the cyclocondensation of 4-alkoxy-1,1,1-trichloro-3-alken-2-ones **366** with hydroxylamine hydrochloride using toluene as solvent and pyridine as base under MWI for 6 min. The reaction required 8–16 h to give 60–90% yields under conventional heating (02TL7005).

The oximation of citronellal **368** was performed under MWI in the CMR to give an 82% yield of the corresponding oxime after 1.5 min of heating. When a mixture of the oxime and chloramine T in ethanol was heated in the CMR for 1.5 min, 3,3,6-trimethyl-3,3a,4,5,6,7-hexahydro-2,1-benzisoxazole **369** was obtained in 78% yield (Scheme 93) (94JOC3408).



368 **369**

Scheme 93

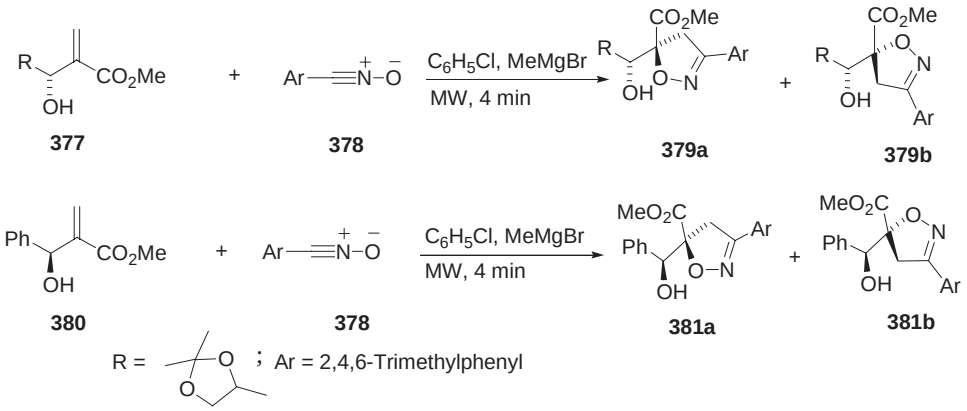


Scheme 94

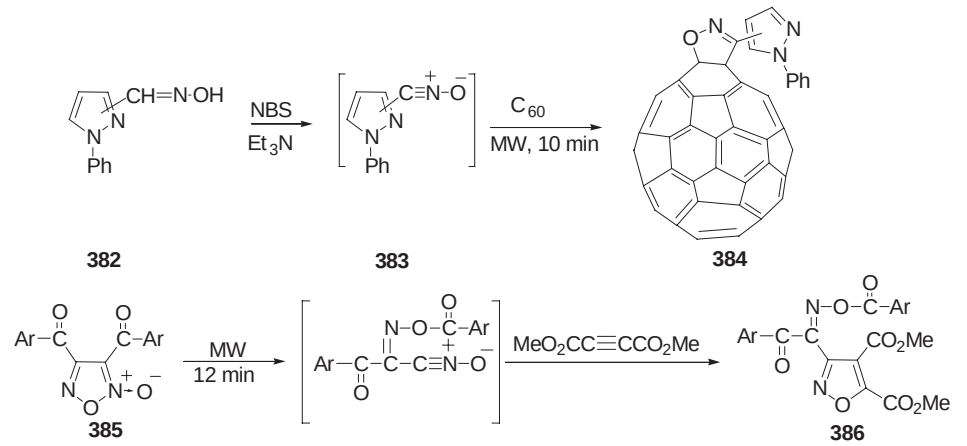
The 1,3-dipolar cycloaddition of a nitrile oxide with a dipolarophile to give isoxazoles or isoxazolines is readily achieved in the presence of catalytic amounts of PTSA, under MWI. Nitrile oxides **373** can be readily generated under MWI from the aromatic aldoximes **370** by halogenation and dehydrohalogenation with NCS/Al_2O_3 or by dehydrohalogenation of chlorohydroxamic acid **371** by Al_2O_3. Dehydration of **372** also gave **373**. The *in situ* reaction of the generated nitrile oxides with disubstituted alkenes in dry media on a solid mineral support gave the isomeric isoxazolines **374a** and **374b** in 65–76% yield. When dimethyl maleate was used as a dipolarophile, the reaction proceeded to give the isomeric isoxazoline **374b** in lower yield (20–44%). Similarly, indene gave **375a** and **375b**, but no reaction with trisubstituted alkenes was observed (Scheme 94) (94JCR(S)116, 97TL8855, 99JCR(S)718).

The 1,3-dipolar reactions of oxime chlorides **371** over alumina with various alkynes under MWI were carried out without solvent using a monomode reactor over 30 min to give moderate yields (40–60%) of the cycloadducts **376a** and **376b** (Scheme 94) (94JCR(S)116, 99JCR(S)718).

1,3-Dipolar cycloadditions of mesitonitrile oxide **378** to Baylis-Hillman alkenes **377** and **380** in the presence of a Grignard reagent as a Lewis acid under MWI proceeded regioselectively to give only the 5-substituted isoxazolines **379** and **381** in 34 and 40% yields, respectively, within less than 5 min instead of days. The isomers **379a** and **381a** were obtained as the main products, whereas in the absence of a Lewis acid, the ratio of **381a** to **381b** was 43:57 (Scheme 95). Thus, the addition of a Grignard reagent



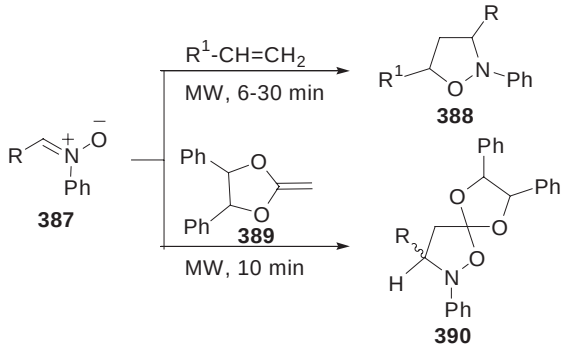
Scheme 95



Scheme 96

reversed the diasteroselectivity of the cycloaddition. The stereocenter in the β-position has little effect on the diastereoisomeric ratio (99TL167, 00T5465).

The nitrile oxide **383** was generated from pyrazole oxime **382** by treatment with NBS in the presence of Et_3N and then reacted *in situ* with C_{60} under MWI to give 3′-(*N*-phenylpyrazolyl)isoxazoline[4′,5′:1,2][60]fullerene **384** in 22% yield after isolation by flash chromatography (Scheme 96). Although the same reactions, under thermal conditions, gave similar yields, significant accelerating effect occurred under MWI. These new isoxazoline-fused organofullerenes showed a better acceptor ability than unsubstituted C_{60} due to the combined effect of the electronegativity of the oxygen atom linked to the C_{60} core and the electron-deficient character of C-3 of the isoxazoline ring. The cyclic voltammetry measurements showed a strong donor pyrazole ring and a better acceptor ability of the fullerene moiety compared to pristine C_{60} (99TL4889).



Scheme 97

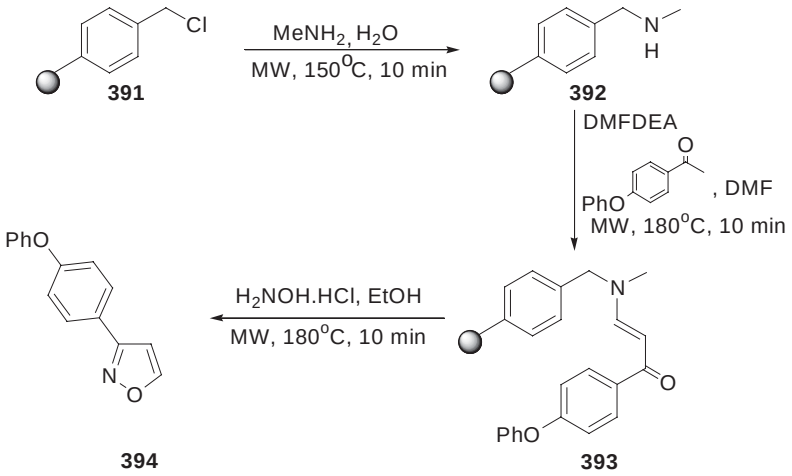
The isoxazoles can also be prepared via the rearrangement and subsequent cycloaddition of 3,4-dibenzoyl furoxan **385** with dimethyl acetylenedicarboxylate under MWI for 12 min, via benzoylnitrile oxide to give **386** in 60% yields (Scheme 96). Increasing the reaction time gave no significant improvement in yields, but decomposition of the product occurred. Several structurally varied dipolarophiles including phenyl acetylene, styrene, phenyl styrene, *N*-methylmaleimide and 4-phenyl-3-butyn-2-one underwent clean and remarkably fast cycloaddition with diaroyl furoxans under this procedure (98SC2415).

Isoxazolines **388** were prepared in 76–90% yields by the 1,3-dipolar cycloaddition of nitrones **387** with alkenes under MWI for 6–30 min (97SC2563). MWI induced ketene acetals **389** to react with 1,3-dipoles or compounds **387** within a few minutes to give excellent yields (79–95%) of cycloadducts **390**. Since **389** is achiral (meso), adducts **390** were obtained as a racemic mixture (Scheme 97). The stereochemical disposition of the dioxolane ring substituents have been inferred by NOE difference experiments (94JCS(P1)3595). Cycloadditions of cyclic ketene acetals under classical thermal conditions were generally performed at high temperatures ($>100\,^{\circ}C$) with long reaction times.

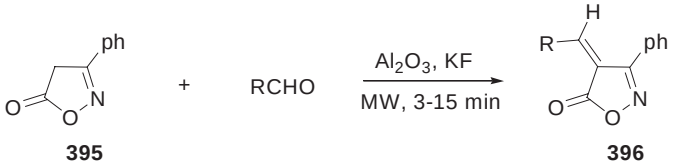
Merrifield resin **391** with methylamine in water at 150 °C for 10 min under MWI in a single-mode MW cavity formed the solid supported benzylmethylamine **392** in high yield (86%). The resin after washing was treated with dimethylformamide diethyl acetal (DMFDEA) and 4-phenoxyacetophenone at 180 °C for 10 min under MWI in the presence of DMF to form the solid supported benzyl methyl aminopropenone **393**. It was finally treated with hydroxylamine hydrochloride in ethanol at 180 °C for 10 min under MWI to form (4-phenoxy)phenylisoxazole **394** in 81% yield and 85% purity (Scheme 98) (03S1025).

The dry condensation of 3-phenylisoxazol-5-one (**395**) with aromatic aldehydes by adsorption on KF/Al_2O_3 under MWI gave the *E*-isomer of 3-phenyl-4-arylmethylene isoxazol-5-one (**396**) in 71–92% yields (Scheme 99). Neutral alumina without microwave caused only partial condensation, due to the insufficient basicity of the alumina catalyst (93SC2251).

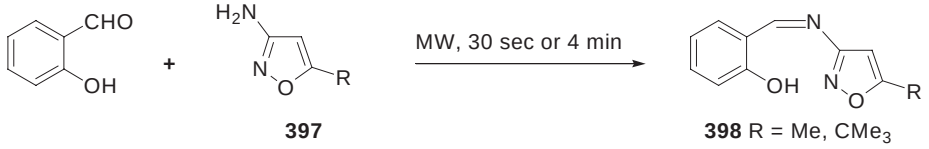
The synthesis of Schiff bases is often carried out with acid catalysts and generally by refluxing the mixture of aldehyde or ketone and amine (40CRV297). Stoichometric



Scheme 98



Scheme 99

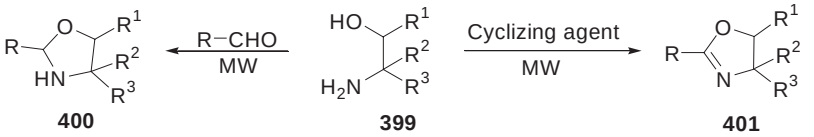


Scheme 100

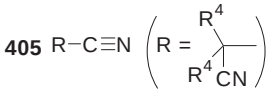
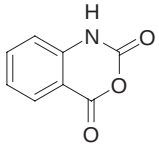
solid–solid reaction was successfully employed but the reaction time was relatively longer (98JCS(P2)989). To shorten the reaction time, MW-mediated reaction of heterocyclic amines with aldehydes was efficiently performed (97BSB393). Salicylaldehyde and an equivalent of 3-amino-5-substituted-isoxazole **397** were mixed together in an open Erlenmeyer flask and the mixture was subjected to MWI for 30 s or 4 min to give the respective Schiff bases **398** in 87 and 96% yields, respectively (Scheme 100) (02SC2395).

3. *Oxazoles and Thiazoles*

Many of the standard synthetic procedures of oxazolines required strongly acidic conditions in combination with high temperatures over long times and proceeded in low yields (63JOC2759, 73T3417, 91CB1173).



400 **399** **401**

Cyclizing agent	Conditions	%Yield of **401**
402 	Al_2O_3-KF, 4-6 min	58-93
403 RCO_2H	2-5 min	80-95
404 R−C≡N	$ZnCl_2$, 15-60 min	18-94
405 	Kaolinitic clay or Montmorillonite K_{10}	76-93
406 	Kaolinitic clay PhCl, 20 min	45-70

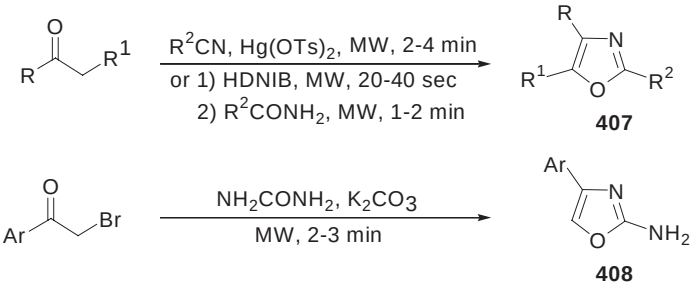
Scheme 101

Introducing the MW technique for the synthesis of this ring system facilitated the process in a shorter time and the products were obtained in good yields. β-Aminoalcohols with varied substituents on the chain carbons are excellent precursors for the synthesis of oxazoles and oxazolidenes via the insertion of one carbon atom. Various one carbon inserting agents have been used in this regard as cyclizing agents. The condensation between aminoalcohols **399** such as ephedrine and an aldehyde under solvent-free conditions using a focused MW reactor gave 1,3-oxazolidines **400** in excellent yields and diastereoselectivities (Scheme 101) (01MI4).

The synthesis of oxazolines **401** was achieved by the reaction of imino ether hydrochlorides **402** with **399** in the presence of KF supported on alumina; the reaction was carried out in an open vessel. The expected oxazolines **401** were obtained in fairly good yields (Scheme 101). The oxazolines were also obtained in almost the same yield by irradiating the free imino ether and **399** in a closed vessel using alumina as a solid support without KF (95SC659).

Successful preparation of different oxazolines **401** from carboxylic acids **403** and α, α, α-tris(hydroxymethyl)methylamine **399** was achieved by MWI in a domestic oven over less than 5 min. All reactions proceeded rapidly to give 2-substituted-4,4-dihydroxymethyl oxazolines **401** in high yields (Scheme 101) (96SL245).

A rapid and high yielding procedure for the synthesis of 2-substituted-4,4-dimethyl oxazolines **401** was achieved under MWI from nitriles **404** and β-aminoalcohols **399** using a mild Lewis acid catalyst (Scheme 101). The reactions are generally clean,



Scheme 102

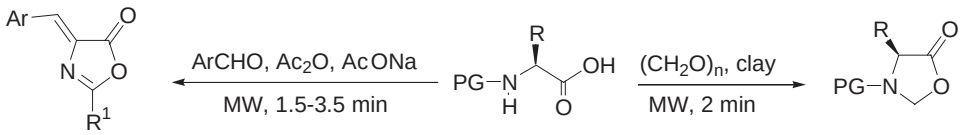
proceed well for both aromatic and heteroaromatic nitriles while aliphatic nitriles require longer times to achieve comparable yields of products (96SC1335).

Natural kaolinitic clay catalyzed the reaction of dialkyl malononitrile **405** with *β*-aminoalcohols **399** under MWI to give mono-oxazolines **401** in 76–93% yields. The selective formation of **401** was also achieved using montmorillonite K_{10} clay catalyst (Scheme 101). The formation of the mono-oxazolines rather than bis-oxazolines could be due to the steric hindrance of the neopentyl type center of the disubstituted malononitrile derivatives (99JCR(S)252).

Similarly, kaolinitic clay catalyzed the preparation of 2-(*o*-aminophenyl)oxazoline **401** in 45–70% yields by MWI of isatoic anhydride **406** with *β*-aminoalcohol **399** for 20 min in a domestic oven; classical heating required 20 h (00JCS(P1)999).

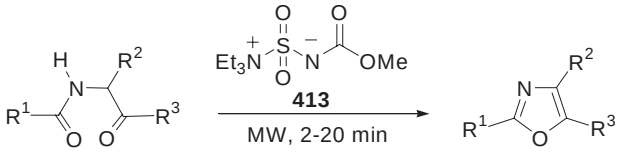
5-Alkyl-4-aryl-2-phenyloxazoles and 4-aryl-2-phenyloxazoles **407** were prepared from aromatic ketones with benzonitrile in the presence of mercury(II)*p*-toluenesulfonate under MWI. Aromatic α-methylene ketones provided better yields (47–86%) than the aromatic α-methyl ketones (Scheme 102) (00TL5891). Furthermore, MWI of carbonyl compounds with [hydroxyl-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB) for 20–40 s followed by adding amides and reirradiation by MW for 1–2 min gave the trisubstituted oxazoles **407** in 58–94% yields (03TL123). 2-Amino-4-aryloxazoles **408** were prepared in 92–94% yields by MWI of phenacyl bromides and urea in the presence of K_2CO_3 for 2–3 min in a domestic MW oven (02JHC1045). The short time, the high yield, and the simple work-up offer significant advantages over existing methods for the multi-substituted oxazole ring formations.

N-protected oxazolidin-5-ones derived from amino acids are versatile synthons used in the synthesis of several bioactive molecules and their key intermediates. In general, the most common method involved heating N-protected α-amino acids with paraformaldehyde in the presence of catalytic amount of PTSA in toluene or benzene for several hours until the solution became homogeneous with azeotropic removal of water, cumbersome and time-consuming (57JA5736, 83JOC77). Recently, the synthesis of N-protected 5-oxazolidinones **410** using amino acids **409**, paraformaldehyde and PTSA in toluene was accomplished by MWI for 3–6 min in a domestic MW oven. A simple work-up gave **410** in 81–98% yields. On the other hand, the present approach can be carried out easily because it circumvents the removal of water by azeotropic distillation (02TL9461). MWI of *N*-Ts-α-amino acids



411 R^1 = Me, C_6H_5 **409** PG = Ts, Ac, Bz **410**

Scheme 103



412 **414**

Scheme 104

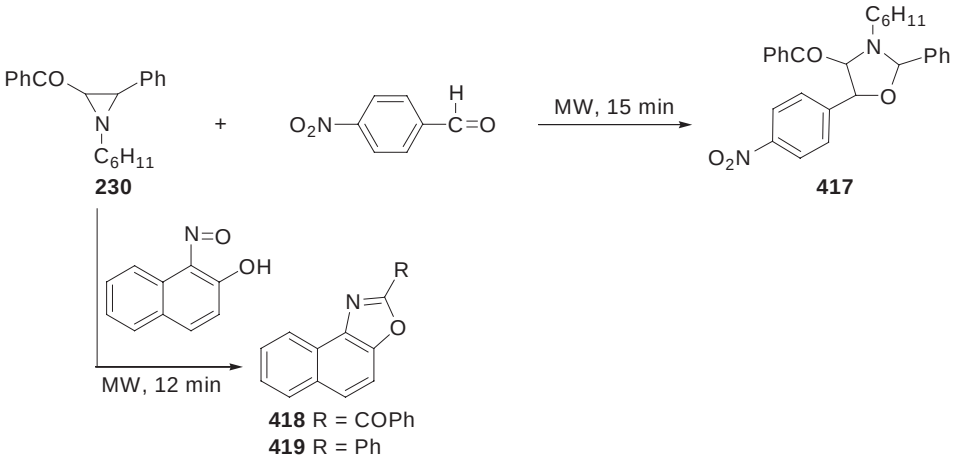
415 **416**

Scheme 105

409 and paraformaldehyde in the presence of clay for 2 min gave the corresponding *N*-Ts-oxazolidinone **410** in excellent yields (91–96%) (Scheme 103). Similarly, *N*-Ac and *N*-Bz oxazolidinones were prepared in 90–94% yields. However, *N*-Boc and *N*-Cbz amino acids under these conditions led to intractable mixture of products. This might be due to the cleavage of Boc and Cbz groups under these conditions (99SC4071). When the reaction was carried out at room temperature using $MgSO_4$ in CH_2Cl_2 it took 96 h (95T3015). When a mixture of acyl glycines **409** (R = H; PG = Me, C_6H_5), aromatic aldehyde, acetic anhydride and sodium acetate was irradiated in a MW oven for 1.5–3.5 min, 4-arylidene-2-substituted-5-oxazolones **411** were obtained in 78–90% yields (01MI5, 05UP2). Similar yields were obtained by classical heating for 15 min (75S749).

An efficient variation of the Robinson–Gabriel oxazole synthesis was described for oxazoles **414**. Thus, cyclodehydration of 2-acylamino carbonyl compounds **412** with Burgess reagent **413** as a mild dehydrating agent under monomode MWI yielded the oxazoles **414** (72–100%) within several minutes (Scheme 104) (99SL1642).

MWI of the anti-α-iodo derivative **415** in DMF afforded enantiomerically pure (4*R*, 5*S*)-2-oxazolidin-2-one **416** in 85% yield (Scheme 105). The *trans* configuration was assigned by analysis of the ^{1}H-NMR spectral data (03SL797).



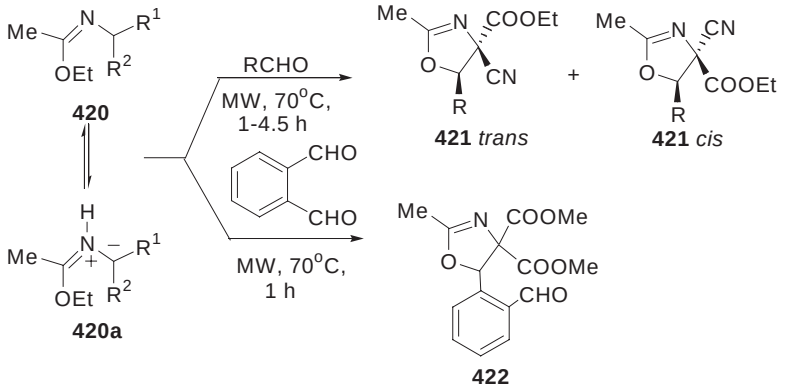
Scheme 106

Compound **230** and *p*-nitrobenzaldehyde were mixed together without solvent in an Erlenmeyer flask and subjected to MWI for 15 min in a commercial MW oven to afford the oxazolidine derivative **417** in 80% yield. The reaction involved cleavage of the 2,3-bond of **230** to an azomethine ylide intermediate and then subsequent [2,3] cycloaddition to the carbonyl group of the aldehyde. Similarly, **230** underwent 1,3-dipolar cycloaddition to the nitrogen–oxygen bond of 1-nitroso-2-naphthol followed by cleavage of the intermediate oxadiazolidine to a nitrone and cyclization of the latter to afford both 2-benzoyl naphtho[1,2-*d*]oxazole **418** (50%) and 2-phenylnaphtho[1,2-*d*]oxazole **419** (35%) (Scheme 106) (96TL4203).

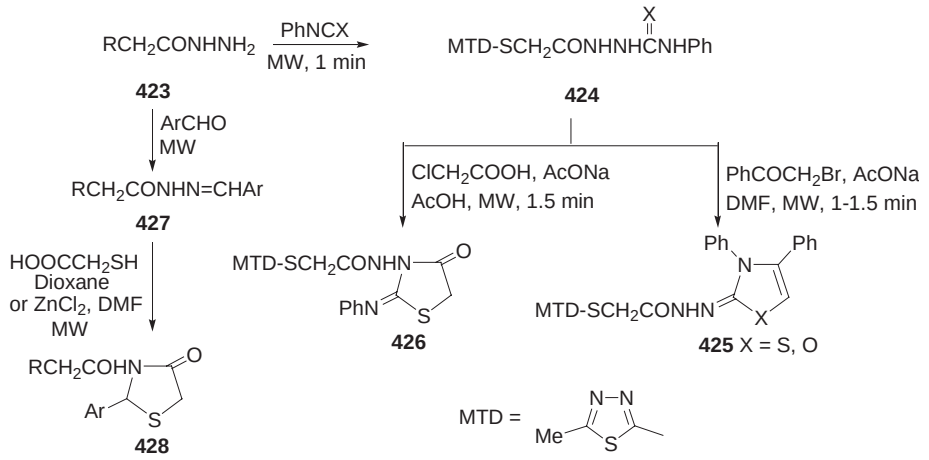
The cycloaddition of the imidate **420**, found to be in equilibrium with the azomethine ylide **420a** as a result of the thermal 1,2-prototropy, with aromatic aldehyde was effected by heating their mixture at 70 °C without solvent in an oil bath to give ethyl 4-cyano-2-methyl-2-oxazoline-4-carboxylates **421** as a mixture of *cis* and *trans* diastereoisomers. When the reaction was conducted in a focused MW oven, the cycloadducts **421** were formed with the same diastereomeric ratio, but higher yields (87–98%) were obtained in a shorter time (00MI5).

Dimethyl 5-(2-formylphenyl)-2-methyl-4,5-dihydrooxazole-4,4-dicarboxylate (**422**) was prepared in 83% yield from imidate **420** and phthalaldehyde after MWI at 70 °C in a Synthewave 402 reactor for 1 h (Scheme 107) (99JCR(S)32).

Treatment of hydrazide **423** with phenyl isothiocyanate and phenyl isocyanate in ethanol under MWI for 1 min gave the thiosemicarbazide and semicarbazide derivatives **424** (86–88%) that were then cyclized with phenacyl bromide to give thiazole (77%) and oxazole (79%) derivatives **425**, respectively. When thiosemicarbazide **424** (X = S) reacted with chloroacetic acid under MWI it yielded thiazolidinone **426** in 71% yield (Scheme 108) (97G263). MWI of the hydrazides **423** with aromatic aldehydes gave the corresponding hydrazones **427**, whose cyclization with thioglycolic acid was also achieved by MW to give the thiazolidinone derivatives **428** in 59–89% yields (97IJC(B)175, 00JIC46).



Scheme 107

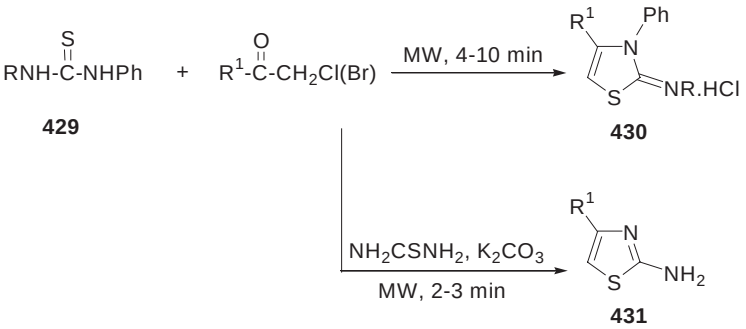


Scheme 108

Thiazoles were conventionally prepared from α-halo ketones and thioamides or thioureas. Other methods have been also introduced in view of the pharmacological importance of the thiazole derivatives (61JOC828, 86IJC966, 92JCS(P1)207). The obvious limitations have been the use of strong mineral acids under drastic conditions.

Reactions of thiourea **429** and α-chloro ketones were carried out without solvent under MWI at 80 °C to give thiazolinium salts **430** in 77–98% yields; under classical heating, much lower yields were observed (Scheme 109). In order to obtain the iminothiazolines, the reaction was performed in the presence of basic alumina in solvent-free conditions under MWI (98TL8093).

2-Amino-4-substituted thiazoles **431** were prepared in 92–94% yields by MWI of a mixture of phenacyl halides, thiourea and potassium carbonate in a domestic MW oven for 2–3 min (02JHC1045).



Scheme 109

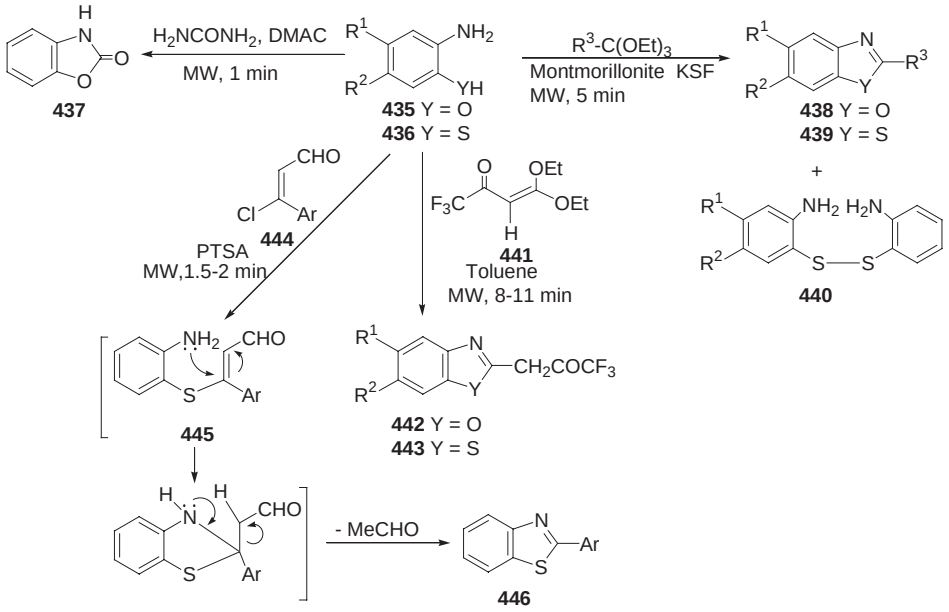
133 R^1 = Ar, R^2 = H
432 R^1 = Me, R^2 = Ac

433 R^1 = Ar, R^2 = H
434 R^1 = Me,R^2 = Ac

Scheme 110

Thiazole derivatives **433** and **434** were obtained in excellent yields (86–94%) from the reaction of thioamides with α-tosyloxy ketones **133** and **432**, respectively, in the presence of acidic montmorillonite K_{10} clay after irradiation in a MW oven for 2–5 min. The mechanistic pathway involves a nucleophilic displacement of the tosylate group in **133** or **432** by the sulfur atom followed by intramolecular nucleophilic attack of the nitrogen atom in thioamide on the carbonyl carbon and elimination of a water molecule (Scheme 110) (98JCS(P1)4093).

The benzoxazole and thiazole analogs were constructed from aminophenols and thiophenols by the addition of one carbon atom to form the five-membered heterocycles. Numerous methods are available for the synthesis of 2-arylbenzothiazoles (57JA427, 70CPB587, 78JOC2296, 79JHC13, 84S145, 92JOC2883), but most methods suffer from long reaction periods, the use of corrosive acids and toxic metallic compounds that result in the generation of waste streams. Thus, condensation of 2-aminophenol **435** and urea in *N*,*N*-dimethylacetamide (DMAC) under MWI led to the evolution of ammonia and the formation of benzoxazolin-2-one **437** in 89% yield (96JCR(S)92). A rapid and convenient condensation of **435** with *ortho* esters was catalyzed by clay without solvent under MWI to give the benzoxazoles **438** in 55–76% yields. Similarly, 2-aminothiophenol (**436**) gave benzothiazoles **439** in addition to disulfide **440** and it was necessary to conduct the reaction under nitrogen whereby only a trace of disulfide **440** was observed, but the quantity of the disulfide increased when the quantity of montmorillonite KSF increased. This was attributed to the presence of Fe^{3+} in the KSF clay (96SC2895). On the other hand, the condensation of several aldehydes with 2-aminothiophenol (**436**) on silica gel or montmorillonite K_{10} in the presence of nitrobenzene under MWI gave the respective

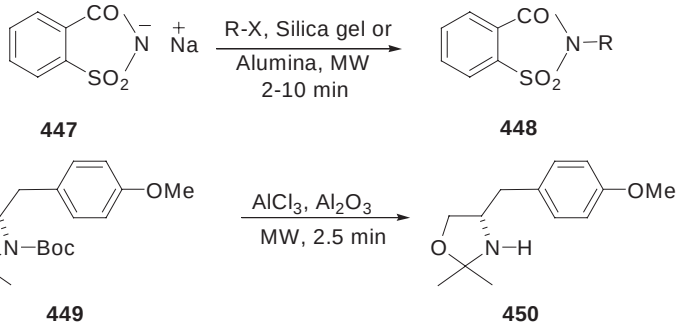


Scheme 111

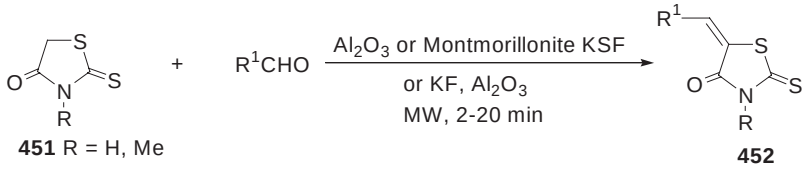
2-arylbenzothiazoles **439** in good yields (61–98%) and high purity. Nitrobenzene was used to oxidize the initially formed benzothiazolines by an electron transfer reaction (97TL6395). A number of 1,3-azole derivatives **438** and **439** were prepared in 84–97% yields by the cyclization of **435** or **436** with either benzaldoximes on $Ca(OCl)_2/Al_2O_3$ or aromatic aldehydes in the presence of MnO_2/SiO_2 under MWI within 4 and 5 min, respectively. Moreover, fusion of **435** with aromatic acids under MWI for 12 min gave 2-arylbenzoxazoles **438** in 84–86% yields (Scheme 111) (98T8055). A facile route to 2-arylbenzoxazoles **438** has been developed by MWI of a mixture of *o*-aminophenols **435** and acid chlorides in 1,4-dioxane for 15 min. The ease of synthesis and work-up allowed the parallel synthesis of a 48-membered library of benzoxazoles in 46–89% yields. The thermal heating required 2–72 h (03TL175). The reaction times were considerably shortened and the products were obtained in higher yields and better purity compared to conventional heating.

Recently, the reaction of a 1.25:1 ratio of *o*-aminothiophenol **436** and *β*-chlorocinnamaldehydes **444** in the presence of PTSA under MWI in a MW oven for 1.5–2 min gave 2-arylbenzothiazoles **446** in 52–85% yields (Scheme 111). The proposed mechanism involves initial nucleophilic displacement of chlorine by sulfur to give **445**, followed by nucleophilic addition of nitrogen to the conjugated C=C leading to ring closure. When carried out under similar conditions of time and temperature in a preheated oil bath, the yields of **446** were quite low indicating that the effect of MWI is not purely thermal (02SC3541).

The insertion of only one carbon to form five-membered heterocycles can be induced also by condensation of trifluoroacetyl ketene diethyl acetal (**441**) with



Scheme 112



Scheme 113

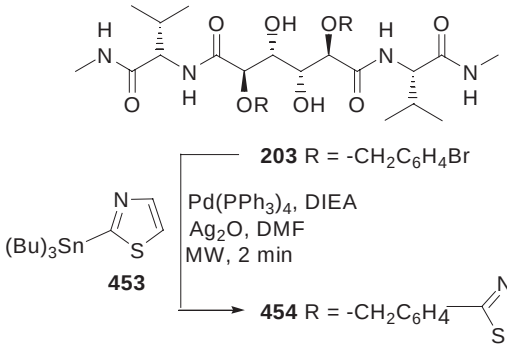
o-aminophenols **435** and *o*-aminothiophenols **436**, either under conventional thermal conditions (94JFC47) or by MWI (97T5847) to give, respectively, the benzoxazoles **442** and benzothiazoles **443** in 93–96% yields (Scheme 111).

The N-alkylation of saccharin **447** was achieved by MWI of a mixture of saccharin, alkyl halide, and silica gel or alumina to give the N-alkylated saccharin **448** in 21–91% yield (Scheme 112). The reaction was very rapid and the role of supports was indispensable, silica gel GF_{254} and alumina G were most efficient. The cumulative effects of supports and phase-transfer catalysis without solvent allowed the synthesis to be accelerated in a MW oven. The presence of a support is essential as alkylation without a support was very difficult and gave low yields (<10%) (94SC301).

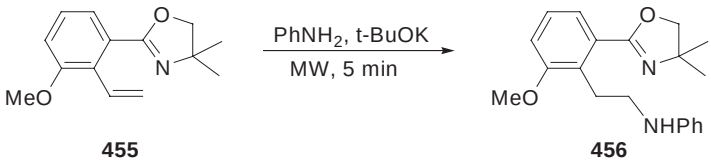
Selective deprotection of *t*-Boc oxazolidine derivative **449** was achieved by using $AlCl_3/Al_2O_3$ under MWI to give **450** in 90% yield (Scheme 112) (98TL5631).

Rhodanine and its N-methyl derivative **451** were condensed with aromatic aldehydes adsorbed on alumina, potassium fluoride on alumina or montmorillonite KSF as supports without solvent under MWI for 2–20 min to give **452** in 56–90% yields (89JCS(CC)386, 98MI1). Under similar conditions with conventional thermal activation, the condensation of **451** (R = Me) with piperonal yielded **452** in 12% yield (Scheme 113).

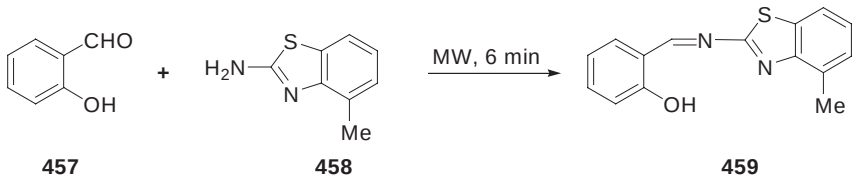
A peptide containing the thiazole ring **454** exhibited good inhibitory potencies on the protease enzymes assay with K_i in the nanomolar range. It was synthesized in 53% yield by mixing **203**, tributyl-2-thiazolyltin **453**, palladium tetrakis(triphenylphosphine), DIEA and silver(I)oxide in DMF solvent in a Pyrex tube and



Scheme 114



Scheme 115



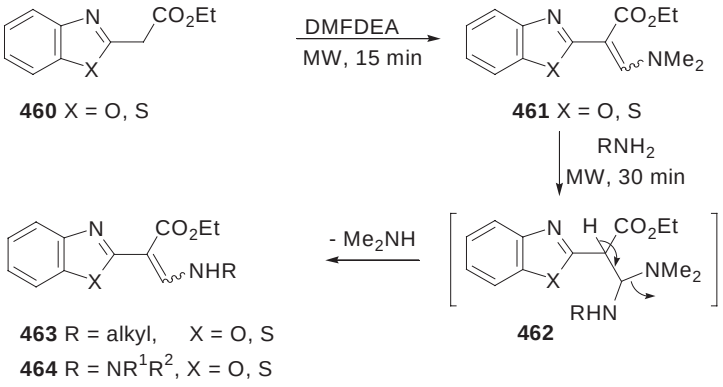
Scheme 116

degassed under a nitrogen flow for 5 min. Then, the tube was sealed with a Teflon septum and irradiated in a MW reactor for 2 min at 60 W to give **454** (Scheme 114) (99JMC3835).

Hydroamination of 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline (**455**) with aniline in the presence of potassium *tert*-butoxide using 1:10:1 ratio gave the corresponding *β*-phenylethylamine **456** by irradiation in a domestic MW oven. The reaction was complete in 5 min and a quantitative yield was obtained (Scheme 115) (01SL875).

Salicyaldehyde (**457**) condensed with 2-amino-4-methylbenzothiazole (**458**) without solvent under MWI for 6 min in a domestic oven to give 2-{[4-methylbenzothiazole-2-yl)imino]methyl}-phenol (**459**) in 82% yield (Scheme 116) (02SC2395).

Ethyl 3-dimethylamino acrylate derivatives **461** were easily prepared in good yields (70–83%) by irradiation of a mixture of **460** and *N*,*N*-dimethylformamide diethyl acetal (DMFDEA) at 90 °C for 15 min without solvent under focused MWI. Reaction of **461** with volatile amines using solvent-free conditions assisted by



Scheme 117

focused MWI gave β-enamino esters **463** in 90–97% yields. The mechanism was believed to be an addition–elimination on **458** to give the aminal intermediate **462** that could not be isolated but lost; dimethylamine gave **463**. The ^{1}H-NMR spectra indicates that compounds **463** (X = S) have the *E* configuration, but the analogs **463** (X = O) exist as a mixture of *E*/*Z* diastereomers (98TL8453). Similarly, the 3-dimethylamino acrylates **461** were mixed with hydrazines and submitted to MWI for 30 min to give the β-hydrazino acrylate **464** in 71–93% yields (Scheme 117) (01S581).

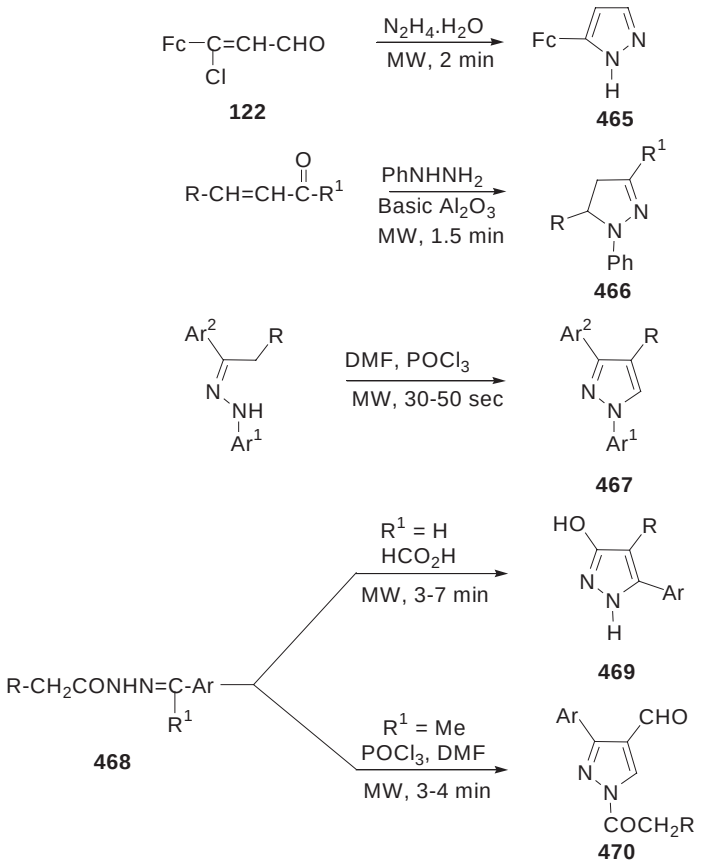
4. *1,2-Diazoles (Pyrazoles and Indazoles)*

The reaction of β-functionalized carbonyl compounds with hydrazine derivatives is a main method for the synthesis of pyrazoles. This condensation usually requires heating that now has been replaced by MWI as shown in the following examples. Thus, 3-chloro-3-ferrocenylacrylaldehyde (**122**) with hydrazine hydrate in a MW oven for 2 min gave the ferrocenylpyrazole **465** in 83% yield (Scheme 118) (94CCC175).

α,β-Unsaturated compounds, chalcones, were condensed with phenylhydrazine under MWI in acetic acid or by irradiating a solution of both reactants in dichloromethane using basic alumina to give 1,3,5-triarylpyrazolines **466** (80–82%) (Scheme 118) (99SC3237).

Vilsmeier reagent (DMF-$POCl_3$) is an effective intramolecular cyclizing agent used to prepare a number of heterocyclic compounds. Thus, Vilsmeier reaction of α-alkylacetophenone phenylhydrazones with DMF/$POCl_3$ under MWI for 30–50 s gave 4-alkyl-1,3-diarylpyrazoles **467** in 45–78% yields. In the conventional heating method the mixtures were heated in an oil bath at 90 °C for 4–5 h to afford the same pyrazoles with a slight variation in their yields (Scheme 118) (02JHC1129).

Cyclocondensation of hydrazones **468** with formic acid on MW heating for 3–7 min gave the corresponding pyrazoles **469** in 75–86% yields (00IJC(B)458) while **468** with $POCl_3$ in DMF under MWI for 3–4 min gave **470** in 75–83% yields (97IJC(B)175).

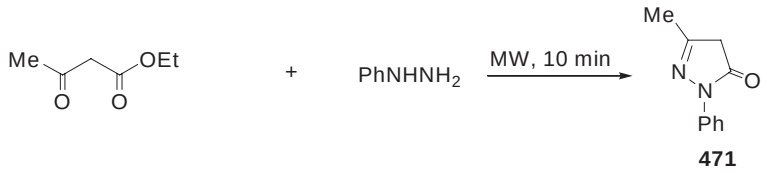


Scheme 118

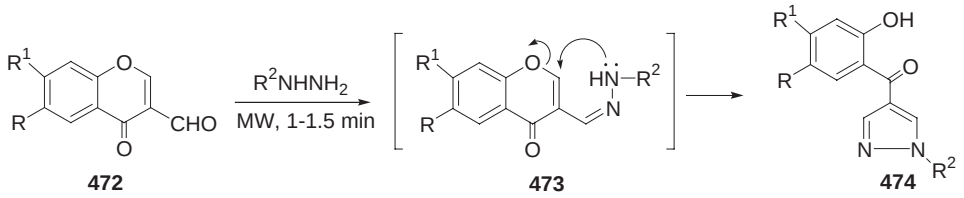
Pyrazolones are an important class of antipyretic and analgesic compounds. 3-Methyl-1-phenyl-5-pyrazolone (**471**) was obtained quantitatively and rapidly by the Knorr condensation of ethyl acetoacetate with phenylhydrazine under MWI (Scheme 119) (90SC3213).

The synthesis of 4-(2-hydroxybenzoyl)pyrazoles **474** was reported (78JIC386) using either a Fries migration of a pyrazolyl ester of phenolic compounds or a Friedel–Craft reaction of phenols with 1-phenylpyrazole-4-carboxylic acid chloride. The preparation of the acid chloride or the corresponding acid involves a number of steps (54JCS2293). This has been overcome by the reaction of 3-formylchromones **472** with hydrazines in ethanol initially furnishing hydrazones **473** that has been further converted into **474** by refluxing in AcOH or ethanolic KOH. Better yields of **474** were achieved in a single step by applying MWI instead of conventional heating of **472** with hydrazines. The reactions were completed within 1–4.5 min without solvent and in good yields (67–89%) (Scheme 120) (98SC4571).

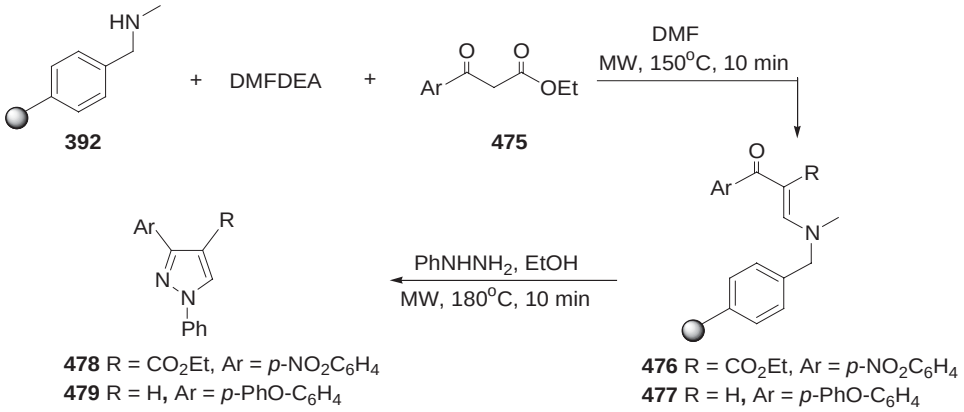
Merrifield resin (**392**) was treated with DMF/DEA together with 4-nitrobenzoyl acetate (**475**) in DMF at 150 °C for 10 min under MWI to form the solid-phase



Scheme 119



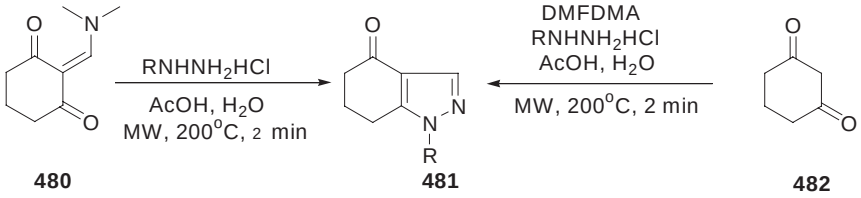
Scheme 120



Scheme 121

bound benzyl aminopropenone **476**. Magic angle spinning ^{1}H-NMR (MAS-NMR) analysis indicated the formation of compound **476** but no yield was determined due to the low resolution. When **476** was mixed with phenylhydrazine in ethanol and exposed to MWI at 180 °C for 10 min, ethyl 1-phenyl-3-(4-nitrophenyl)-pyrazole-4-carboxylate **478** was obtained in 92% yield and 91% purity based on HPLC/MS analysis. Under similar conditions, **477** reacted with phenylhydrazine in the presence of acetic acid to give 1-phenyl-5-(4-phenoxyphenyl)pyrazole **479** in 81% yield and 93% purity (Scheme 121) (03S1025).

Equimolar mixtures of enaminoketone **480** and hydrazine hydrochlorides in AcOH/H_2O were subjected to MW heating to afford 1-substituted-1,5,6,7-tetrahydro-4*H*-indazol-4-ones **481**. The reactions were complete in 2 min at 200 °C and the products were isolated in 65–99% yields. Alternatively, under similar conditions, a mixture of dimethylformamide dimethyl acetal, 1,3-cyclohexanedione (**482**) and



Scheme 122

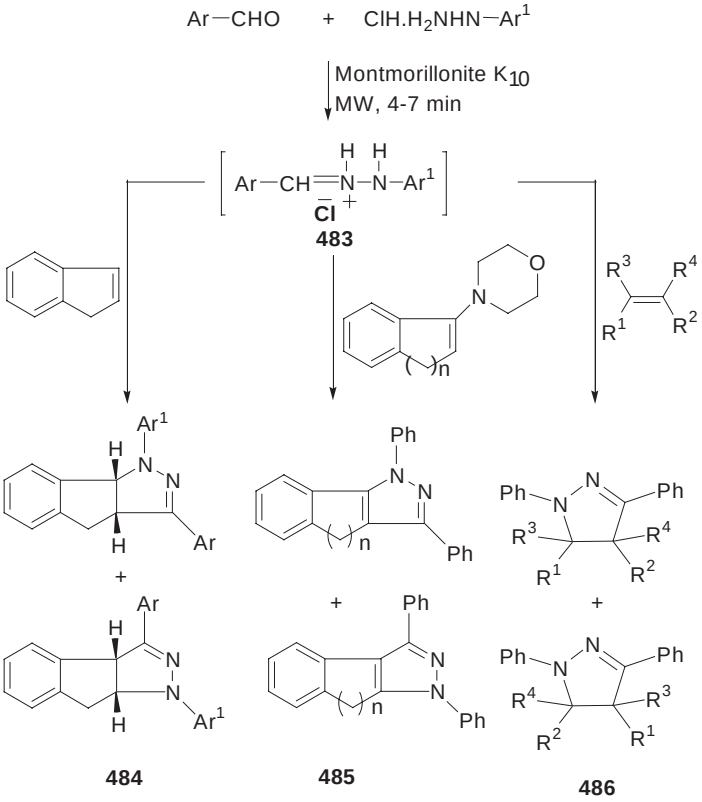
hydrazines in $AcOH/H_2O$ gave products **481** in 66–87% yields. The microwave reactions were also run in other solvents, but water proved optimal. The reactions in aqueous media displayed unique reactivity and selectivity. In addition to the short reaction times, a facile purification by precipitation of the products from the aqueous media was achieved. An unusual reaction was observed with 4,5-dihydroimidazol-2-ylhydrazine. N-unsubstituted indazole **481** (R = H) was the product in 80% yield (Scheme 122). Loss of the imidazoline fragment occurred in the cyclization step, as shown by GS/MS analysis (02S1669).

Dipolarophile **483** is an interesting precursor for the synthesis of pyrazoles and pyrazolines. It could be generated by irradiating a mixture of aromatic aldehydes and arylhydrazine hydrochlorides under MWI using montmorillonite K_{10} clay. Pyrazoles **484–486** were prepared in a single step in good yields (60–75%) by [3 + 2] cycloaddition of dipolarophiles **483** with alkenes or cycloalkenes using montmorillonite K_{10} in dry media under MWI in a domestic oven (Scheme 123). The reactions were complete in 4–7 min (98MI2).

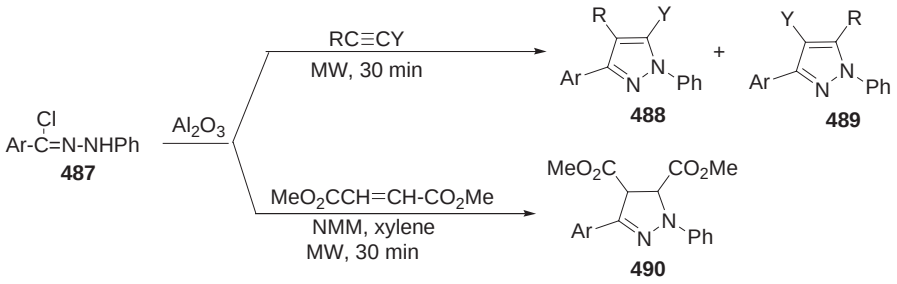
Trapping the 1,3-dipoles generated *in situ* from hydrazonyl chlorides **487** with various alkynes without solvent under MWI using a monomode reactor over 30 min gave pyrazole cycloadducts **488** and **489** in 40–60% yields. However, compound **487** reacted with a variety of alkenes in the presence of *N*-methylmorpholine (NMM) in xylene at 130 °C during 30 min under MWI to give **490** in better yields (55–85%) (Scheme 124) (99JCR(S)718).

Under MWI, 4- and 5-pyrazolyl hydrazones **491** reacted with electron-poor dipolarophiles within 10–45 min either at atmospheric pressure in a focused MW reactor or in closed Teflon tubes in a domestic oven to give [4,3′] or [5,3′] bipyrazolyl adducts **493–496** in 22–84% yields (Scheme 125). The MWI produces the thermal isomerization of **491** to the corresponding azomethine imines **492** that undergoes 1,3-dipolar cycloaddition with double- or triple-bonded dipolarophiles (98T13167). These cycloadditions need prolonged heating and vigorous conditions and several dipolarophiles do not react under classical heating (87CSR89).

The reaction of nitrile imines **498**, generated by the action of triethylamine on hydrazonyl chlorides **497**, with enaminones **499** in dry benzene required a reflux for 8 h to afford the pyrazole derivatives **500** in 69–82% yields. MWI was used to facilitate this cycloaddition and also to prepare the 1,3-dipole *in situ*. Thus, a mixture of **497** and **499** in the presence of triethylamine was irradiated in a domestic MW oven for 10 min to give **500** in improved yields (90–95%) (Scheme 126) (04JCR(S)174).

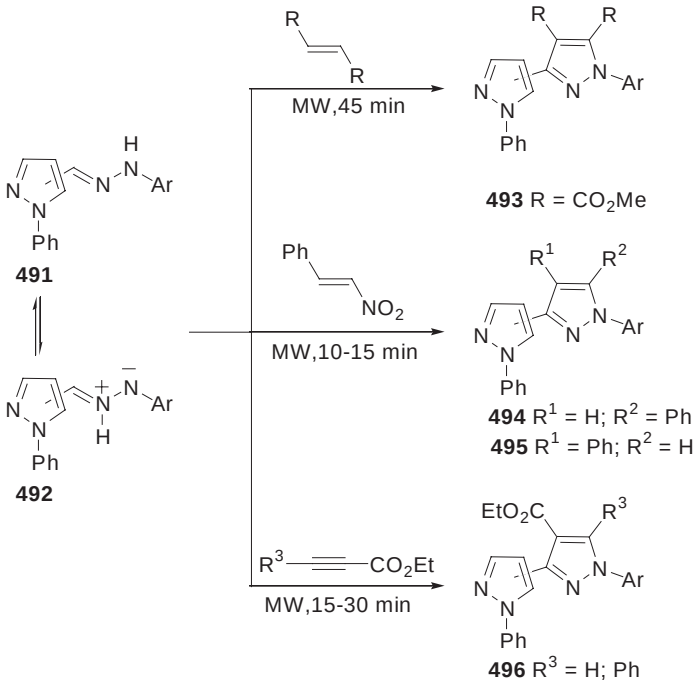


Scheme 123

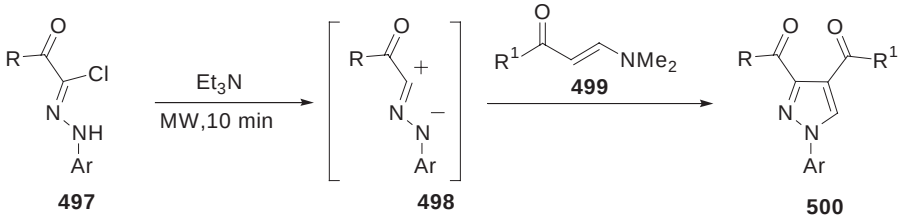


Scheme 124

The design of novel organic molecules containing electron donor (D) and electron acceptor (A) moieties constitutes a promising field due to their interesting optical and electronic properties. When the *p*-substituted phenylhydrazones **501** reacted with [60]fullerene in *o*-dichlorobenzene or trichlorobenzene solvent under MWI, adduct **502a** formed in 6% yield. Only traces of **502b** were detected and **502c** was not formed at all. On the other hand, when nitrile imines **503**, generated *in situ* from the cor-



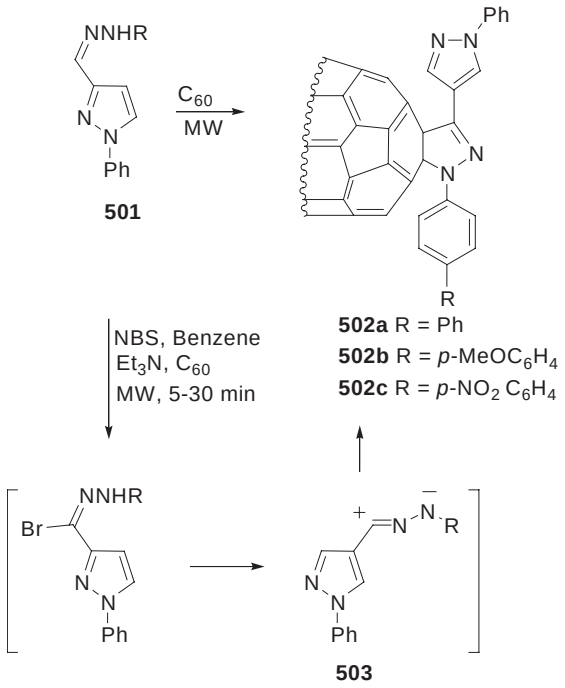
Scheme 125



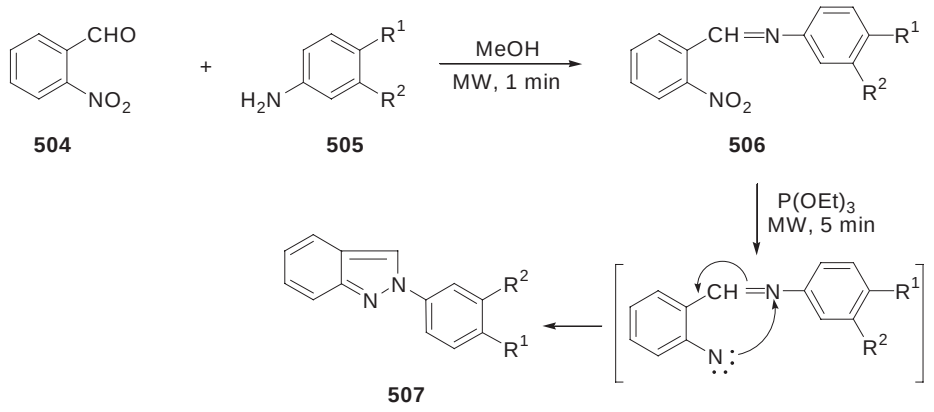
Scheme 126

responding hydrazone **501** by the action of NBS in the presence of Et_3N, reacted with C_{60} under MWI compounds **502a–c** formed in 20–38% yields (Scheme 127). The magnitude of low field shift in the ^{1}H-NMR of the donor unit when linked to C_{60} provided direct information for charge-transfer (CT) interactions between the donor moiety and the [60] fullerene acceptor. Intramolecular CT interactions were possible with both the N-phenyl and C-pyrazolyl groups (99TL1587).

A relatively few examples of indazoles have been prepared under MWI. Thus, the Schiff base **506** was obtained in 84% yield when a mixture of *o*-nitrobenzaldehyde **504** and *p*-anisidine **505** in methanol was irradiated by MW for about 1 min in an open flask. It was deoxygenated using triethyl phosphite under MWI for about 5 min



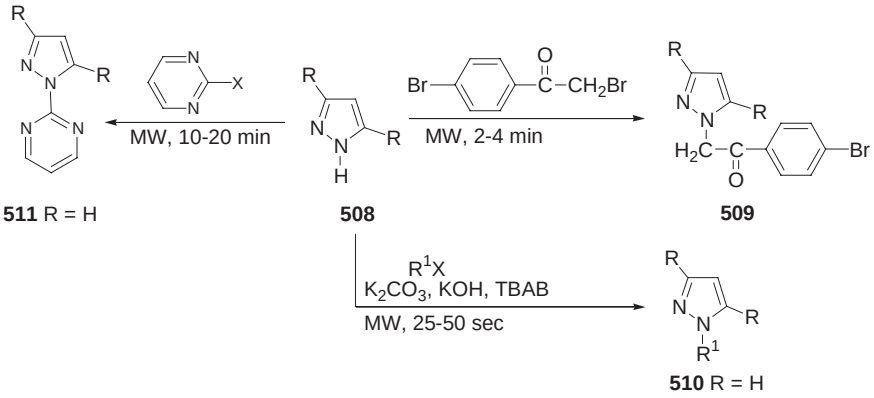
Scheme 127



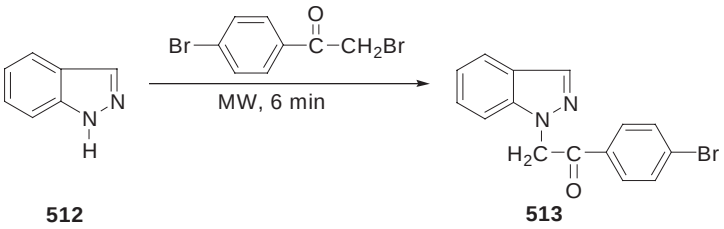
Scheme 128

to give indazoles **507** in 82% yield (Scheme 128). Under conventional conditions, the reaction required several hours of heating under argon and the yield was about 70% (02S1578).

N-alkylation of pyrazoles **508** with *p*-bromophenacyl bromide under MWI in solvent-free conditions gave only the *N*−1 alkylated products **509** in ⩾98% yield



Scheme 129



Scheme 130

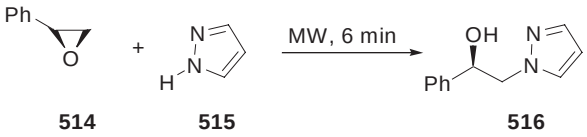
within 2–4 min. This could be a consequence of the absence of solvent that prevented a tautomeric equilibrium (96H539). Alkylation of **508** was also achieved under MWI using alkyl halides and K_2CO_3, KOH and TBAB to give the *N*-alkylated pyrazoles **510** in 61–89% yields (Scheme 129) (97H715).

2-(1*H*-pyrazol-1-yl)pyrimidines (**511**) were prepared by direct displacement of the pyrimidyl halide with pyrazole **508** by classical heating which required a long time and gave low yields. However, **508** with 2-chloro or 2-bromopyrimidine under MWI for 10–20 min in a focused monomode MW reactor afforded **511** in 67 and 75% yields, respectively (Scheme 129) (02T887).

Similarly, reaction of indazole **512** with *p*-bromophenacyl bromide under MWI and solvent-free conditions gave *N*−1 alkylated product **513** in 96% yield (Scheme 130) (96H539).

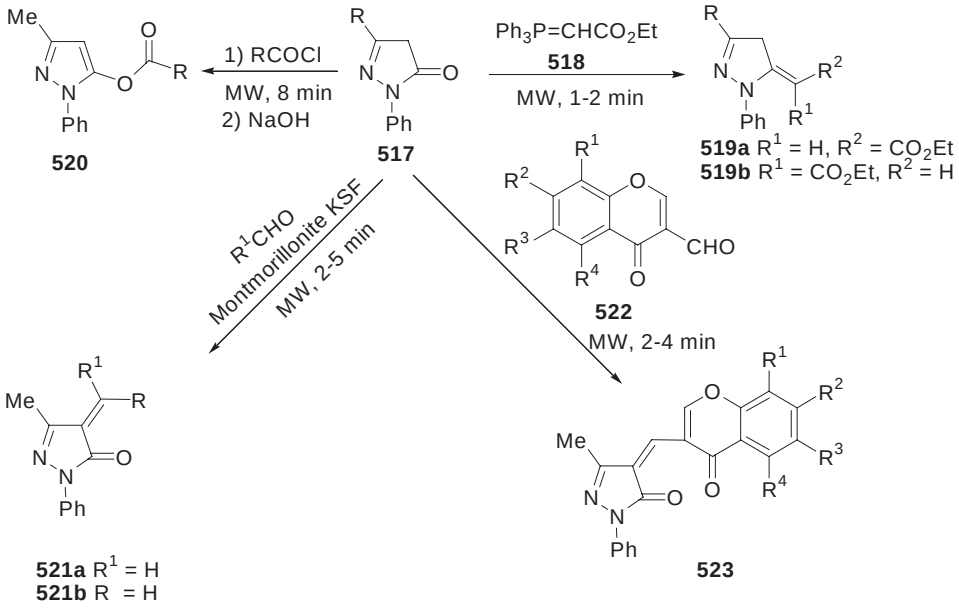
MW-assisted ring opening of (*R*)-styrene epoxide (**514**) with pyrazole (**515**) gave the corresponding (1*R*)-2-(1-pyrazolyl)-1-phenylethanol (**516**) in 88% yield. The reaction required a prolonged irradiation time (6 min) and high irradiation power (510 W) for complete conversion of the starting material (Scheme 131). The application of MW heating increased both the chemo- and regioselectivity compared to conventional heating methods (98TL5509).

Wittig olefination of carbonyl compounds has great importance in organic synthesis (65OR270), but carbonyl amide groups are not sufficiently reactive towards



514 **515** **516**

Scheme 131



520

517

519a R^1 = H, R^2 = CO_2Et
519b R^1 = CO_2Et, R^2 = H

522

521a R^1 = H
521b R = H

523

Scheme 132

phosphoranes to undergo Wittig reactions as compared with aldehydes and ketones. However, under MW conditions, a remarkable rate enhancement and drastic reduction of reaction time were observed. Thus, pyrazolone derivatives **517** and the two carbon-stable yilde, ethoxycarbonylmethylene(triphenyl)phosphorane (**518**), were mixed in 1:1.2 ratio and heated to 90 °C in a MW oven to give a mixture of isomers **519a** and **519b** in 80–86% yields after irradiation for 1–2 min (Scheme 132) (99TL165).

Under normal conditions, acylation of 1-phenyl-3-methylpyrazole-5-one (**517**) (R = Me) with one equivalent of acid chlorides or anhydrides in the presence of calcium hydroxide in ethanol or dioxane gave the respective 4-acyl derivatives (59ACSA1668, 81IZV118, 83MI1, 97MI2). The 4-acyl-5-acyloxypyrazoles were obtained with 2 mol of acid chlorides in ethyl ether, whereas in the absence of solvent, 5-acyloxypyrazoles were obtained (81IZV118). When a mixture of **517** and acid chlorides in absence of solvent was irradiated for 8 min in a MW oven followed by decomposition of the unreacted acid chloride, 5-acyloxypyrazoles **520** were obtained in 37–87% yields, depending on the substituent in the acid chloride (Scheme 132) (02SC2549).

The condensation of **517** (R = Me) with arylcarboxaldehyde in presence of acidic KSF clay without solvent under MWI gave a mixture of *Z* and *E* isomers of 1-phenyl-3-methyl-4-(arylmethylene)-5-pyrazolones **521a** and **521b** in 71–92% yields (Scheme 132). Generally, the *Z* isomer was preferred as deduced by their ^{1}H-MNR spectra on the basis of the chemical shift of the methyl group (90SC3213).

Condensation of **517** (R = Me) with 4-oxo-(4H)-1-benzopyran-3-carboxaldehydes (**522**) on an alumina support under solvent-free conditions and MWI within 2–4 min afforded 3-methyl-4-[(chromon-3-yl)methylene]-1-phenyl pyrazolin-5-(4H)-one (**523**) in 59–87% yields. The efficiency of this dry reaction was evaluated by a comparison with the same reaction in refluxing dioxane using a catalytic amount of triethylamine that required 45 min. The yields were lower (48–80%) (Scheme 132) (02SC497).

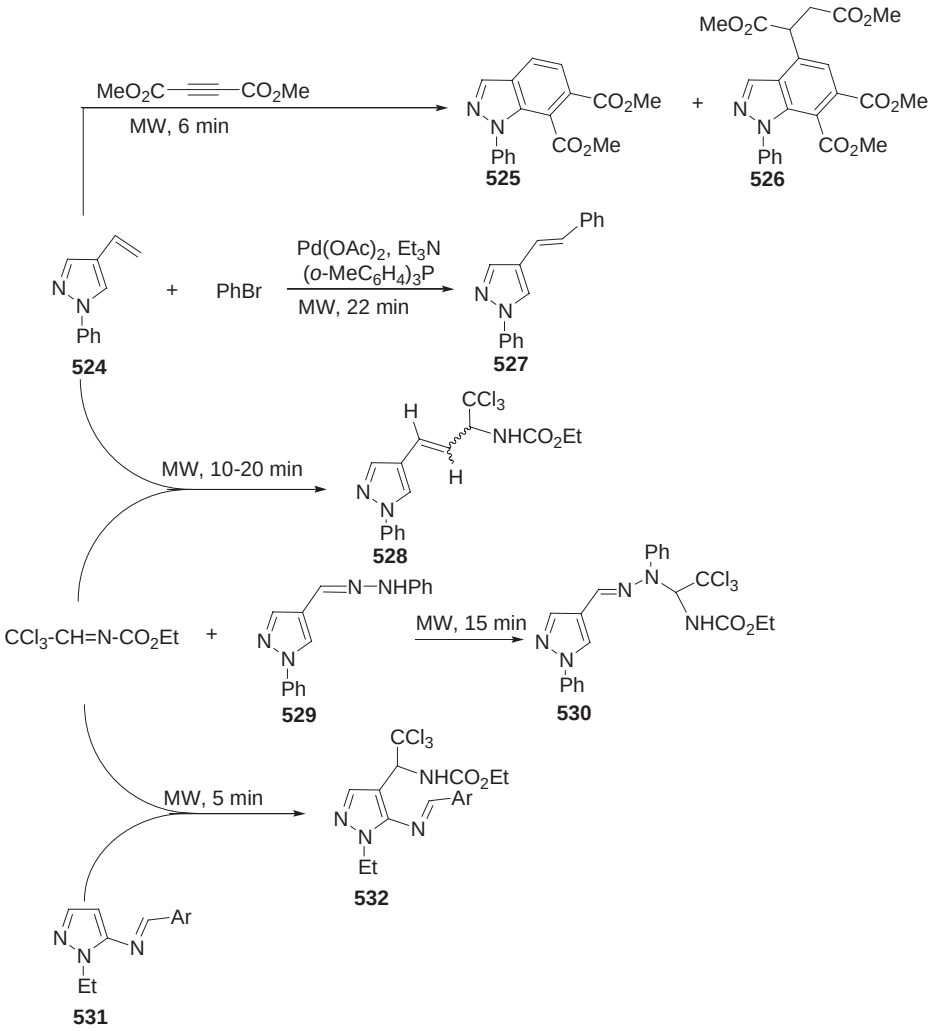
Cycloaddition of **524** with dimethyl acetylenedicarboxylate (DMAD) under MWI gave indazoles **525** and **526** within 6 min in 10 and 62% yields, respectively (96T9237). Palladium-catalyzed reaction of bromobenzene with 1-phenyl-4-vinyl-pyrazole (**524**) can be carried out under MWI in the absence of solvent in 22 min to give **527** in 78% instead of 39% yield obtained by classical heating (97SL269).

The reaction of vinylpyrazole **524** with ethyl-*N*-trichloroethylidenecarbamate was conducted under focused MW within 10–20 min in solvent-free conditions. The reaction took place by an electrophilic substitution of the exocyclic double bond that was activated by conjugation with the pyrazole ring. The 1-phenyl-4-vinylpyrazole gave the *trans* and *cis* isomers **528** in 70 and 15% yield, respectively (Scheme 133). The thermodynamic *trans* isomers were the only products (22–31%) in the reaction of 3- and 5-vinylpyrazoles. Under conventional heating in an oil bath no reaction occurred under similar conditions of temperature and time. Reaction of the pyrazolylhydrazone **529** with ethyl-*N*-trichloroethylidenecarbamate produced **530** (41%) as a result of the Michael addition to the conjugated imine through the NH group. Pyrazolylimine **531** reacted with ethyl-*N*-trichloroethylidenecarbamate by an electrophilic substitution at the activated 4-position of the pyrazole ring to give **532** (58%) (Scheme 133); under conventional heating decomposition of the starting material took place (99T9623).

5. *1,3-Diazoles (Imidazoles and Benzimidazoles)*

Irradiation of a mixture of the acyloin and urea in a MW oven for 3–5 min followed by removal of the excess urea on washing with water gave 4,5-disubstituted-4-imidazolin-2-ones **533** in 30–80% yields (Scheme 134). The typical conditions involved the reflux of a mixture of the acyloin and urea in a solvent with an acid catalyst for 1–6 h (97OPP687).

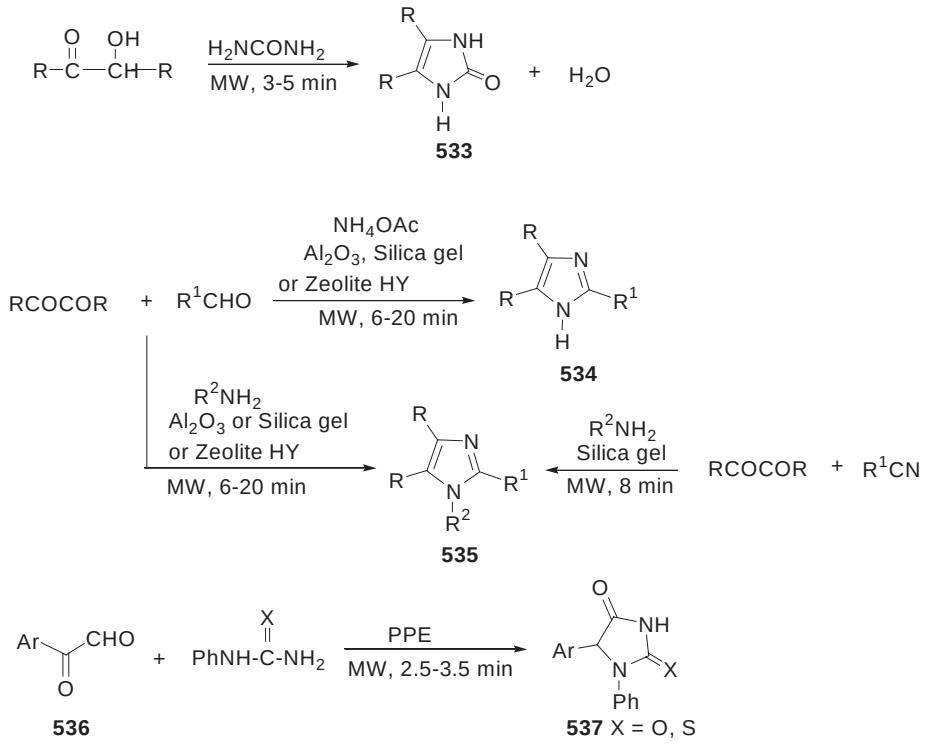
Imidazoles **534** and **535** were obtained in 67–82% yields by the condensation of a 1,2-dicarbonyl compound with an aldehyde in the absence and presence of an amine, respectively, using acidic alumina impregnated with ammonium acetate as the solid support under MWI for 20 min (00TL5031). The three-component condensation of benzil, benzaldehyde derivatives and ammonium acetate catalyzed by zeolite HY or silica gel was also carried out under MWI to give **534** (R^2 = Ph) within only 6 min. The best yields were achieved with zeolite HY (80–94%) (00M945). In the classical approach, this condensation required long times (1.5–10 h) and refluxing in HOAc



Scheme 133

under an inert atmosphere (00M945). When the same reaction was carried out in the presence of primary amines, tetrasubstituted imidazoles **535** were obtained in 42–91% yields (Scheme 134). However, the yields with zeolite HY were lower than with silica gel because the acidic Brönsted sites were neutralized by amine base. Excess zeolite HY was necessary (00MI6). On the other hand, compounds **535** were also prepared in 58–92% yields by MWI of a mixture of benzyl, arylnitriles and primary amines in the presence of silica gel catalyst (03TL1709).

2,4,5-Trisubstituted imidazoles **534** were prepared in 76–99% yields from 1,2-diketones and aldehydes in the presence of ammonium acetate and acetic acid by MWI for 5 min (04OL1453). Alkylation of **534** ($R = R^1 = Me$) with benzyl

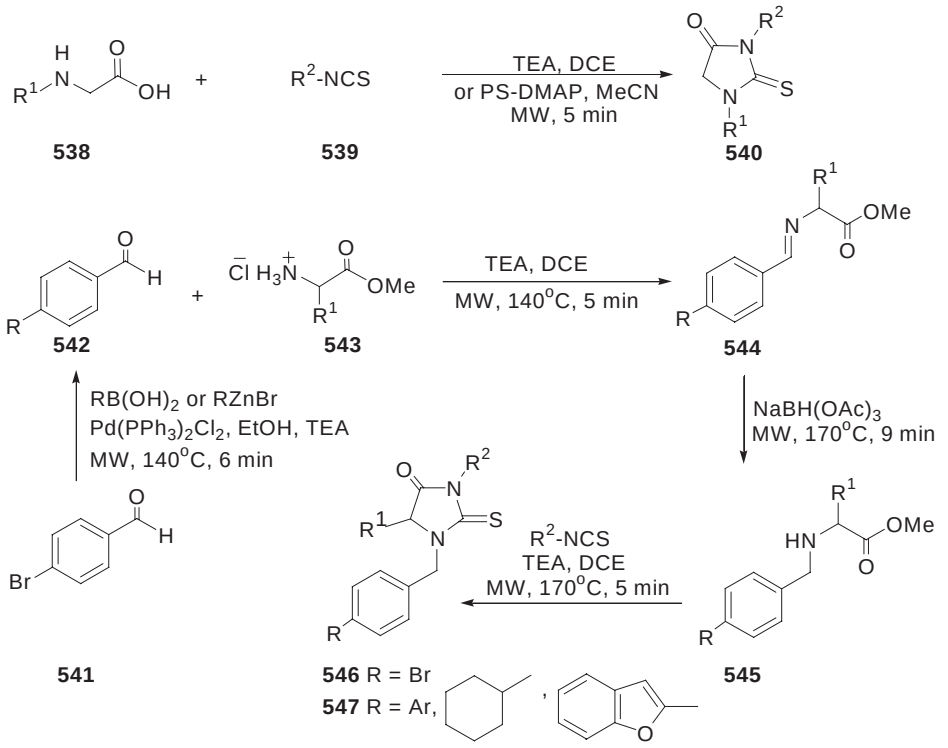


Scheme 134

chloride in the presence of triethylamine base and acetonitrile solvent was also carried out under MWI (5 min) to give the respective *N*-benzyl derivative in 93% yield (04OL1453).

Hydantoins and thiohydantoins were prepared under MWI starting with arylglyoxals **536** that were prepared in 68–81% yields from acetophenones either by using SeO_2/dioxane or SeO_2/SiO_2 under MWI for 7–10 min. Subsequent irradiation of a mixture of **536** and phenyl urea or thiourea in the presence of polyphosphoric ester (PPE) as a reaction mediator gave 1,5-disubstituted hydantoins **537** in 81–95% yields (Scheme 134). Lower yields were obtained under conventional thermal conditions (02S75).

The cyclization of *N*-aryl and *N*-alkyl amino acids **538** with isothiocynates **539** under MWI gave thiohydantoins **540** within 5 min in high yield (56–91%) and purity when using polystyrene-bound dimethylaminopyridine (PS-DMAP) or triethylamine (TEA) base; the PS-DMAP gave a slightly lower yield compared to TEA. On the other hand, *p*-bromobenzaldehyde **541** was treated with amino acid ester hydrochloride **543** together with TEA at 140 °C for 5 min under MWI in 1,2-dichloroethane (DCE) to form the imine **544**. Further heating of **544** with $NaBH(OAc)_3$ for 9 min gave the *N*-benzylated amino acid ester **545**. Subsequent reaction of **545** with the isothiocyanate and TEA by heating for another 5 min gave the *N*-(*p*-bromo)benzylated thiohydantoins **546** in 57–94% yields. A carbon–carbon coupling reaction

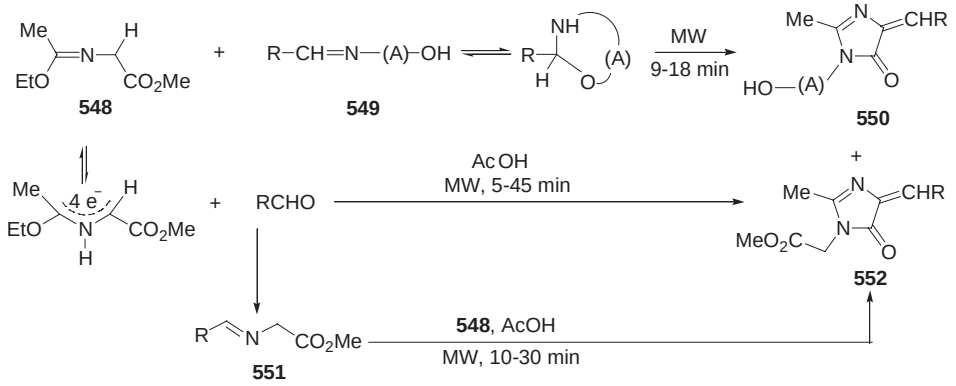


Scheme 135

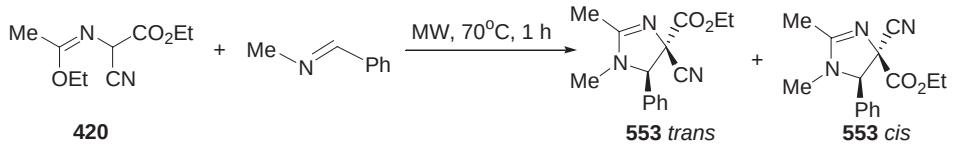
between *p*-bromobenzaldehyde **541** and boronic acid $RB(OH)_2$ or organozinc bromide RZnBr gave **542** that underwent reductive amination and finally cyclization, presenting a method suitable for the synthesis of a number of thiohydantoins **547** in 30–70% yields (Scheme 135). The theoretical number of possible compounds attainable with this approach is very large, based on commercially available starting materials (01SL1893).

1,3-Dipolar cycloaddition reactions of imidate **548** with iminoalcohols **549** were carried out at 70 °C without solvent. ^{1}H-NMR analysis of the crude product indicated the formation of imidazolone **550** as a major component together with by-product **552**. An acceleration of the cycloaddition and yield enhancements of imidazolones **550** (65–85%) were achieved by irradiating equimolar mixture of **548** and **549** in a Maxidigest MX 350 prolabo MW reactor for 9–18 min at 45–180 W (Scheme 136). The chemical reactivity in this cycloaddition was analyzed according to frontier molecular orbital (FMO) theory (95T6757). 4-Alkylidene-1*H*-imidazol-5(4*H*)-ones **552** were obtained in good to excellent yields (71–98%) by 1,3-dipolar cycloaddition of imidate **548**, aldehydes and acetic acid catalyst under solvent-free conditions using MWI (Scheme 136). They were also obtained from **548** and aldimines **551** as dipolarophiles under microwave (97S287) conditions.

The addition of imidate **420** to commercially available *N*-benzylidenemethylamine as a dipolarophile without solvent at 70 °C in an oil bath or under focused MWI gave



Scheme 136

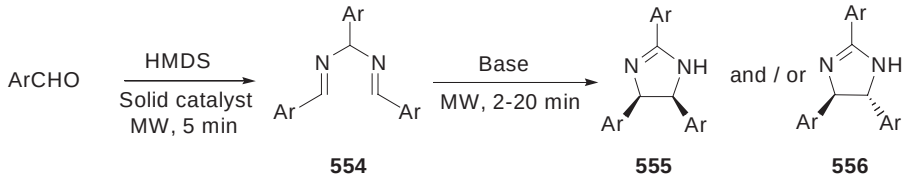


Scheme 137

ethyl 4-cyano-2-methyl-5-phenyl-2-imidazoline-4-carboxylate (**553**) in 91% yields. ^{1}H-NMR analysis of the crude mixture showed the presence of two diastereoisomers, *trans*/*cis* (85/15) (Scheme 137). Focused MWI reduced the time from 3 to 1 h (00MI5).

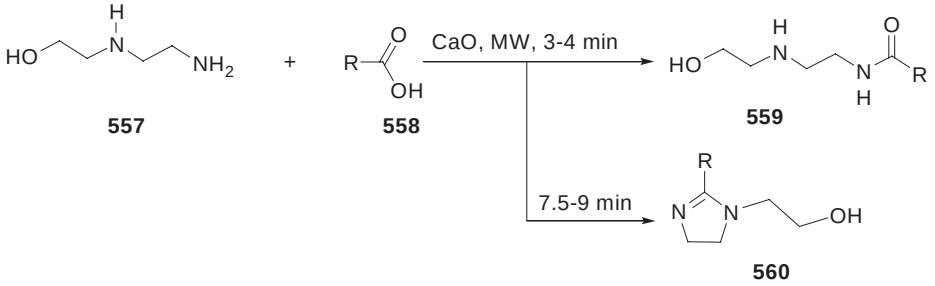
MWI of a mixture of benzaldehyde (Ar = Ph) and hexamethyldisilazane (HMDS) in the presence of a solid catalyst such as silica gel for 5 min afforded **554** (Ar = Ph) in 79% yield; higher yields (89–94%) were achieved on addition of a small amount of alumina. On the other hand, bentonite and montmorillonite K_{10} afforded lower yields (26–45%) of **554**. Irradiation of **554** for 5 min with NaOMe in methanol gave *cis*-imidazoline **555** (Ar = Ph) in 55% yield, but with one equivalent of *t*-BuOK in *t*-BuOH, *trans*-imidazoline **556** (Ar = Ph) was obtained exclusively after 5 min. Other bases such as DBN or DBU afforded **555** and/or **556** depending on the amount of base and irradiation time. In a one-pot synthesis, a mixture of benzaldehyde, HMDS, alumina and one equivalent of DBN or DBU was irradiated for 10 min to give the *cis*-imidazoline **555** (Ar = Ph) in 85% yield (Scheme 138). Under similar conditions, substituted benzaldehydes afforded **555** in high yields (82–86%) (03SL1117).

The general procedure to synthesize long-chain 2-alkyl-1-(2-hydroxyethyl)-2-imidazolines **560** and their amide precursors **559** involved dehydration between aminoethylethanolamine (**557**) and fatty acids **558** at high temperatures and long times. However, efficient preparation of **559** and **560**, through the condensation of **557** and **558** under solvent-free conditions using CaO as support in both a domestic MW and a monomode MW oven took place within 3–9 min (Scheme 139). The



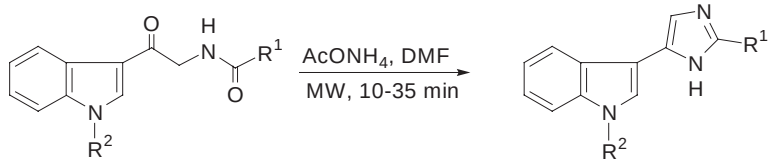
554 555 556

Scheme 138



557 558 559 560

Scheme 139



561 562

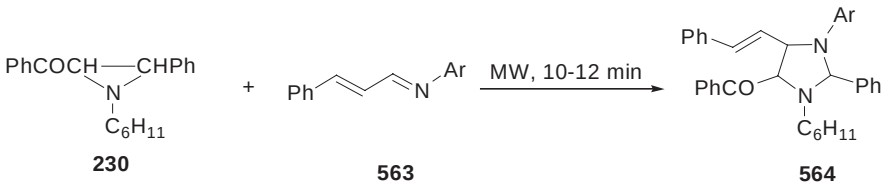
Scheme 140

products were obtained with high purity (>95%) and yield (90–98%), greater than those obtained by thermal heating (03SL1847).

Conversion of ketoamides **561** into the corresponding 2,4-disubstituted imidazoles **562** was carried out by classical heating with ammonium acetate in DMF solvent at 130 °C for 12–16 h. However, optimal conditions for the synthesis of **562** (50–75%) were found to be 10–35 min under MWI. Thus, the ketoamide **561** (R^1 = 3-indolyl; R^2 = H) provided the antifungal nortopsentin D **562** under MWI in a higher yield (75%) than that (25%) obtained under conventional heating (Scheme 140). Only the 2-(4-pyridyl) derivative **562** (R^1 = 4-pyridyl; R^2 = H) was obtained under MWI in a lower yield than the classical heating (01SL218).

2-Benzoyl-1-cyclohexyl-3-phenylaziridine (**230**) with cinnamylideneaniline (**563**) under MWI without solvent gave the imidazolidine derivatives **564** in 70–75% yield (Scheme 141) (96TL4203).

Benzimidazoles are generally prepared by the condensation of *o*-phenylenediamine with organic acids employing hydrochloric acid (53ZOB957), polyphosphoric acid (57JA427), boric acid (62ZOB2624) or *p*-toluene sulphonic acid (80MI1) as catalyst.



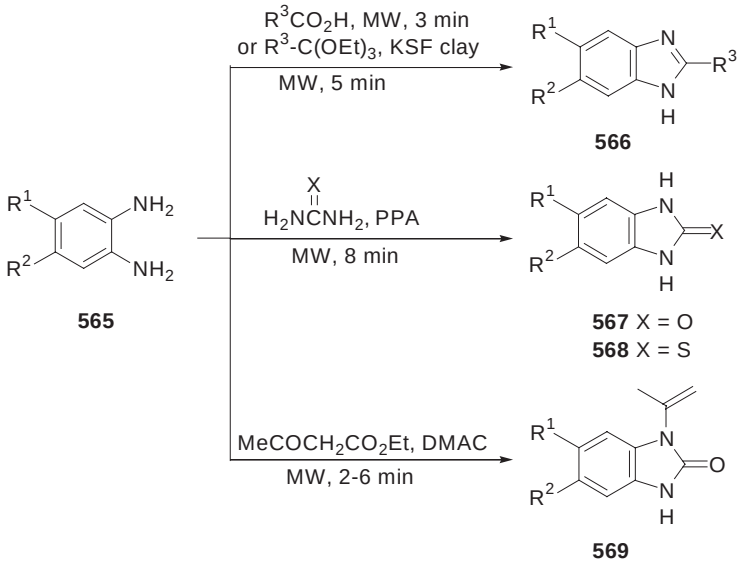
Scheme 141

These reactions are often carried out under high pressure and require long times. Several improved procedures have been reported (83IJC(B)917, 00S1380, 00SC2191).

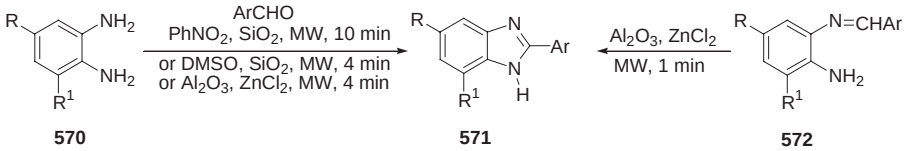
Formic acid served as both the reagent and the reaction medium for the conversion of *o*-diaminobenzene (**565**) to benzimidazole (**566**) ($R^1 = R^2 = H$) in 79% yield by conventional heating for 3 h, but only 3 min were required to achieve this reaction under MWI in a comparable yield (90H741). MWI of a mixture of *o*-phenylenediamine **565** and dicarboxylic acids in the presence of polyphosphoric acid for 10 min afforded a series of bis(2-benzimidazolyl)alkanes in 85–94% yields (01MI6). Cyclocondensation of *N*-(carbotrifluoromethyl)-*o*-arylenediamines on montmorillonite K_{10} in dry media under MWI within 2 min in a domestic oven gave a series of 2-triluoromethylbenzimidazoles **566** ($R^3 = CF_3$) in good yields (75–96%) (01T163). In conventional heating, this cyclocondensation was not observed under the same conditions.

The reaction of **565** with *ortho* esters can be catalyzed by KSF clay without solvent under MWI to give **566** rapidly in good yields (96SC2895). The use of mineral supports or fusion in dry media under MWI was also described. Thus, reaction of **565** with benzaldoximes using $Ca(OCl)_2/Al_2O_3$ or with aromatic aldehydes using MnO_2/SiO_2 in a monomode Synthewave 402 reactor furnished **566** ($R^3 = Ar$) in 75–94% yields. Fusion of **565** with 2-nitro or 4-fluorobenzoic acids under MWI gave **566** ($R^3 = Ar$) in 85 and 81% yields, respectively (Scheme 142) (98T8055). However, an efficient and practical route for the synthesis of benzimidazoles was achieved under MWI using polyphosphoric acid (PPA) catalyst. Thus, a mixture of *o*-phenyenediamine **565**, organic acid and PPA was irradiated in a household MW oven for 6–8 min to give 2-substituted benzimidazoles **566** in 39–88% yields. Under similar conditions, **565** with urea or thiourea in presence of PPA under MWI gave 2-benzimidazol-2-one **567** (86%) and 2-benzimidazol-2-thione **568** (71%), respectively (Scheme 142) (02SC3703).

The condensation of **565** with urea in a mixture of *N*,*N*-dimethylacetamide (DMAC) and diethylene glycol (DEG) solvent resulted in the rapid formation of benzimidazolin-2-ones **567** in high yields (88–94%) when subjected to MWI (96JCR(S)92). Condensation of **565** with ethyl acetoacetate or benzoyl acetoacetate in dry media using a catalytic acidic support such as montmorillonite KSF and bentonite K_{10} under MWI for 4 min in a domestic oven gave benzimidazoles **566** (R^3 = Me, Ph) in 75–96% yields (95TL3683). Condensation of **565** with ethyl acetoacetate in DMAC under MWI efficiently produced *N*-(α-methyl vinyl)benzimidazolin-2-ones **569** in 76–81% yields (96JCR(S)92).



Scheme 142

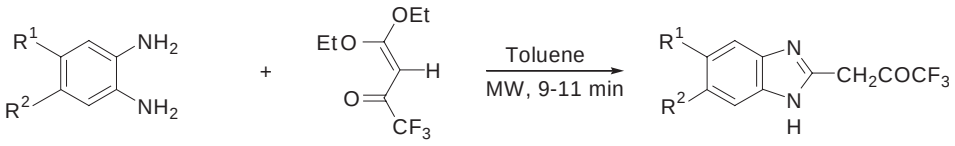


Scheme 143

The oxidative heterocyclization of *o*-phenylenediamine **570** with aldehydes in the presence of nitrobenzene or dimethylsulfoxide impregnated on silica gel was carried out under MWI for 4–10 min to give benzimidazoles **571** in 69–97% yields. When UV irradiation was used as an energy source, lower yields (12–28%) were obtained within 10 min (98TL4481).

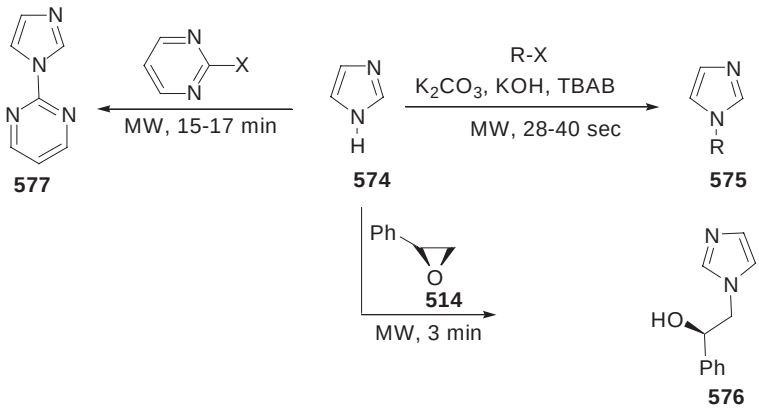
The condensation of 3-nitro-5-trifluoromethyl-*o*-phenylenediamine (**570**) with aromatic aldehydes in the presence of a catalytic amount of anhydrous zinc chloride adsorbed on alumina under MWI for 4 min in a domestic oven gave 2-aryl-5-trifluoromethyl-7-nitrobenzimidazoles **571** in 72–90% yields. The thermal heating required 2 h and gave 62–80% yields. Alternatively, Schiff's base **572** and anhydrous zinc chloride are adsorbed on alumina and heated for 1 min in a MW oven to give the corresponding 2-arylbenzimidazoles **571**. Thus, the formation of **571** from **570** involves the initial formation of a Schiff's base followed by cyclization (Scheme 143) (02SC2467).

Condensation of *o*-phenylenediamines **565** with trifluoroacetyl ketene diethyl acetal (**441**) in toluene under MWI in 980 W multimode reactor gave 2-trifluoroacetonyl benzimidazoles **573** in 86–92% yields (Scheme 144) (97T5847).

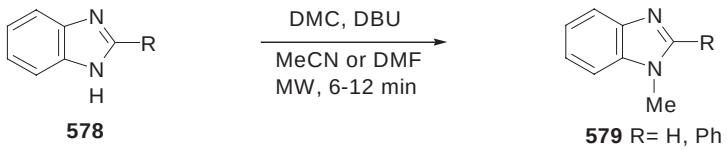


565 441 573

Scheme 144



Scheme 145



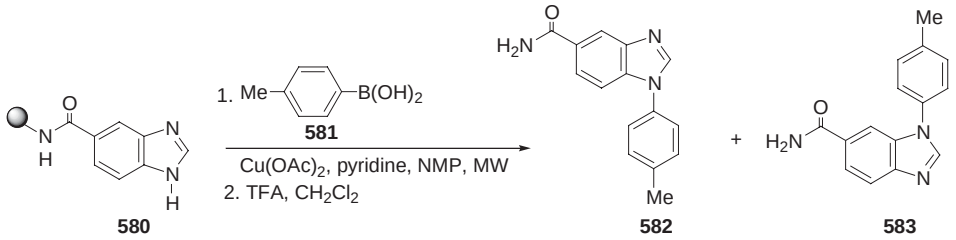
Scheme 146

Under MWI, imidazole (**574**) reacted remarkably fast with alkyl halides to give exclusively *N*-alkylated imidazoles **575** (73–89%) (Scheme 145) (97H715).

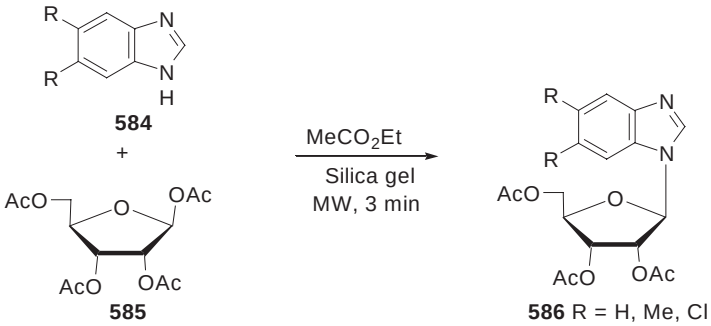
Heating a 1:1 mixture of imidazole (**574**) and (*R*)-styrene epoxide (**514**) in a pressure tube for 3 min in a MW oven gave (1*R*)-2-(1-imidazolyl)-1-phenylethanol (**576**) in about 90% yield (Scheme 145) (98TL5509). The nucleophilic substitution reaction of 2-chloropyrimidine with **574** by MWI without solvent gave 2-(1*H*-imidazol-1-yl)pyrimidine (**577**) in 62% yield. However, 2-bromopyrimidine was more reactive leading to a better yield of **577** (88%) (Scheme 145) (02T887).

Methylation of benzimidazoles **578** with DMC in the presence of DBU catalyst and acetonitrile or DMF solvent under MWI gave **579** in 6–12 min and 96–97% yields (Scheme 146). A rate acceleration up to a 30-fold was observed when MW conditions were employed in comparison to thermal heating (01OL4279).

Benzimidazole-5-carboxylic acid was coupled to polystyrene–polyethyleneglycol (PS–PEG) resin (PAL linker) to afford benzimidazole derivative **580**. Reaction of



Scheme 147

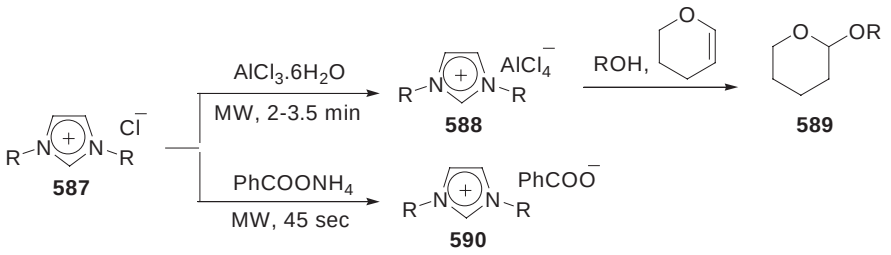


Scheme 148

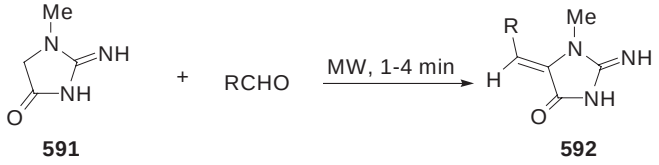
580 with *p*-tolyl boronic acid (**581**) and $Cu(OAc)_2$ in pyridine and *N*-methylpyrrolidinone (NMP) base and solvent at 80 °C for 48 h gave, after cleavage from the resin, a 30% yield of **582** and **583**. The irradiation of this mixture in a domestic MW oven and then cleavage gave the same products in 56% yield and 69% purity in less than 5 min (Scheme 147) (99TL1623).

The use of MWI in the chemistry of nucleosides, nucleotides and nucleic acids is extremely scarce. Benzimidazoles (**584**) reacted with 1,2,3,5-tetra-*O*-acetyl-*β*-D-ribofuranose (**585**) under MWI for 3 min at 350 W in a domestic oven, and the resulting nucleosides **586** were isolated by flash chromatography. The best results were obtained by employing silica gel as the solid support to give **586** in 17–26% yields, but 40–71% of the unreacted bases were recovered (Scheme 148) (02MI5).

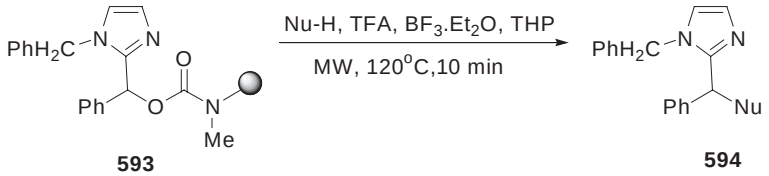
The use of ionic liquids such as dialkylimidazolium tetrachloroaluminates $[C_4MIM]AlCl_4$ **588** as recyclable catalysts, without much loss of activity, has been explored in the protection of alcohols as their tetrahydropyranyl(THP)ethers **589**. Moreover, they also catalyzed the deprotection of THP ethers to the alcohols by a reaction with excess methanol. MW heating provided a more uniform highly viscous medium on heating a mixture of alkylimidazolium chloride **587** and $AlCl_3$ till the solid $AlCl_3$ phase slowly disappeared, and a complete conversion then resulted in a clear single phase of pure products **588** in 100% yield (Scheme 149) (02MI6). The dialkylimidazolium tetrachloroaluminate **588** as a chloroaluminate melt was reported to be more complex than that reported above (02MI7).



Scheme 149



Scheme 150

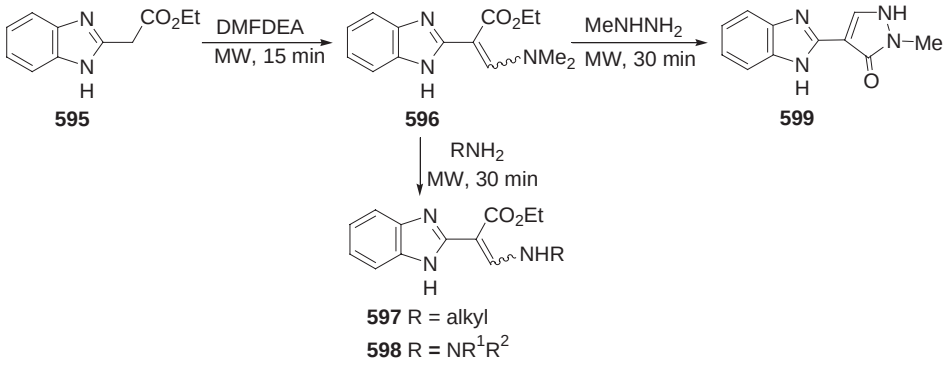


Scheme 151

Dialkyl imidazolium benzoates **590** at room temperature are liquids, non-volatile, odorless, recyclable, non-flammable and thermally stable. A number of these ionic liquids were used as good solvents and catalysts in the peracylation of several simple and sulfated carbohydrates (94JES73, 99JCS(D)2133). Recently, imidazolium chloride **587** was mixed with ammonium benzoate and the contents were microwaved in a test tube for 45 s to give dialkylimadazolium benzoate **590** in 86–87% yields (Scheme 149) (03SL1283). Similarly, 1,3-dialkylimidazolium tetrafluoroborates were prepared under MWI from **587** and ammonium tetrafluoroborate (02TL5381).

Creatnine or 2-imino-1-methylimidazol-4-one **591** is a polar molecule, thus adsorbing MW efficiently. It readily condensed with aldehydes under MWI without a catalyst or solvent to give good yields (77–93%) of **592** within 1–4 min (Scheme 150). The reaction was generally stereospecific and the major or the only isomer was the *Z* one (95SC3135).

Solvolysis reactions were found to be useful in the transformation of carbamates into various functionalized azole derivatives (01OL157, 02TL189). Thus, cleavage of resin-bound 2-substituted imidazole **593** with nucleophiles in the presence of trifluoroacetic acid (TFA) and boron trifluoride etherate catalyst in tetrahydropyran (THP) at 60 °C overnight gave the imidazole derivatives **594** (Scheme 151). MWI at 120 °C using the same equivalents of reagents as in the thermal reaction gave similar



Scheme 152

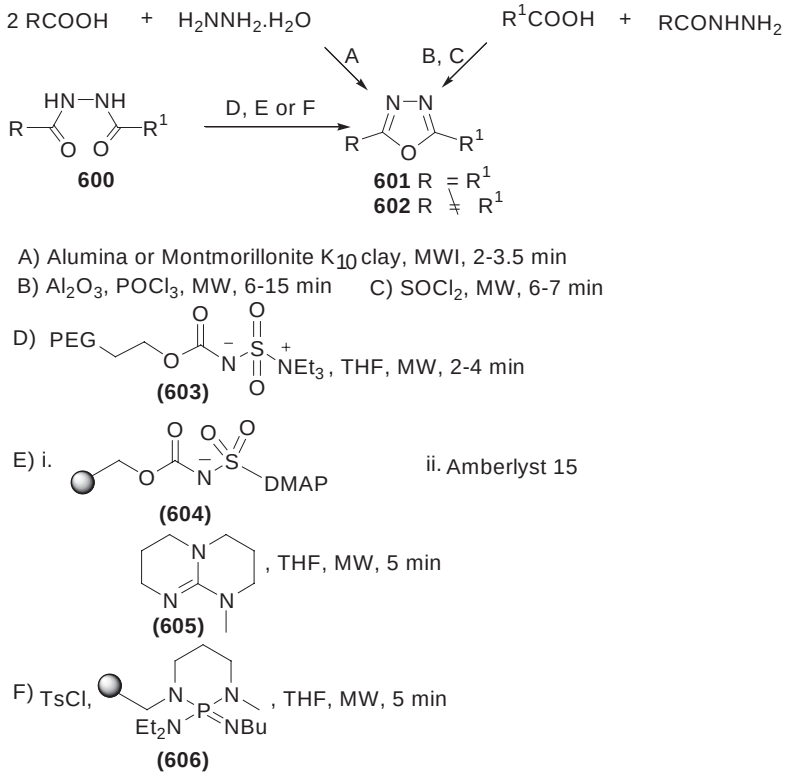
isolated yields (50–70%), but reactions were complete in only 10 min. Moreover, the purity as measured by LC/MS of the crude products was consistently improved under MW-assisted conditions compared to that of the thermal reaction (02OL4017).

New α-hetero-β-enamino esters **597** were obtained in 94–98% yields from ethyl 3-dimethylamino acrylate **596** and various volatile amines using solvent-free conditions assisted by focused MWI. Compounds **597** adopted the (*E*)-s-*cis*/*trans* configuration, stabilized by hydrogen bonding as indicated by a strong downfield shift of the imino group on C-3 (Scheme 152) (98TL8453). Under similar conditions, α-hetero-β-hydrazine acrylates **598** were prepared in 95% yield from **596** and a variety of hydrazines. *N*-methylhydrazine with 3-dimethylamino acrylate **596** without solvent under MWI afforded cyclized **599** in 96% yield (Scheme 152). The mechanism was believed to be an aza-annulation after the successive loss of dimethylamine and ethanol (98S967, 01S581).

C. Heterocycles with Three Heteroatoms

1. *Oxadiazoles*

The synthesis of 2,5-disubstituted 1,3,4-oxadiazoles **601** from acids and hydrazine hydrate using acidic alumina or montmorillonite K_{10} clay as solid supports under MWI for 2–3.5 min was reported (03OPP426). Unsymmetrical 1,3,4-oxadiazoles **602** were also obtained by reacting benzhydrazide with carboxylic acids under the same conditions. The products were obtained in good yields (84–89%) even for those normally obtained in low yields by conventional heating, including oxadiazoles derived from heterocyclic or *o*-substituted phenyl derivatives. A number of commercially available hydrazides were treated with different carboxylic acids in the presence of phosphorous oxychloride and alumina under MWI in a domestic oven for 6–15 min to give **602** in 81–96% yields (Scheme 153). Conventionally, syntheses of this class of compounds have been achieved in 4–9 h with lower yield (04MI2).



Scheme 153

MWI of hydrazides, aromatic acids and thionyl chloride for 6–7 min afforded 1,3,4-oxadiazoles **602** in 75–80% yields (97IJC(B)175). The aryloxyacetic acid hydrazides, as precursors for oxadizoles, were prepared in 90–99% yields by irradiating methylaryloxyacetates with hydrazine hydrate in a MW oven for 1 min (04SC377).

The cyclodehydration of 1,2-diacylhydrazines **600** in the synthesis of 1,3,4-oxadiazoles **602** involved strong reagents such as $SOCl_2$, $POCl_3$, polyphosphoric acid or sulfuric acid. The application of polymer-supported reagents is particularly attractive since the need for tedious work-up and purification procedures is eliminated (00JCS(P1)3815). The cyclodehydration of 1,2-dibenzoylhydrazine **600** with polymer-supported Burgess reagent **603** in THF at reflux for 3 h led to a 40% conversion into 2,5-diphenyl-1,3,4-oxadiazole (**601**) ($R = R^1 = Ph$) (Scheme 153). When the reaction was carried out under MW conditions, the oxadiazole was isolated in 96% yield and 91% purity by HPLC. The method was extended to a series of 1,2-diacylhydrazines to give 1,3,4-oxadiazoles **601** or **602** in 70–96% yields (99TL3275).

The use of polystyrene-supported Burgess reagent **604** in the synthesis of **601** or **602** provides an advantage over the PEG reagent, whereby clean products are obtained simply by filtration of the reagent from the mixture. Treatment of 1,2-dibenzoylhydrazine with **604** in refluxing THF gave clean conversion into the

oxadiazole **601** (R = R^1 = Ph), although the reaction was incomplete after 18 h (20% conversion, LC/MS). However, under MWI, it was formed (60% conversion) after 20 min. A basic additive such as guanidine base **605** provided a dramatic increase in the rate of cyclization by deprotonating the hydrazide NH; the reaction was complete after 4 h under thermal conditions and after 5 min under MWI. In each case, the crude reaction mixture was simply shaken with Amberlyst 15 to remove **605** and DMAP, producing **601** (R = R^1 = Ph) in a quantitative yield. The MWI procedure was found to be successful for the synthesis of a number of 1,3,4-oxadiazoles **601** and **602** in 53–100% yields (Scheme 153) (01SL382).

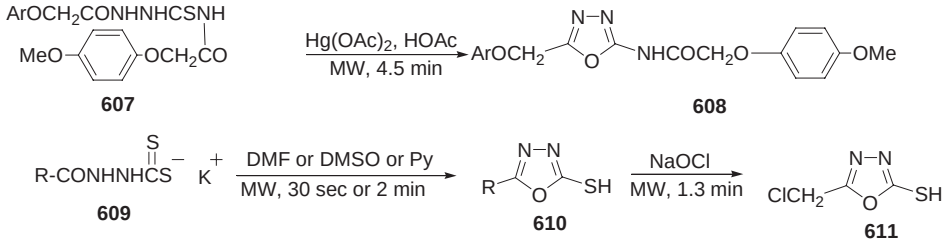
The cyclization of **600** using tosyl chloride and polymer-bound phosphazene base **606** was achieved under both thermal (THF, reflux, 4 h), and MWI conditions (THF, 5 min), and no Amberlyst 15 washing was required (01SL382).

Although 2,5-disubstituted 1,3,4-oxadiazoles can be prepared from substituted thiosemicarbazides by conventional methods (96IJC(B)111, 96MI2, 95PJS402, 93IJC(B)1190), these methods always have to be performed at high temperature and the isolated yields were frequently low. However, 1-aryloxyacetyl-4-(4-methoxyphenyloxyacetyl)thiosemicarbazides **607** and mercuric acetate in a solution of glacial acetic acid gave on exposure to MWI for 4.5 min 2-(4-methoxyphenyloxyacetylamido)-5-aryloxymethyl-1,3,4-oxadiazoles (**608**) in excellent yields (86–91%) (Scheme 154) (02SC1097).

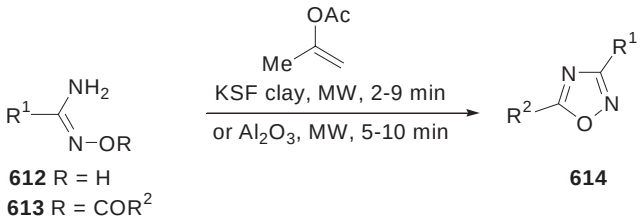
The synthesis of 5-substituted-2-mercapto-1,3,4-oxadiazoles **610** from acyldithiocarbazinate salts **609** seemed ideal for MW heating considering the polar nature of salt **609**. The reaction took 30 s using DMF or DMSO as solvent and 2 min in the case of pyridine, and the yields were satisfactory (69–84%) (Scheme 154). When classical heating was employed the conversion of **609** to **610** into pyridine, required 30 min for completion (02SC111).

Rapid chlorination of the side-chain methyl group of 2-mercapto-5-methyl-1,3,4-oxadiazole **610** (R = Me) was reported using sodium hypochlorite under MWI to give **611** in 95% yield (Scheme 154) (98JCR(S)586).

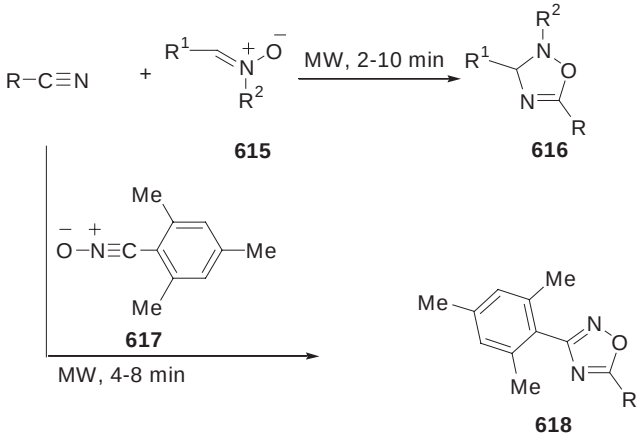
MWI of a mixture of oxime **612** and isopropenyl acetate adsorbed on KSF clay gave the 1,2,4-oxadiazole **614** (R^2 = Me) in 50–67% yields. The reaction was complete within 2–9 min. When compounds **613** were adsorbed on Al_2O_3 and subjected to MWI for 5–10 min, oxadiazoles **614** were obtained in 58–95% yields (Scheme 155) (95SC1451).



Scheme 154



Scheme 155

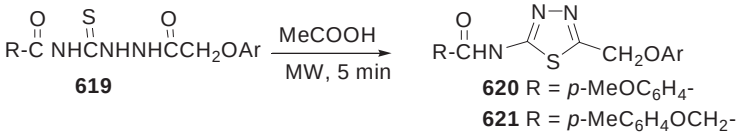


Scheme 156

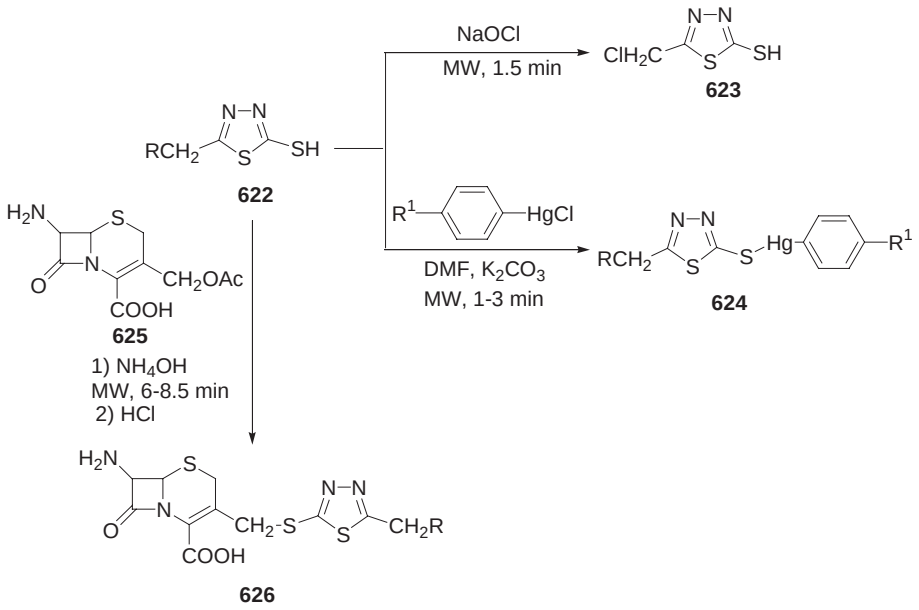
MWI induced the 1,3-dipolar cycloadditions of aliphatic and aromatic nitriles with nitrones **615** or nitrile oxides **617** under solvent-free conditions within 2–10 min to give the corresponding 2,3-dihydro-1,2,4-oxadiazoles **616** (29–91%) and 1,2,4-oxadiazoles **618** (29–98%), respectively (Scheme 156). Nitrile oxides are less stable than nitrones, but they are more reactive as 1,3-dipoles and their resulting 1,2,4-oxadiazoles adducts are more stable than their 2,3-dihydro-1,2,4-oxadiazoles. These facts could explain the good yields of the 1,2,4-oxadiazoles obtained from the non activated nitriles (96H1021).

2. *Thiadiazoles*

2,5-Disubstituted 1,3,4-thiadiazoles were synthesized via the cyclization of 1,4-disubstituted thiosemicarbazides in the presence of concentrated sulfuric acid, acetic acid, phosphoric acid or hydrochloric acid under reflux. A rapid and efficient method to prepare 2-(4-methoxybenzoylamido)-5-aryloxymethyl-1,3,4-thiadiazoles **620** was achieved by irradiating a mixture of thiosemicarbazides **619** and glacial acetic acid in a commercial MW oven for 5 min (00SC3971). Similarly, 2-(4-tolyloxyacetylamido)-5-aryloxymethyl-1,3,4-thiadiazoles **621** were prepared (Scheme 157). The



Scheme 157



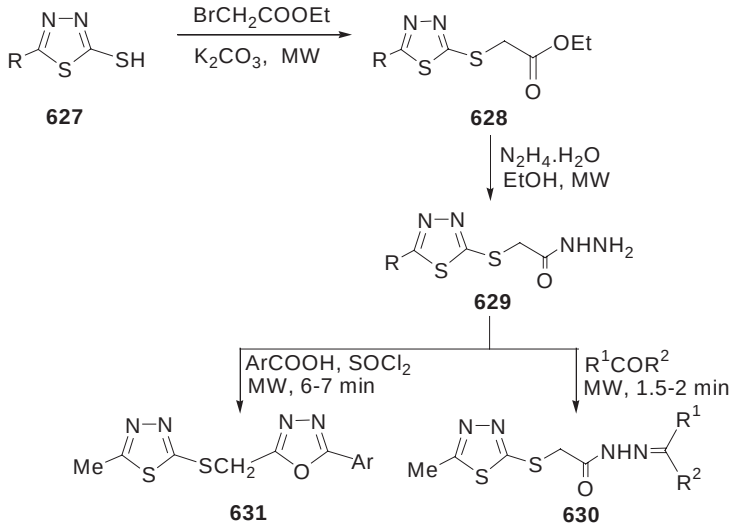
Scheme 158

products were obtained in better yields (84–97%) and shorter reaction times than in the conventional methods (01SC19).

Rapid chlorination of 2-mercapto-5-methyl-1,3,4-thiadiazole (**622**) (R = H) was reported using sodium hypochlorite under MWI to give **623** in 89% yield (Scheme 158) (98JCR(S)586).

Mercury derivatives of substituted 1,3,4-thiadiazoles **624** were synthesized by reaction of **622** with aryl mercuric chloride under MWI in open vessels using a domestic MW oven (Scheme 158). The reaction time was reduced and accompanied by improved yields over those in the conventional method (97M1291).

Coupling of cephalosporin **625** with a heterocyclic thiol in the presence of sodium bicarbonate requires 23 h to 6 days (71JPP7102339, 71JPP7102255, 75JAP(K)75131981). Modification this method required 48 h using phosphate buffer at pH 6.4 or BF_3 etherate (75JAP(K)75131986, 93JOC2296). Recently, a mixture of 5-substituted-1,3,4-thiadiazol-2-thiol **622**, cephalosporin **625** and aqueous ammonia was subjected to MWI followed by acidification with HCl to give **626** in 80–85% yields. The reaction time was decreased from 4–5 h to 6–8.5 min with improved yields, compared to conventional heating (Scheme 158) (99CL487).



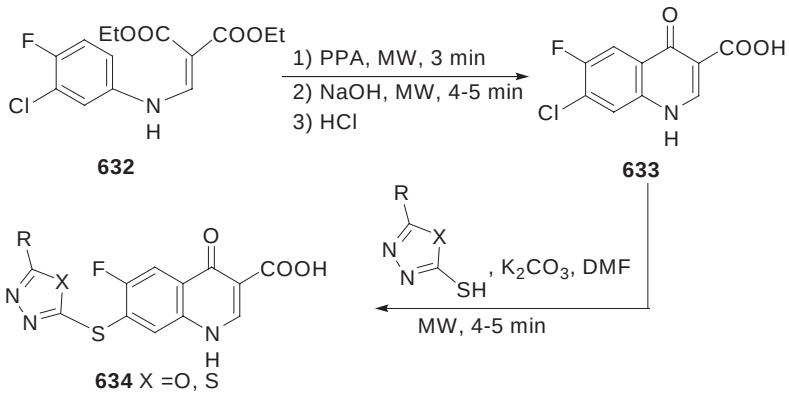
Scheme 159

Alkylation of 2-mercapto-1,3,4-thiadiazoles **627** with ethyl bromoacetate in the presence of potassium carbonate under MWI gave ethyl (5-substituted-1,3,4-thiadiazolyl-2-thio)acetate **628** in 82–86% yields. Hydrazinolysis of the ester **628** with hydrazine hydrate in ethanol was carried out under MWI to give hydrazides **629** in 77–85% yields (98MI3). Cyclization of **629** (R = Me) with aromatic acids in the presence of thionyl chloride under MWI in an open vessel using a domestic MW oven gave **631** in 73–88% yields after 6–7 min; the conventional method required a reflux for 6–8 h and led to 62–75% yield of **631** (98MI4) (Scheme 159). Hydrazide **629** when treated with substituted benzaldehydes or acetophenones furnished the corresponding hydrazones **630**; reactions were complete in 1.5–2 min under MWI as compared with 3–4 h of conventional heating (97G263).

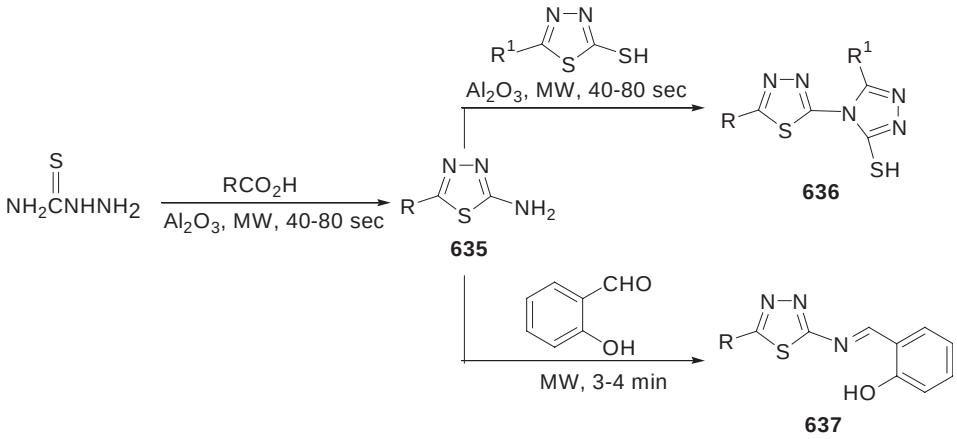
Cyclization of diethyl-3-chloro-4-fluoroanilinomethylene malonate **632** in polyphosphoric acid (PPA) under MWI for 3 min yielded the cyclized ester which upon alkaline hydrolysis afforded quinolone derivative **633** in 78% yield. Formal nucleophilic substitution of the chlorine in **633** with mercapto substituted 1,3,4-thiadiazoles or oxadiazoles was also achieved under MWI for 4–5 min furnishing **634** in 50–72% yields (Scheme 160) (98M961).

2-Amino-5-substituted-1,3,4-thiadiazoles **635** were prepared in 69–80% yields by MWI of thiosemicarbazide and carboxylic acids using acidic alumina as solid support. The reaction took 40–80 s instead of 5–7 h of required thermal heating. MWI of **635** with 2-mercapto-1,3,4-oxadiazoles under similar conditions gave **636** in 77–93% yields within 40–80 s (00SC3031).

The condensation of salicylaldehyde with **635** was efficiently performed under MWI without solvent to form the corresponding salicylaldimines **637** in 84–98% yields (Scheme 161) (02SC2395).



Scheme 160

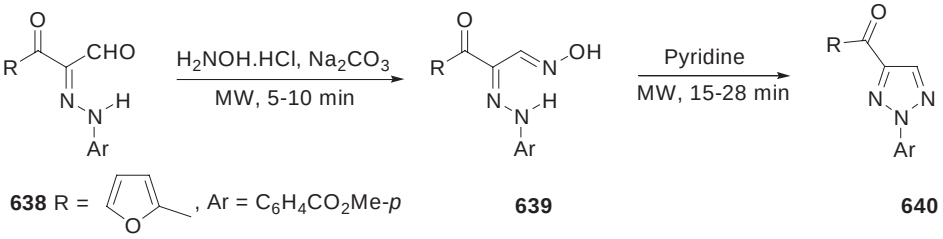


Scheme 161

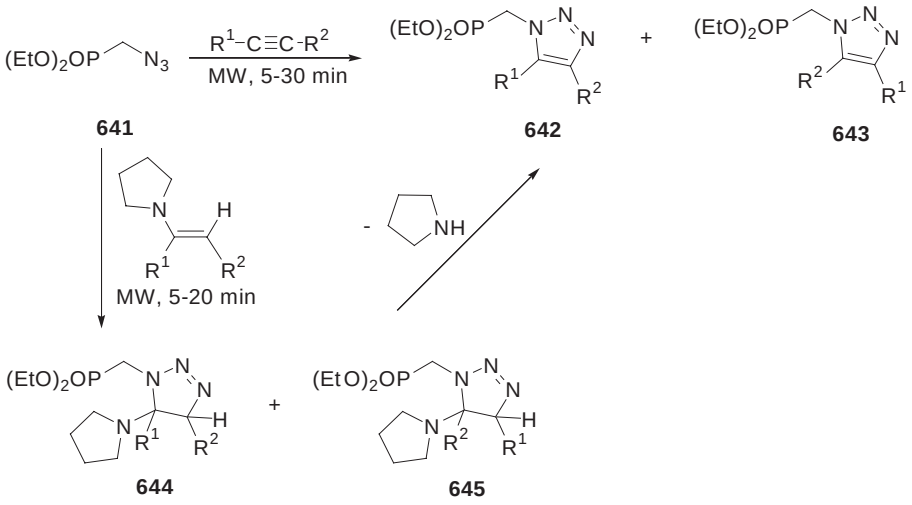
3. *1,2,3-Triazoles*

Reaction of 3-(2-furoyl)-2-(2-methoxycarbonylphenylhydrazono)-3-oxopropanal **638** with hydroxylamine hydrochloride in the presence of sodium carbonate and a few drops of ethanol under MWI for 5–10 min afforded oxime **639** in 82 instead of the 74% yield obtained by the conventional method. When a mixture of **639** and pyridine was placed in a MW oven and irradiated for 15–28 min, triazole derivative **640** was obtained in 66% yield. Conventional heating for 1 h afforded **640** in 56% yield (Scheme 162) (03MI3).

1,3-Dipolar cycloaddation of azides to alkynes is a versatile route to 1,2,3-triazoles (84CHEC669). Electron-deficient acetylenes can be added to azidomethylphosphate **641** to form the regioisomeric substituted 1,2,3-triazoles **642** and **643** but under drastic reaction conditions such as high temperature and very long reaction times



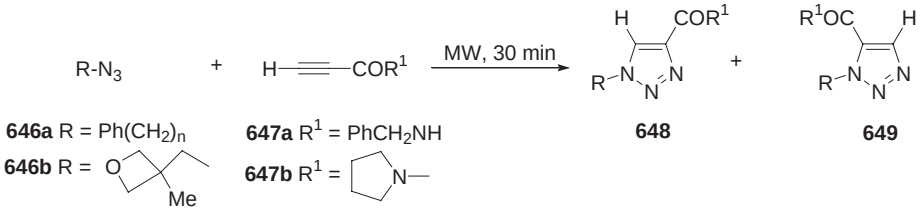
Scheme 162



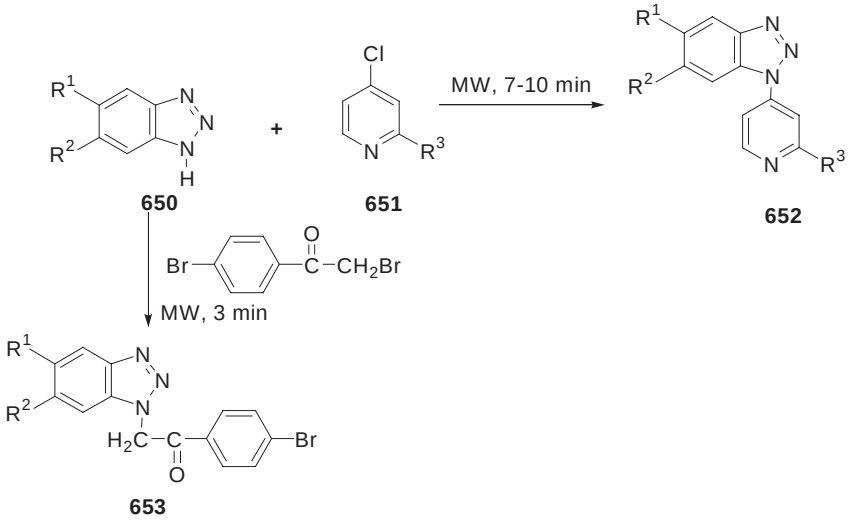
Scheme 163

(30–40 h). However, alkyltriazoles **642** and **643** can be effectively prepared in higher yields under solvent-free conditions by using MW activation within very short times (5–30 min). Similarly, **642** and **643** were formed in 30–55% yields by MWI of **641** with functionalized enamines within 5–20 min (Scheme 163) (98H161).

Only rare examples of 1,3-dipolar cycloaddition of azides to acetylenic amides have been reported and require 24 h to 1 week to be completed (84JAN885, 89H2083). Recently, MWI of benzyl azide **646a** ($n = 1$) and *N*-benzyl-2-propynamide **647a** at 55 °C for 30 min gave two regioisomers **648a** and **649a** with predominant formation of the more polar and sterically less congested regioisomer **648a** in 65% yield. However, the thermal reaction failed to induce any cycloaddition at 55–60 °C and the starting materials were recovered unchanged even after 24 h. Under MWI conditions (85 °C, 30 min), the reaction of **646a** with acetylenic compounds **647b** gave a mixture of regioisomers **648** and **649** in 3:1 ratio. Under similar conditions, 3-(azidomethyl)-3-methyloxetane **646b** with acetylenic amides gave triazoles **648** in 80–84% yields (Scheme 164) (02JOC9077).



Scheme 164

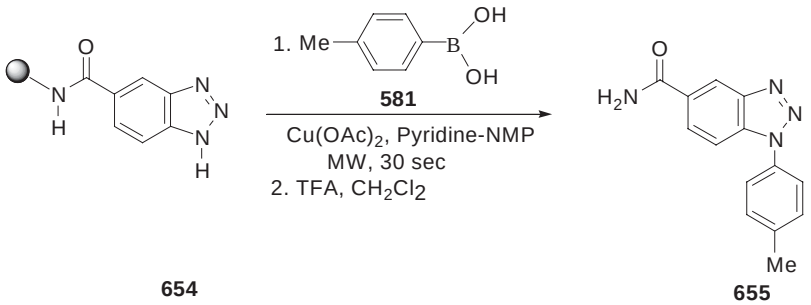


Scheme 165

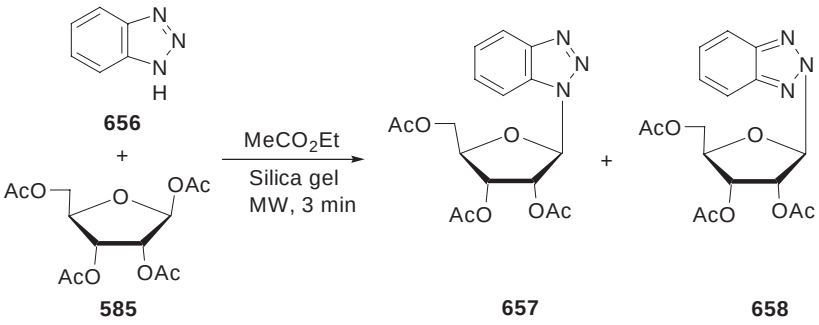
Irradiation of an equimolar mixture of 4-chloropyridine **651** and benzotriazole **650** in a domestic MW oven in a dry media using silica gel or montmorillonite solid supports gave the corresponding pyridylbenzotriazole **652** in moderate yield (<50%). However, when a non-supported mixture was irradiated in the absence of solvent, the condensation product **652** ($R^1 = R^2 = R^3 = H$) was obtained in a good yield (90%) (Scheme 165) (93TL2673).

In the alkylation of benzotriazole **650** with *p*-bromophenacyl bromide under MWI in dry media, the *N*-1 alkylated product **653** was mainly obtained as a consequence of the absence of solvent that suppresses a tautomeric equilibrium. The overall yield was about 95% and the *N*-1 alkylated isomer was about 80% (Scheme 165). The mass spectrometry data for compound **653** verified that no quaternization occurred (96H539).

N-Arylation of **654** with *p*-tolylboronic acid (**581**) in the presence of $Cu(OAc)_2$ and pyridine-NMP was carried out by MW heating in a domestic oven to give **655** in a 55% yield after cleavage of the product from the resin by treatment with a 1:1 mixture of trifluoroacetic acid (TFA) and CH_2Cl_2 for 40 min at room temperature (Scheme 166). The yield is dramatically increased compared to the solution phase reaction of benzotriazole, which only provided an 11% yield of the product at room temperature (99TL1623).



Scheme 166



Scheme 167

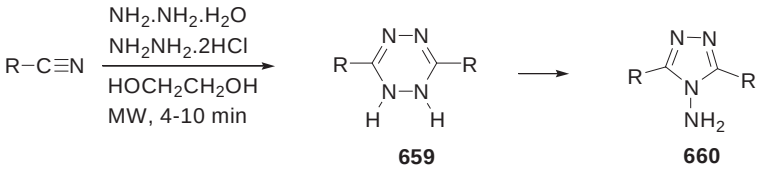
When benzotriazole (**656**) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**585**) were dissolved in ethyl acetate and irradiated by MW, a mixture of isomeric nucleosides **657** and **658** in 44 and 5% yield, respectively, was obtained in addition to the recovery of 45% of the base (Scheme 167) (02MI5).

4. *1,2,4-Triazoles*

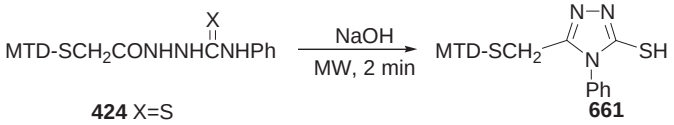
A number of symmetrically 3,5-disubstituted-1,2,4-triazoles **660** were prepared in 58–96% yields from aromatic or heterocyclic nitriles with hydrazine dihydrochloride in the presence of an excess of hydrazine hydrate in ethylene glycol under MWI for 4–10 min. The initial dihydro-1,2,4,5-tetrazine **659** product has an orange color. It rearranged under acidic conditions into the corresponding 4-amino-1,2,4-triazole **660**. The addition of hydrazine dihydrochloride was used to generate protons which promoted the rearrangement of **659** into the triazole **660**. Without the dihydrochloride, the main product was **659** (Scheme 168) (00TL1539).

Cyclization of the thiosemicarbazide **424** by NaOH under MWI for 2 min gave the 1,2,4-triazole-3-thiol derivative **661** in 72% yield (Scheme 169) (97G263).

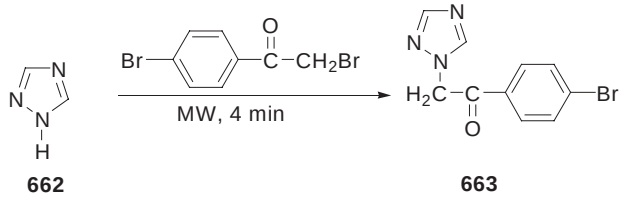
N-1 alkylation of 1,2,4-triazole (**662**) with *p*-bromophenacyl bromide in dry media under MWI gave **663** within 4 min in 96% yield (Scheme 170) (96H539).



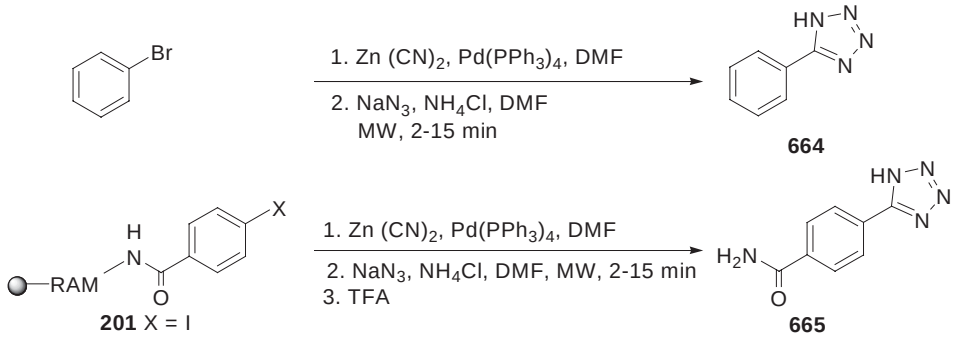
Scheme 168



Scheme 169



Scheme 170



Scheme 171

D. Heterocycles with Four Heteroatoms

1. *Tetrazoles*

Nitriles are valuable intermediates that can be transformed into a broad spectrum of compounds like tetrazoles. MWI accelerated the Pd-catalyzed cyanation of

bromobenzene with $Zn(CN)_2$, and subsequent cyclization of the formed benzonitrile with sodium azide to give tetrazole **664** in high yield (96%). The method was also applied to the conversion of iodide **201** to tetrazole **665** (72%) on a solid support, where a Rink linker on tentaGel was used (Scheme 171) (00JOC7984, 02ACR717).

Acknowledgments

The authors thank the AvH and DFG for the partial support.

References

40CRV297	M. M. Sprung, *Chem. Rev.*, **26**, 297 (1940).
53ZOB957	L. S. Efros, *Zh. Obshch. Khim.*, **23**, 957 (1953) [*CA* **48**, 8223 (1954)].
54JCS2293	I. L. Finar, *J. Chem. Soc.*, 2293 (1954).
56JAN102	K. J. Watanabe, *J. Antibiot.*, 102 (1956).
57JA427	D. W. Hein, R. J. Alheim, and J. J. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).
57JA1265	C. W. Waller, C. F. Wolf, W. J. Strein, and B. L. Hutchings, *J. Am. Chem. Soc.*, **79**, 1265 (1957).
57JA1482	N. J. Leonard, L. A. Miller, and J. W. Berry, *J. Am. Chem. Soc.*, **79**, 1482 (1957).
57JA5736	D. Ben-Ishai, *J. Am. Chem. Soc.*, **79**, 5736 (1957).
59ACSA1668	B. S. Jensen, *Acta Chem. Scand.*, **13**, 1668 (1959).
59JOC388	A. G. Prapas, *J. Org. Chem.*, **24**, 388 (1959).
61AG114	K. Gewald, *Angew. Chem.*, **73**, 114 (1961).
61JOC828	M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).
61JOC1681	T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961).
62ZOB2624	L. N. Pushkina, S. A. Mazalov, and I. Y. Postovskii, *Zh. Obshch. Khim.*, **32**, 2624 (1962) [*CA* **58**, 9049 (1963)].
63HCA870	R. Schwyzer, A. Costopanagiotis, and P. Sieber, *Helv. Chim. Acta*, **46**, 870 (1963).
63JOC2759	P. Allen and J. Ginos, *J. Org. Chem.*, **28**, 2759 (1963).
64NAT1064	F. Arcamone, S. Penco, P. Orezzi, V. Nicolella, and A. Pirelli, *Nature*, **203**, 1064 (1964).
65OR270	A. Maercker, *Org. React.*, **14**, 270 (1965).
68JHC757	H. S. Broadbent, W. S. Burnham, R. K. Olsen, and R. M. Sheeley, *J. Heterocycl. Chem.*, **5**, 757 (1968).
69JCS(C)1252	A. D. B. Sloan, *J. Chem. Soc. C*, 1252 (1969).
69JOC3187	N. Castagnoli, *J. Org. Chem.*, **37**, 3187 (1969).
70CPB587	Y. Kanaoka, T. Hameda, and O. Yonemitsu, *Chem. Pharm. Bull.*, **18**, 587 (1970).
71BCJ645	T. Tsuji, *Bull. Chem. Soc. Jpn.*, **62**, 645 (1971).
71IJC1209	V. P. Arya and S. P. Ghate, *Indian J. Chem.*, **9**, 1209 (1971).
71JPP7102255	K. Harada, M. Hashimoto, and R. Kawahara, Jpn. Pat. 71102255 (1971) [*CA* **75**, 5918 (1971)].
71JPP7102339	T. Takano and S. Shin, Jpn. Pat. 7102339 (1971) [*CA* **75**, 2920 (1971)].
73T3417	C. Lion and J. E. Dubois, *Tetrahedron*, **29**, 3417 (1973).
75JAP(k)75131981	M. Iwanami, I. Isaka, M. Murakami, M. Fujimoto, T. Maeda, N. Kawahara, and T. Shibanuma, Jpn. Kokai Pat. 75131981 (1975) [*CA* **85**, 21397 (1976)].

75JAP(k)75131986 M. Hatanaka, T. Ishimaru, and T. Shinuchi, Jpn. Kokai Pat. 75131986 (1975) [*CA* **85**, 46706 (1976)].

75S749 Y. S. Rao and R. Filler, *Synthesis*, 749 (1975).

76JOC1735 A. I. Meyers and M. E. Ford, *J. Org. Chem.*, **41**, 1735 (1976).

77TL3643 I. Ojima, S. Inaba, and K. Yoshida, *Tetrahedron Lett.*, 3643 (1977).

78JIC386 C. K. Ghosh and K. K. Mukhopadhyay, *J. Indian Chem. Soc.*, **55**, 386 (1978).

78JOC2296 D. L. Boger, *J. Org. Chem.*, **43**, 2296 (1978).

79JHC13 V. I. Cohen, *J. Heterocycl. Chem.*, **16**, 13 (1979).

80JCE527 M. B. Hocking, *J. Chem. Educ.*, **57**, 527 (1980).

80MI1 T. Yoshiyuki and Y. Kazuaki, *Hokkaido Daigaku Kogakubu Kenkyu Hokoku*, 45 (1980) [*CA* **93**, 204537 (1980)].

80TL2077 I. Ojima and S. Inaba, *Tetrahedron Lett.*, **21**, 2077 (1980).

80TL2081 I. Ojima and S. Inaba, *Tetrahedron Lett.*, **21**, 2081 (1980).

81IZV118 A. Terebenina, N. Iordanov, B. Iordanov, and G. Borisov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **14**, 118 (1981).

81S545 I. Ojima, S. Inaba, and M. Nagai, *Synthesis*, 545 (1981).

82JOC2487 G. F. Koser, A. G. Relenyi, A. N. Kalso, L. Rebrovic, and H. Wettach, *J. Org. Chem.*, **47**, 2487 (1982).

83IJC(B)917 V. P. Reddy, P. L. Prasunamba, P. S. N. Reddy, and C. V. Ratnam, *Indian J. Chem., Sect. B*, **22B**, 917 (1983).

83JA1697 H. H. Wasserman, R. P. Robinson, and C. G. Carter, *J. Am. Chem. Soc.*, **105**, 1697 (1983).

83JOC77 R. M. Freidinger, J. S. Hinkle, D. S. Perlow, and B. H. Arison, *J. Org. Chem.*, **48**, 77 (1983).

83MI1 X. Dong, F. Liu, and Y. Zhao, *Acta Chimica Sinica*, **41**, 848 (1983).

83TL4707 K. Ikeda, K. Achiwa, and M. Sekiya, *Tetrahedron Lett.*, **24**, 4707 (1983).

84CHEC669 H. Wamhoff, in: "*Comp. Heterocycl. Chem.*" (A. R. Katritzky and C. W. Rees, eds.), Vol. 5, p. 669, Pergamon Press, New York (1984).

84JAN885 R. C. Mearman, C. E. Newall, and A. P. Tonge, *J. Antibiot.*, **37**, 885 (1984).

84JCS(CC)883 K. Okano, T. Morimoto, and M. Sekiya, *J. Chem. Soc., Chem. Commun.*, 883 (1984).

84JOC1056 T. Shono, K. Tsubata, and N. Okinaya, *J. Org. Chem.*, **49**, 1056 (1984).

84S145 A. Osuka, Y. Uno, H. Horiuchi, and H. Suzuki, *Synthesis*, 145 (1984).

84TL2143 J. E. Dubois and G. Axiotis, *Tetrahedron Lett.*, **25**, 2143 (1984).

85JCS(CC)240 G. Gainelli, M. Contento, A. Drusiani, M. Panunzio, and L. Plessi, *J. Chem. Soc., Chem. Commun.*, 240 (1985).

85TL1411 R. K. Boeckman Jr. and J. C. Potenza, *Tetrahedron Lett.*, **34**, 1411 (1985).

86IJC(B)966 R. Dahiya and H. K. Pujari, *Indian J. Chem., Sect. B*, **25B**, 966 (1986).

86T623 B. C. Chen, Z. -Z. Guang, A. R. Katritzky, and T. I. Yousaf, *Tetrahedron*, **42**, 623 (1986).

86TL4945 R. J. Giguere, T. L. Bray, S. M. Duncan, and G. Majetich, *Tetrahedron Lett.*, **27**, 4945 (1986).

87CSR89 R. Grigg, *Chem. Soc. Rev.*, **16**, 89 (1987).

87TL277 C. Gennari, I. Venturini, G. Gislon, and G. Schimperna, *Tetrahedron Lett.*, **28**, 277 (1987).

87TL4331 G. Guanti, E. Narisano, and L. Banfi, *Tetrahedron Lett.*, **28**, 4331 (1987).

87TL4335 G. Guanti, E. Narisano, and L. Banfi, *Tetrahedron Lett.*, **28**, 4335 (1987).

89CCC1666 A. Perjessy, A. A. Avetisyan, A. A. Aknazaryan, and G. S. Melikyan, *Collect. Czech. Chem. Commun.*, **54**, 1666 (1989).
89CIL607 D. Villemin, B. Labiad, and Y. Ouhilal, *Chem. Ind. (London)*, **18**, 607 (1989).
89H2083 D. Habick, W. Barth, and M. Rosner, *Heterocycles*, **29**, 2083 (1989).
89JCS(CC)386 A. B. Alloum, B. Labiad, and D. Villemin, *J. Chem. Soc., Chem. Commun.*, 386 (1989).
89SC3579 K. L. Reed, J. T. Gupton, and T. L. Solarz, *Synth. Commun.*, **19**, 3579 (1989).
90H741 A. K. Bose, M. S. Manhas, M. Ghosh, V. S. Raju, K. Tabei, and Z. Urbanczyk-Lipkowska, *Heterocycles*, **30**, 741 (1990).
90SC3207 D. Villemin and B. Labiad, *Synth. Commun.*, **20**, 3207 (1990).
90SC3213 D. Villemin and B. Labiad, *Synth. Commun.*, **20**, 3213 (1990).
90SL533 M. S. Cooper, H. Heaney, A. J. Newbold, and W. R. Sanderson, *Synlett.*, 533 (1990).
91CB1173 C. Bolmn, K. Weickhardt, M. Zehnder, and T. Ranff, *Chem. Ber.*, **124**, 1173 (1991).
91CSR1 D. M. P. Mingos and D. R. Baghurst, *Chem. Soc. Rev.*, **20**, 1 (1991).
91JOC6968 A. K. Bose, M. S. Manhas, M. Ghosh, M. Shah, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, A. G. Chaudhary, and K. J. Barakat, *J. Org. Chem.*, **56**, 6968 (1991).
91OPP683 R. A. Abramovitch, *Org. Prep. Proc. Int.*, **23**, 683 (1991).
91SL121 Z. Chen, X. Wang, W. Lu, and J. Yu, *Synlett.*, 121 (1991).
91TL2363 J. Berlan, P. Giboreau, S. Lefeuvre, and C. Marchand, *Tetrahedron Lett.*, **32**, 2363 (1991).
92JCS(P1)207 O. Prakash, N. Rani, and S. Goyal, *J. Chem. Soc., Perkin Trans. 1*, 207 (1992).
92JOC2883 R. J. Perry, B. D. Wilson, and R. J. J. Miller, *J. Org. Chem.*, **57**, 2883 (1992).
92SC1137 A. Petit, A. Loupy, P. Maillard, and M. Momenteau, *Synth. Commun.*, **22**, 1137 (1992).
92SL795 R. A. Abramovitch and A. Bulman, *Synlett.*, 795 (1992).
92TL3603 B. K. Banik, M. S. Manhas, Z. Kaluza, K. J. Barakat, and A. K. Bose, *Tetrahedron Lett.*, **33**, 3603 (1992).
92TL7631 W. B. Wang and E. J. Roskamp, *Tetrahedron Lett.*, **33**, 7631 (1992).
93IJC(B)1190 S. N. Sawhney, P. K. Sharma, and A. Gupta, *Indian J. Chem., Sect. B*, **32B**, 1190 (1993).
93JCS(P1)999 R. S. Varma, M. Varma, and A. K. Chatterjee, *J. Chem. Soc., Perkin Trans. 1*, 999 (1993).
93JOC2296 J. Kant, *J. Org. Chem.*, **58**, 2296 (1993).
93JOC5558 G. B. Jones and B. J. Chapman, *J. Org. Chem.*, **58**, 5558 (1993).
93MI1 T. J. McCarthy, C. S. Dence, and M. J. Welch, *Appl. Radiat. Isot.*, **44**, 1129 (1993).
93SC419 D. Villemin, B. Labiad, and A. Loupy, *Synth. Commun.*, **23**, 419 (1993).
93SC2251 D. Villemin, B. Martin, and B. Garrigues, *Synth. Commun.*, **23**, 2251 (1993).
93SL575 A. K. Bose, B. K. Banik, K. J. Barakat, and M. S. Manhas, *Synlett.*, 575 (1993).
93TL2123 F. Texier-Boulett, R. Latouche, and J. Hamelin, *Tetrahedron Lett.*, **34**, 2123 (1993).
93TL2673 A. Molina, J. J. Vaquero, J. L. Garcia-Navio, and J. Alvarez-Builla, *Tetrahedron Lett.*, **34**, 2673 (1993).

93TL5071 B. Rechsteiner, F. Texier-Boullet, and J. Hamelin, *Tetrahedron Lett.*, **34**, 5071 (1993).

94CCC175 M. Puciova, P. Ertl, and S. Toma, *Collect. Czech. Chem. Commun.*, 175 (1994).

94CJC2483 B. Oussaid and B. Garrigues, *Can. J. Chem.*, **72**, 2483 (1994).

94JCR(S)116 B. Touaux, B. Klein, F. Texier-Boullet, and J. Hamelin, *J. Chem. Res. (S)*, 116 (1994).

94JCR(S)146 D. Villemin and B. Martin, *J. Chem. Res. (S)*, 146 (1994).

94JCS(P1)3595 A. Diaz-Ortiz, E. Diaz-Barra, A. de la Hoz, P. Prieto, and A. Moreno, *J. Chem. Soc., Perkin Trans. 1*, 3595 (1994).

94JES73 R. T. Carlin, H. C. De Long, J. Fuller, and P. C. Trulove, *J. Electrochem. Soc.*, **141**, L73 (1994).

94JFC47 B. Narsaiah, A. Sivaprasad, and R. V. Venkataratnam, *J. Fluorine Chem.*, **66**, 47 (1994).

94JOC3408 T. Cablewski, A. F. Faux, and C. R. Strauss, *J. Org. Chem.*, **59**, 3408 (1994).

94MI1 K. P. C. Vollhardt and N. E. Schore, Organic Chemistry, 2nd edn, W.H. Freeman and Co., New York (1994), p. 880.

94SC301 D. Jinchang, G. Hengjie, W. Jinzhu, and L. Caizhen, *Synth. Commun.*, **24**, 301 (1994).

94SC1809 D. Abenhaim, A. Loupy, C. Mahieu, and D. Semeria, *Synth. Commun.*, **24**, 1809 (1994).

94SC2417 Z. Rongshun, H. Pinjie, and D. Shushan, *Synth. Commun.*, **24**, 2417 (1994).

94SL221 O. Prakash, N. Saini, and P. K. Sharma, *Synlett.*, 221 (1994).

94SL935 P. Ruault, J. F. Pilard, B. Touaux, F. Texier-Boullet, and J. Hamelin, *Synlett*, 935 (1994).

95AJC1665 C. R. Strauss and R. W. Trainor, *Aust. J. Chem.*, **48**, 1665 (1995).

95JOC473 N. Kihara, Y. Nakawaki, and T. Endo, *J. Org. Chem.*, **60**, 473 (1995).

95JOC2456 K. D. Raner, C. R. Strauss, R. W. Trainor, and J. S. Thorn, *J. Org. Chem.*, **60**, 2465 (1995).

95PJS402 A. H. Mandour, N. M. Fawzy, T. H. El-Shihi, and Z. E. El-Bazza, *Pak. J. Sci. Ind. Res.*, **38**, 402 (1995).

95SC1 R. A. Abramovitch, Q. Shi, and D. Bogdal, *Synth. Commun.*, **25**, 1 (1995).

95SC659 B. Oussaid, J. Berlan, M. Soufiaoui, and B. Garrigues, *Synth. Commun.*, **25**, 659 (1995).

95SC1451 B. Oussaid, L. Moeini, B. Martin, D. Villemin, and B. Garrigues, *Synth. Commun.*, **25**, 1451 (1995).

95SC3135 D. Villemin and B. Martin, *Synth. Commun.*, **25**, 3135 (1995).

95SC3141 D. Villemin and M. Hammadi, *Synth. Commun.*, **25**, 3141 (1995).

95T3015 A. Gonzalez, R. Lavilla, J. F. Piniella, and A. A. Larena, *Tetrahedron*, **51**, 3015 (1995).

95T6757 J. M. Lerestif, J. Perrocheau, F. Tonnard, J. P. Bazureau, and J. Hamelin, *Tetrahedron*, **51**, 6757 (1995).

95T10403 S. Caddick, *Tetrahedron*, **51**, 10403 (1995).

95TL1779 E. R. Perez, A. L. Marreo, R. Perez, and M. A. Autie, *Tetrahedron Lett.*, **36**, 1779 (1995).

95TL2165 A. Acosta, P. de la Cruz, P. De Miguel, E. Diez-Barra, A. de la Hoz, F. Langa, A. Loupy, M. Majdoub, N. Martin, C. Sanchez, and C. Seoane, *Tetrahedron Lett.*, **36**, 2165 (1995).

95TL3683 K. Bougrin and M. Soufiaoui, *Tetrahedron Lett.*, **36**, 3683 (1995).

96H539 E. Perez, E. Sotelo, A. Loupy, R. Mocelo, M. Suarez, R. Perez, and M. Autie, *Heterocycles*, **43**, 539 (1996).

96H1021 A. Diaz-Ortiz, E. Diaz-Barra, A. de la Hoz, A. Moreno, M. J. Gomez-Escalonilla, and A. Loupy, *Heterocycles*, **43**, 1021 (1996).
96IJC(B)111 B. S. Vashi, D. S. Mehta, and V. H. Shah, *Indian J. Chem., Sect. B*, **35B**, 111 (1996).
96JCR(S)92 M. S. Khajavi, M. Hjihadi, and R. Naderi, *J. Chem. Res. (S)*, 92 (1996).
96JCR(S)338 F. M. Moghaddam, A. Sharifi, and M. R. Saidi, *J. Chem. Res. (S)*, 338 (1996).
96JCR(S)429 A. Saoudi, J. Hamelin, and H. Benhaoua, *J. Chem. Res. (S)*, 492 (1996).
96JOC7355 L. Bagnell, T. Gablewski, C. Strauss, and R. W. Trainor, *J. Org. Chem.*, **61**, 7355 (1996).
96JOC9582 M. Larhed and A. Hallberg, *J. Org. Chem.*, **61**, 9582 (1996).
96LA739 B. Garrigues, C. Laporte, R. Laurent, A. Laporterie, and J. Dubac, *Liebigs Ann. Chem.*, 739 (1996).
96MI1 H. Beyer and W. Walter, Handbook of Organic Chemistry, Prentice Hall Europe, London-Munich (1996), p. 497.
96MI2 F. A. Omar, N. M. Mahfouz, and M. A. Rahman, *Eur. J. Med. Chem. Chim. Ther.*, **31**, 819 (1996).
96SC1335 D. S. Clarke and R. Wood, *Synth. Commun.*, **26**, 1335 (1996).
96SC2895 D. Villemin, M. Hammadi, and B. Martin, *Synth. Commun.*, **26**, 2895 (1996).
96SL245 A. L. Marrero-Terrero and A. Loupy, *Synlett.*, 245 (1996).
96SL873 D. Bogdal, J. Pielichowski, and A. Boron, *Synlett.*, 873 (1996).
96T617 M. Majdoub, A. Loupy, A. Petit, and S. Roudesli, *Tetrahedron*, **52**, 617 (1996).
96T9237 A. Diaz-Ortiz, J. R. Carrillo, E. Diaz-Barra, A. de la Hoz, M. J. Gomez-Escalonilla, A. Moreno, and F. Langa, *Tetrahedron*, **52**, 9237 (1996).
96T14995 M. Lacova, J. Chovancova, E. Veverkova, and S. Toma, *Tetrahedron*, **52**, 14995 (1996).
96TL1695 A. Diaz-Ortiz, P. Prieto, A. Loupy, and D. Abenhaim, *Tetrahedron Lett.*, **37**, 1695 (1996).
96TL4203 A. Boruah, B. Baruah, D. Prajapati, J. S. Sandhu, and A. C. Ghosh, *Tetrahedron Lett.*, **37**, 4203 (1996).
96TL6989 A. K. Bose, M. Jayaraman, A. Okawa, S. S. Bari, E. W. Robb, and M. S. Manhas, *Tetrahedron Lett.*, **37**, 6989 (1996).
96TL8219 M. Larhed, G. Lindeberg, and A. Hallberg, *Tetrahedron Lett.*, **37**, 8219 (1996).
97BSB393 J. J. V. Eynde and D. Fromont, *Bull. Soc. Chim. Belg.*, **106**, 393 (1997).
97CSR233 S. A. Galema, *Chem. Soc. Rev.*, **26**, 233 (1997).
97G263 M. Kidwai and R. Kumar, *Gazz. Chim. Ital.*, **127**, 263 (1997).
97H715 D. Bogdal, J. Pielichowski, and K. Jaskot, *Heterocycles*, **45**, 715 (1997).
97IJC(B)86 V. Sridar, *Indian J. Chem., Sect. B*, **36B**, 86 (1997).
97IJC(B)175 M. Kidwai, P. Kumar, Y. Goel, and K. Kumar, *Indian J. Chem., Sect. B*, **36B**, 175 (1997).
97JOC2505 J. An, L. Bagnell, T. Cablewski, C. R. Strauss, and R. W. Trainor, *J. Org. Chem.*, **62**, 2505 (1997).
97JOC5583 M. Larhed, M. Hoshino, S. Hadida, D. P. Curran, and A. Hallberg, *J. Org. Chem.*, **62**, 5583 (1997).
97M1291 M. Kidwai, K. R. Bhushan, P. Kumar, and R. Kumar, *Monatsh. Chem.*, **128**, 1291 (1997).

97MI1 D. M. P. Mingos and A. Whittaker, in *"Microwave Dielectric Heating Effects in Chemical Synthesis in Chemistry under Extreme or Non Classical Conditions"* (R. V. Eldik and C. D. Hubbard, eds.), p. 479, Wiley, New York (1997).

97MI2 J. Li, X. Wang, and Q. Zhao, *Huaxue Shiji.*, **19**, 112 (1997).

97OPP671 R. Perez, E. R. Perez, M. Saurez, L. Gonzalez, A. Loupy, M. L. Jimeno, and C. Ochoa, *Org. Prep. Proc. Int.*, **29**, 671 (1997).

97OPP687 J. C. Feng, Q. H. Meng, Y. Liu, and L. Dai, *Org. Prep. Proc. Int.*, **29**, 687 (1997).

97S287 G. Kerneur, J. M. Lerestif, J. P. Bazureau, and J. Hamelin, *Synthesis*, 287 (1997).

97SC533 S. Y. Kim, P. S. Kwon, T. W. Kwon, S. K. Chung, and Y. T. Chang, *Synth. Commun.*, **27**, 533 (1997).

97SC1327 H. M. S. Kumar, P. K. Mohanty, M. S. Kumar, and J. S. Yadav, *Synth. Commun.*, **27**, 1327 (1997).

97SC1553 D. Bogdal, J. Pielichowski, and K. Jaskot, *Synth. Commun.*, **27**, 1553 (1997).

97SC2051 B. M. Khadikar and P. M. Bendale, *Synth. Commun.*, **27**, 2051 (1997).

97SC2563 B. Baruah, D. Prajapati, A. Boruah, and J. S. Sandhu, *Synth. Commun.*, **27**, 2563 (1997).

97SC3677 G. Babu and P. T. Perumal, *Synth. Commun.*, **27**, 3677 (1997).

97SC3705 T. Beregszaszi and A. Molnar, *Synth. Commun.*, **27**, 3705 (1997).

97SC4073 F. M. Moghaddam and R. Emami, *Synth. Commun.*, **27**, 4073 (1997).

97SC4091 P. S. Kwon, Y. M. Kim, C. J. Kang, and T. W. Kwon, *Synth. Commun.*, **27**, 4091 (1997).

97SC4335 G. V. Salmoria, E. L. Dall' Oglio, and C. Zucco, *Synth. Commun.*, **27**, 4335 (1997).

97SL269 A. Diaz-Ortiz, P. Prieto, and E. Vazquez, *Synlett.*, 269 (1997).

97T2599 P. de la Cruz, A. de la Hoz, and F. Langa, *Tetrahedron*, **53**, 2599 (1997).

97T5847 A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, **53**, 5847 (1997).

97T12131 Q. Xu, B. Chao, Y. Wang, and D. C. Dittmer, *Tetrahedron*, **53**, 12131 (1997).

97TL2027 U. M. Lindstrom, R. Franckowiak, N. Pinault, and P. Somfai, *Tetrahedron Lett.*, **38**, 2027 (1997).

97TL6395 A. Ben-Alloum, S. Bakkas, and M. Soufiaoui, *Tetrahedron Lett.*, **36**, 6395 (1997).

97TL7029 R. S. Varma, R. Dahiya, and R. K. Saini, *Tetrahedron Lett.*, **38**, 7029 (1997).

97TL7867 P. Perio, M. J. Dozias, P. Jacquault, and J. Hamelin, *Tetrahedron Lett.*, **38**, 7867 (1997).

97TL8089 S. Chandrasekhar, M. Takhi, and G. Uma, *Tetrahedron Lett.*, **38**, 8089 (1997).

97TL8855 B. Syassi, K. Bougrin, and M. Soufiaoui, *Tetrahedron Lett.*, **38**, 8855 (1997).

98CJC525 R. N. Gedye and J. B. Wei, *Can. J. Chem.*, **76**, 525 (1998).

98CL159 Y. Nishiyama, H. Ohashi, K. Itoh, and N. Sonoda, *Chem. Lett.*, 159 (1998).

98CSR213 C. Gabriel, S. Gabriel, E. H. Grant, B. S. J. Halstead, and D. M. P. Mingos, *Chem. Soc. Rev.*, **27**, 213 (1998).

98H161 F. Louerat, K. Bougrin, A. Loupy, A. M. O. de Retana, J. Pagalday, and F. Palacios, *Heterocycles*, **48**, 161 (1998).

98JCR(S)34 M. Bortolussi, R. Bloch, and A. Loupy, *J. Chem. Res. (S)*, 34 (1998).

98JCR(S)272 H. N. Borah, R. C. Boruah, and J. S. Sandhu, *J. Chem. Res. (S)*, 272 (1998).
98JCR(S)324 R. Varma, D. Kumar, and R. Dahiya, *J. Chem. Res. (S)*, 324 (1998).
98JCR(S)586 M. Kidwai, S. Kohli, and P. Kumar, *J. Chem. Res. (S)*, 586 (1998).
98JCR(S)668 A. Sharifi, M. Bolourtchian, and F. Mohsenzadeh, *J. Chem. Res. (S)*, 668 (1998).
98JCR(S)672 A. Shaabani, *J. Chem. Res. (S)*, 672 (1998).
98JCS(P1)4093 R. S. Varma, D. Kumar, and P. J. Liesen, *J. Chem. Soc., Perkin Trans. 1*, 4093 (1998).
98JCS(P2)989 J. Schmeyers, F. Toda, J. Boy, and G. Kaupp, *J. Chem. Soc., Perkin Trans. 2*, 989 (1998).
98JOC6234 H. Shiraishi, T. Nishitani, S. Sakaguchi, and Y. Ishii, *J. Org. Chem.*, **63**, 6234 (1998).
98M961 M. Kidwai, P. Misra, R. Kumar, P. K. Saxena, R. Gupta, and S. Bradoo, *Monatsh. Chem.*, **129**, 961 (1998).
98MI1 A. Ben-Alloum, S. Bakkas, K. Bougrin, and M. Soufiaoui, *New J. Chem.*, 809 (1998).
98MI2 B. Syassi, K. Bougrin, M. Lamiri, and M. Soufiaoui, *New J. Chem.*, 1545 (1998).
98MI3 M. Kidwai, R. Kumar, A. Srivastava, and H. P. Gupta, *Bioorg. Chem.*, **26**, 289 (1998).
98MI4 M. Kidwai, Y. Goel, and P. Kumar, *Indian J. Pharm. Sci.*, **60**, 396 (1998).
98OPP87 B. Pchelka and J. Plenkiewicz, *Org. Prep. Proc. Int.*, **30**, 87 (1998).
98S967 M. A. A. Meziane, M. Rahmouni, J. P. Bazureau, and J. Hamelin, *Synthesis*, 967 (1998).
98S1213 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault, and P. Mathe, *Synthesis*, 1213 (1998).
98SC2017 M. Bolourtchian, R. Zadmard, and M. R. Saidi, *Synth. Commun.*, **28**, 2017 (1998).
98SC2415 D. Karmakar, D. Prajapati, and J. S. Sandhu, *Synth. Commun.*, **28**, 2415 (1998).
98SC3201 D. Villemin and B. Martin, *Synth. Commun.*, **28**, 3201 (1998).
98SC3765 J. C. Feng, B. Liu, L. Dai, and N. S. Bian, *Synth. Commun.*, **28**, 3765 (1998).
98SC3811 H. M. S. Kumar, B. V. Subbareddy, S. Anjaneyulu, and J. S. Yadav, *Synth. Commun.*, **28**, 3811 (1998).
98SC4087 R. S. Varma and R. Dahiya, *Synth. Commun.*, **28**, 4087 (1998).
98SC4571 G. Sabitha, R. S. Babu, and J. S. Yadav, *Synth. Commun.*, **28**, 4571 (1998).
98SC4577 G. Sabitha and M. Syamala, *Synth. Commun.*, **28**, 4577 (1998).
98SL147 J. G. Siro, J. Martin, J. L. Garcia-Nvio, M. J. Remuioan, and J. J. Vaquero, *Synlett.*, 147 (1998).
98T4561 S. Jolivet-Fouchet, J. Hamelin, F. Texier-Boullet, L. Toupet, and P. Jacquault, *Tetrahedron*, **54**, 4561 (1998).
98T8055 K. Bougrin, A. Loupy, and M. Soufiaoui, *Tetrahedron*, **54**, 8055 (1998).
98T13167 A. Arrieta, J. R. Carrillo, F. P. Cossio, A. Diaz-Ortiz, M. J. Gomez-Escalonilla, A. de la Hoz, F. Langa, and A. Moreno, *Tetrahedron*, **54**, 13167 (1998).
98TL4481 A. Ben-Alloum, S. Bakkas, and M. Soufiaoui, *Tetrahedron Lett.*, **39**, 4481 (1998).
98TL5509 H. Glas and W. R. Thiel, *Tetrahedron Lett.*, **39**, 5509 (1998).

98TL5631 D. Subhas and V. Lakshminarayana, *Tetrahedron Lett.*, **39**, 5631 (1998).
98TL6053 P. de la Cruz, A. de la Hoz, L. M. Font, F. Langa, and M. C. Perez-Rodrigues, *Tetrahedron Lett.*, **39**, 6053 (1989).
98TL6529 M. Sridhar, K. L. Krishna, K. Srinivas, and J. M. Rao, *Tetrahedron Lett.*, **39**, 6529 (1998).
98TL8093 S. Kasmi, J. Hamelin, and H. Benhaoua, *Tetrahedron Lett.*, **39**, 8093 (1998).
98TL8437 R. S. Varma, K. P. Naicker, and P. J. Liesen, *Tetrahedron Lett.*, **39**, 8437 (1998).
98TL8453 Z. Dahmani, M. Rahmouni, R. Brugidou, J. P. Bazureau, and J. Hamelin, *Tetrahedron Lett.*, **39**, 8453 (1998).
99AJC83 C. R. Strauss, *Aust. J. Chem.*, **52**, 83 (1999).
99CL487 M. Kidwai, K. R. Bhushan, and P. Misra, *Chem. Lett.*, 487 (1999).
99JCR(S)32 J. M. Lerestif, S. Feuillet, J. P. Bazureau, and J. Hamelin, *J. Chem. Res. (S)*, 32 (1999).
99JCR(S)252 G. K. Jananeshwara, V. H. Deshpande, and A. V. Bedekar, *J. Chem. Res. (S)*, 252 (1999).
99JCR(S)420 J. A. Seijas, M. P. Vazquez-Tato, M. M. Martinez, and G. Nunez-Corredoira, *J. Chem. Res. (S)*, 420 (1999).
99JCR(S)688 J. -X. Wang, X. Wu, Y. Hu, K. Zhao, and Z. Liu, *J. Chem. Res. (S)*, 688 (1999).
99JCR(S)718 H. Kaddar, J. Hamelin, and H. Benhaoua, *J. Chem. Res. (S)*, 718 (1999).
99JCS(D)2133 J. -D. Holberg and K. R. Seddon, *J. Chem. Soc., Dalton Trans.*, 2133 (1999).
99JCS(P1)2421 J. Habermaann, S. V. Ley, and R. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2421 (1999).
99JCS(P2)2111 P. Goncalo, C. Roussel, J. M. Melot, and J. Vebrel, *J. Chem. Soc., Perkin Trans. 2*, 2111 (1999).
99JHC333 R. W. Sabnis, D. W. Rangnekar, and N. D. Sonawane, *J. Heterocycl. Chem.*, **36**, 333 (1999).
99JHC1565 R. S. Varma, *J. Heterocycl. Chem.*, **36**, 1565 (1999).
99JMC3835 M. Alterman, H. O. Andersson, N. Garg, G. Ahlsen, S. Lovgren, B. Classon, U. H. Danielson, I. Kvarnstrom, L. Vrang, T. Unge, B. Samuelsson, and A. Hallberg, *J. Med. Chem.*, **42**, 3835 (1999).
99JOC3885 C. G. Blettner, W. A. Konig, W. Stenzel, and T. Schotten, *J. Org. Chem.*, **64**, 3885 (1999).
99JOC4539 K. Olofsson, S. Y. Kim, M. Larhed, D. P. Curran, and A. Hallberg, *J. Org. Chem.*, **64**, 4539 (1999).
99JOC5746 B. K. Banik, K. J. Barakat, D. R. Wagle, M. S. Manhas, and A. K. Bose, *J. Org. Chem.*, **64**, 5746 (1999).
99MI1 R. S. Varma, *Green Chem.*, **1**, 43 (1999).
99MI2 R. S. Varma, *Clean Prod. Processes*, **1**, 132 (1999).
99MI3 A. V. El'tsov, N. B. Sokolova, N. M. Dmitrieva, A. D. Grigor'ev, and A. S. Ivanov, *Russ. J. Gen. Chem.*, **69**, 1317 (1999).
99MI4 G. Sabitha, B. V. S. Reddy, S. Abraham, and J. S. Yavada, *Green Chem.*, **1**, 251 (1999).
99MI5 G. W. Muller, W. E. Konnecke, A. M. Smith, and V. D. Khetani, *Org. Process. Rev. Dev.*, **3**, 139 (1999).
99OL611 S. Knapp and K. Malolanarasimhan, *Org. Lett.*, **1**, 611 (1999).
99S254 C. Nemes and J. Y. Laronze, *Synthesis*, 254 (1999).
99SC863 B. Das and B. Venkataiah, *Synth. Commun.*, **29**, 863 (1999).
99SC1349 T. Lipinska, E. Guibe-Jampel, A. Petit, and A. Loupy, *Synth. Commun.*, **29**, 1349 (1999).

99SC2731 A. K. Mitra, A. De, and N. Karchaudhuri, *Synth. Commun.*, **29**, 2731 (1999).
99SC2807 H. M. Meshram, G. Sumithra, G. S. Reddy, Y. S. S. Ganesh, and J. S. Yadav, *Synth. Commun.*, **29**, 2807 (1999).
99SC3237 M. Kidwai and P. Misra, *Synth. Commun.*, **29**, 3237 (1999).
99SC3627 G. K. Jananeshwara, A. V. Bedekar, and V. H. Deshpande, *Synth. Commun.*, **29**, 3627 (1999).
99SC4071 G. V. Reddy, G. V. Rao, and D. S. Iyengar, *Synth. Commun.*, **29**, 4071 (1999).
99SL1597 S. Chandrasekhar, M. B. Padmaja, and A. Raza, *Synlett.*, 1597 (1999).
99SL1642 C. T. Brain and J. M. Paul, *Synlett.*, 1642 (1999).
99SL1745 G. Sabitha, S. Abraham, B. V. S. Reddy, and J. S. Yadav, *Synlett.*, 1745 (1999).
99T9623 J. R. Carrillo, A. Diaz-Ortiz, A. de la Hoz, M. J. Gomez-Escalonilla, A. Moreno, and P. Prieto, *Tetrahedron*, **55**, 9623 (1999).
99T10851 S. Deshayes, M. Liagre, A. Loupy, J. L. Luche, and A. Petit, *Tetrahedron*, **55**, 10851 (1999).
99T13957 H. Shiraishi, T. Nishitani, T. Nishihara, S. Sakaguchi, and Y. Ishii, *Tetrahedron*, **55**, 13957 (1999).
99TL165 G. Sabitha, M. M. Reddy, D. Srinivas, and J. S. Yadov, *Tetrahedron Lett.*, **40**, 165 (1999).
99TL167 P. Micuch, L. Fisera, M. K. Cyranski, and T. M. Krygowski, *Tetrahedron Lett.*, **40**, 167 (1999).
99TL1587 P. de la Cruz, A. Diaz-Ortiz, J. J. Garcia, M. J. Gomez-Escalonilla, A. de la Hoz, and F. Langa, *Tetrahedron Lett.*, **40**, 1587 (1999).
99TL1597 I. L. Pinto, R. L. Jarvest, and H. T. Serafinowska, *Tetrahedron Lett.*, **41**, 1597 (1999).
99TL1623 A. P. Combs, S. Saubern, M. Rafalski, and P. Y. S. Lam, *Tetrahedron Lett.*, **40**, 1623 (1999).
99TL3275 C. T. Brain, J. M. Paul, Y. Loong, and P. J. Oakley, *Tetrahedron Lett.*, **40**, 3275 (1999).
99TL3957 T. N. Danks, *Tetrahedron Lett.*, **40**, 3957 (1999).
99TL4889 P. de la Cruz, E. Espildora, J. J. Garcia, A. de la Hoz, F. Langa, N. Martin, and L. Sanchez, *Tetrahedron Lett.*, **40**, 4889 (1999).
99TL9273 U. M. Lindstrom, B. Olofsson, and P. Somfai, *Tetrahedron Lett.*, **40**, 9273 (1999).
00CRV2537 D. T. McQuade, A. E. Pullen, and T. M. Swager, *Chem. Rev.*, **100**, 2537 (2000).
00CSR239 N. Elander, J. R. Jones, S. Y. Lu, and S. S. Elander, *Chem. Soc. Rev.*, **29**, 239 (2000).
00IJC(B)458 M. Kidwai, K. R. Bhushan, and P. Misra, *Indian J. Chem., Sect. B*, **39B**, 458 (2000).
00JCR(S)179 L. Liao and D. Villemin, *J. Chem. Res. (S)*, 179 (2000).
00JCS(P1)999 A. S. Gajare, N. S. Shaikh, G. K. Jnaneshwara, V. H. Deshpande, T. Ravindranathan, and A. V. Bedekar, *J. Chem. Soc., Perkin Trans. 1*, 999 (2000).
00JCS(P1)3815 S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, and S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 3815 (2000).
00JIC46 M. Kidwai, N. Negi, and P. Misra, *J. Indian Chem. Soc.*, **77**, 46 (2000).
00JOC4537 K. S. A. Vallin, M. Larhed, K. Johansson, and A. Hallberg, *J. Org. Chem.*, **65**, 4537 (2000).

00JOC7984 M. Alterman and A. Hallberg, *J. Org. Chem.*, **65**, 7984 (2000).
00M945 S. Balalaie, A. Arabanian, and M. S. Hashtroudi, *Monatsh Chem.*, **131**, 945 (2000).
00MI1 J. Cleophax, M. Liagre, A. Loupy, and A. Petit, *Org. Process. Res. Dev.*, **4**, 498 (2000).
00MI2 G. S. Owens and M. M. Abu-Omar, *Chem. Commun.*, 1165 (2000).
00MI3 B. Perio and J. Hamelin, *Green Chem.*, **2**, 252 (2000).
00MI4 J. S. Yadav and B. V. S. Reddy, *New J. Chem.*, **24**, 489 (2000).
00MI5 J. Fraga-Dubreuil, J. R. Cherouvrier, and J. P. Bazureau, *Green Chem.*, **2**, 226 (2000).
00MI6 S. Balalaie and A. Arabanian, *Green Chem.*, **2**, 274 (2000).
00OPP81 H. M. S. Kumar, B. V. Subbareddy, P. T. Reddy, D. Srinivas, and J. S. Yadav, *Org. Prep. Proc. Int.*, **32**, 81 (2000).
00S1004 U. Bremberg, S. Lutsen Ko, N. -F. K. Kaiser, M. Larhed, A. Hallberg, and C. Mobert, *Synthesis*, 1004 (2000).
00S1380 M. P. Singh, S. Sasmal, W. Lu, and M. N. Chatterjee, *Synthesis*, 1380 (2000).
00SC171 G. Bratulescu, Y. Le Bigot, and M. Delmas, *Synth. Commun.*, **30**, 171 (2000).
00SC1725 M. Gianotti, G. Martelli, G. Spunta, E. Campana, M. Panunizo, and M. Mendozza, *Synth. Commun.*, **30**, 1725 (2000).
00SC2191 C. G. Penieres, A. I. Bonifas, C. J. G. Lopez, E. J. G. Garica, and T. C. Alvarez, *Synth. Commun.*, **30**, 2191 (2000).
00SC3031 M. Kidwai, P. Misra, K. R. Bhushan, and B. Dave, *Synth. Commun.*, **30**, 3031 (2000).
00SC3971 Z. Li, X. Wang, and Y. Da, *Synth. Commun.*, **30**, 3971 (2000).
00SL75 B. C. Ranu, A. Hajra, and U. Jana, *Synlett.*, 75 (2000).
00SL701 J. S. Yadav, B. V. S. Reddy, R. Srinivas, and T. Ramalingam, *Synlett.*, 701 (2000).
00SL1273 H. M. Meshram, K. C. Sekhar, Y. S. S. Ganesh, and J. S. Yadav, *Synlett.*, 1273 (2000).
00T5465 P. Micuch, L. Fisera, M. K. Cyranski, T. M. Krygowski, and J. Krajcik, *Tetrahedron*, **56**, 5465 (2000).
00T5473 T. Vidal, A. Petit, A. Loupy, and R. N. Gedye, *Tetrahedron*, **56**, 5473 (2000).
00T8769 D. Bogdal and M. Warzala, *Tetrahedron*, **56**, 8769 (2000).
00TL1539 F. Bentiss, M. Lagrenee, and D. Barbry, *Tetrahedron Lett.*, **41**, 1539 (2000).
00TL5031 A. Y. Usyatinsky and Y. L. Khmelnitsky, *Tetrahedron Lett.*, **41**, 5031 (2000).
00TL5891 J. C. Lee and I. G. Song, *Tetrahedron Lett.*, **41**, 5891 (2000).
01AGE4680 C. A. Briehn, M. S. Schiedel, E. M. Bonsen, W. Schuhmann, and P. Bauerle, *Angew. Chem. Int. Engl.*, **40**, 2680 (2001).
01EJO3437 D. R. Greve, J. J. Apperloo, and R. A. J. Janssen, *Eur. J. Org. Chem.*, 3437 (2001).
01JCS(P1)1220 A. Loupy, S. J. Song, S. M. Sohn, Y. M. Lee, and T. W. Kwon, *J. Chem. Soc., Perkin Trans. 1*, 1220 (2001).
01M279 H. -P. Buchstaller, C. D. Siebert, R. H. Lyssy, I. Frank, A. Duran, R. Gottschlich, and C. R. Noe, *Monatsh. Chem.*, **132**, 279 (2001).
01MI1 C. O. Kappe, *Combinatorial Chem.*, 314 (2001).
01MI2 M. Larhed and A. Hallberg, *Drug Discov. Today*, **6**, 406 (2001).
01MI3 D. A. Davies, C. Schnik, J. Silver, J. L. Sosa-Sanchez, and P. G. Riby, *J. Porphyrins Phthalocyanines*, **5**, 376 (2001).
01MI4 N. Kuhnert and T. N. Danks, *Green Chem.*, **3**, 68 (2001).

01MI5 J. -F. Zhou, J. -M. Xu, and H. Zhong, *Hua Xue Yan Jiu Yu Ying Yong*, **13**, 78 (2001).

01MI6 L. -Q. Song, G. -Z. Tan, and X. -L. Xu, *He Cheng Hua Xue*, **9**, 175 (2001).

01OL157 D. J. Hlasta, *Org. Lett.*, **3**, 157 (2001).

01OL4279 W. C. Shieh, S. Dell, and O. Repic, *Org. Lett.*, **3**, 4279 (2001).

01S581 N. Meddad, M. Rahmouni, A. Derdour, J. P. Bazureau, and J. Hamelin, *Synthesis*, 581 (2001).

01S999 J. A. Seijas, M. P. Vazquez-Tato, C. Gonzalez-Bande, M. M. Martinez, and B. Pacios-Lopez, *Synthesis*, 999 (2001).

01S1313 E. Cros, M. Planas, and E. Bardaji, *Synthesis*, 1313 (2001).

01SC19 X. Wang, Z. Li, and Y. Da, *Synth. Commun.*, **31**, 19 (2001).

01SC33 S. M. S. Chauhan, B. B. Sahoo, and K. A. Srinivas, *Synth. Commun.*, **31**, 33 (2001).

01SL218 P. M. Fresneda, P. Molina, and M. A. Sanz, *Synlett.*, 218 (2001).

01SL234 J. C. Lee and J. H. Choi, *Synlett.*, 234 (2001).

01SL382 C. T. Brain and S. A. Brunton, *Synlett.*, 382 (2001).

01SL753 A. de la Hoz, A. Diaz-Ortiz, J. M. Fraile, M. V. Gomez, J. A. Mayoral, A. Moreno, A. Saiz, and E. Vazquez, *Synlett.*, 753 (2001).

01SL875 J. A. Seijas, M. P. Vazquez-Tato, and M. M. Martinez, *Synlett.*, 875 (2001).

01SL1092 B. F. Bonini, C. Femoni, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, and G. Varchi, *Synlett.*, 1092 (2001).

01SL1251 S. P. Chavan, P. Soni, and S. K. Kamat, *Synlett.*, 1251 (2001).

01SL1893 L. Ohberg and J. Westman, *Synlett.*, 1893 (2001).

01T163 K. Bougrin, A. Loupy, A. Petit, B. Daou, and M. Soufiaoui, *Tetrahedron*, **57**, 163 (2001).

01T4365 S. Chatti, M. Bortolussi, and A. Loupy, *Tetrahedron*, **57**, 4365 (2001).

01T4767 B. C. Ranu and A. Hajra, *Tetrahedron*, **57**, 4767 (2001).

01T9199 L. Perrux and A. Loupy, *Tetrahedron*, **57**, 9199 (2001).

01T9225 P. Lidstrom, J. Tiernery, B. Wathey, and J. Westman, *Tetrahedron*, **57**, 9225 (2001).

01TL7181 G. M. Castanedo and D. P. Sutherlin, *Tetrahedron Lett.*, **42**, 7181 (2001).

02ACR717 M. Larhed, C. Moberg, and A. Hallberg, *Acc. Chem. Res.*, **35**, 717 (2002).

02CM1742 A. Afzali, T. L. Breen, and C. R. Kagan, *Chem. Mater.*, **14**, 1742 (2002).

02JHC1045 M. Kidwai, R. Venkataramanan, and B. Dave, *J. Heterocycl. Chem.*, **39**, 1045 (2002).

02JHC1129 S. Selvi and P. T. Perumal, *J. Heterocycl. Chem.*, **39**, 1129 (2002).

02JOC3015 D. Wolker and G. Haufe, *J. Org. Chem.*, **67**, 3015 (2002).

02JOC3961 P. Blanchard, B. Jousselme, P. Frere, and J. Roncali, *J. Org. Chem.*, **67**, 3961 (2002).

02JOC8877 M. Melucci, G. Barbarella, and G. Sotgiu, *J. Org. Chem.*, **67**, 8877 (2002).

02JOC9077 A. R. Katritzky and S. K. Singh, *J. Org. Chem.*, **67**, 9077 (2002).

02MI1 A. Lew, P. O. Krutzik, M. E. Hart, and A. R. Chamberlin, *J. Comb. Chem.*, **4**, 95 (2002).

02MI2 J. Hamelin, J. P. Bazureau, and F. Texier-Boullet, in *"Microwaves in Organic Synthesis"* (A. Louby ed.), p. 253, Wiley-VCH, Weinheim (2002).

02MI3 C. O. Kappe, *Curr. Opin. Chem. Biol.*, **6**, 314 (2002).

02MI4 X. M. He, J. B. Lu, J. M. Lu, and X. L. Zhu, *Hecheng Huaxue*, **10**, 87 (2002) [*CA* **137**, 202686 (2002)].

02MI5 M. Andrzejewska, J. Kaminski, and Z. Kazimierczuk, *Nucleosides, Nucleotides & Nucleic Acids*, **21**, 73 (2002).
02MI6 V. V. Namboodiri and R. S. Varma, *Chem. Commun.*, 342 (2002).
02MI7 V. V. Namboodiri and R. S. Varma, *Chem. Commun.*, 917 (2002).
02MIP1 S. J. Kulkarni, K. V. Raghavan, R. K. Motkuri, and S. Nagabandi, PCT Pat. 0279205 (2002) [*CA* **137**, 279029 (2002)].
02OL2613 A. Finaru, A. Berthault, T. Besson, G. Guillaumet, and S. B. Raboin, *Org. Lett.*, **4**, 2613 (2002).
02OL4017 Y. Deng and D. J. Hlasta, *Org. Lett.*, **4**, 4017 (2002).
02S75 S. Paul, M. Gupta, R. Gupta, and A. Loupy, *Synthesis*, 75 (2002).
02S1502 L. D. S. Yadav and R. Kapoor, *Synthesis*, 1502 (2002).
02S1578 A. K. Bose, M. S. Manhas, S. N. Ganguly, A. H. Sharma, and B. K. Banik, *Synthesis*, 1578 (2002).
02S1669 V. Molteni, M. M. Hamilton, L. Mao, C. M. Crane, A. P. Termin, and D. M. Wilson, *Synthesis*, 1669 (2002).
02SC111 S. Joshi and A. V. Karnik, *Synth. Commun.*, **32**, 111 (2002).
02SC497 B. K. Karale, V. P. Chavan, A. S. Mane, R. V. Hangarge, C. H. Gill, and M. S. Shingare, *Synth. Commun.*, **32**, 479 (2002).
02SC927 H. Z. Li, J. S. Zhang, Y. M. Zhou, and T. S. Li, *Synth. Commun.*, **32**, 927 (2002).
02SC1097 X. Wang, Z. Li, B. Wei, and J. Yang, *Synth. Commun.*, **32**, 1097 (2002).
02SC2395 H. Yang, W. H. Sun, Z. Li, and L. Wang, *Synth. Commun.*, **32**, 2395 (2002).
02SC2467 G. V. Reddy, V. V. V. N. S. Rama Rao, B. Narsaiah, and P. S. Rao, *Synth. Commun.*, **32**, 2467 (2002).
02SC2549 Y. Bai, J. Lu, H. Gan, and Z. Wang, *Synth. Commun.*, **32**, 2549 (2002).
02SC3541 S. Paul, M. Gupta, and R. Gupta, *Synth. Commun.*, **32**, 3541 (2002).
02SC3703 J. Lu, B. Yang, and Y. Bai, *Synth. Commun.*, **32**, 3703 (2002).
02SL343 B. M. Barchin, A. M. Cuadro, and J. Alvarez-Builla, *Synlett.*, 343 (2002).
02SL731 K. B. Lindsay, M. Tang, and S. G. Pyne, *Synlett.*, 731 (2002).
02SL987 B. C. Ranu, S. Samanta, and A. Hajra, *Synlett.*, 987 (2002).
02SL1526 M. Mihara, Y. Ishino, S. Minakata, and M. Komatsu, *Synlett.*, 1526 (2002).
02SL2344 L. D. S. Yadav and R. Kapoor, *Synlett.*, 2344 (2002).
02T887 Y. -J. Cherng, *Tetrahedron*, **58**, 887 (2002).
02T1235 R. S. Varma, *Tetrahedron*, **58**, 1235 (2002).
02T2245 G. Sotgiu, M. Zambianchi, G. Barbarella, and C. Botta, *Tetrahedron*, **58**, 2245 (2002).
02T7355 B. A. Bhanu Prasad, R. Sanghi, and V. K. Singh, *Tetrahedron*, **58**, 7355 (2002).
02TL189 Y. Deng and D. J. Hlasta, *Tetrahedron Lett.*, **43**, 189 (2002).
02TL5381 V. V. Namboodiri and R. S. Varma, *Tetrahedron Lett.*, **43**, 5381 (2002).
02TL7005 M. A. P. Martins, P. Beck, W. Cunico, C. M. P. Pereira, A. P. Sinhorin, R. F. Blanco, R. Peres, H. G. Bonacorso, and N. Zanatta, *Tetrahedron Lett.*, **43**, 7005 (2002).
02TL9461 S. J. Tantry, Kantharaju, and V. V. Suresh Babu, *Tetrahedron Lett.*, **43**, 9461 (2002).
03MI1 H. E. Blackwell, *Org. Biomol. Chem.*, **1**, 1251 (2003).
03MI2 A. R. Katritzky and S. K. Singh, *Arkivoc*, **13**, 68 (2003).

03MI3 K. M. Al-Zaydi, R. M. Borik, and M. H. Elnagdi, *Molecules*, **8**, 910 (2003).

03OPP426 M. Kidwai and R. Mohan, *Org. Prep. Proc. Int.*, **35**, 426 (2003).

03S925 T. Bach and M. Bartels, *Synthesis*, 925 (2003).

03S1025 J. Westman and R. Lundin, *Synthesis*, 1025 (2003).

03S1157 T. Inagaki, T. Fukuhara, and S. Hara, *Synthesis*, 1157 (2003).

03S2185 J. Hamelin, A. Saoudi, and H. Benhaoua, *Synthesis*, **14**, 2185 (2003).

03SL63 A. P. E. Hoener, B. Henkel, and J. C. Gauvin, *Synlett.*, 63 (2003).

03SL797 G. Luppi and C. Tomasini, *Synlett.*, 797 (2003).

03SL1117 H. Uchida, H. Tanikoshi, S. Nakamura, P. Y. Reddy, and T. Toru, *Synlett.*, 1117 (2003).

03SL1283 S. Murugesan, N. Karst, T. Islam, I. M. Wiencek, and R. J. Linhardt, *Synlett.*, 1283 (2003).

03SL1847 R. Martinz-Palou, G. de Paz, J. Marin-Cruz, and L. G. Zepeda, *Synlett.*, 1847 (2003).

03SL2193 V. Y. Pavlov, M. M. Kabachink, E. V. Zobnina, V. P. Timofeev, I. O. Konstantinov, B. G. Kimel, G. V. Ponomarev, and I. P. Beletskaya, *Synlett.*, **14**, 2193 (2003).

03TL123 J. C. Lee, H. J. Choi, and Y. C. Lee, *Tetrahedron Lett.*, **44**, 123 (2003).

03TL175 R. S. Pottrof, N. K. Chadha, M. Katkevics, V. Ozola, E. Suna, H. Ghane, T. Regberg, and M. R. Player, *Tetrahedron Lett.*, **44**, 175 (2003).

03TL1709 S. Balalaie, M. M. Hashemi, and M. Akhbari, *Tetrahedron Lett.*, **44**, 1709 (2003).

04H903 Y. Xu and Q. -X. Guo, *Heterocycles*, **63**, 903 (2004).

04JCR(S)174 M. A. Al-Shiekh, A. M. Salah El-Din, E. A. Hafez, and M. H. Elnagdi, *J. Chem. Res. (S)*, 174 (2004).

04MI1 A. A. dos Santos, E. P. Wendler, F. de A. Marques, and F. Simonelli, *Lett. Org. Chem.*, **1**, 47 (2004).

04MI2 K. M. Khan, Z. Ullah, M. Rani, S. Perveen, S. M. Haider, M. I. Choudhary, Atta-ur-Rahman, and W. Voelter, *Lett. Org. Chem.*, **1**, 50 (2004).

04OL795 X. Lei and J. A. Porco Jr., *Org. Lett.*, **6**, 795 (2004).

04OL1453 S. E. Wolkenberg, D. D. Wisnoski, W. H. Leister, Y. Wang, Z. Zhao, and C. W. Lindsley, *Org. Lett.*, **6**, 1453 (2004).

04SC377 H. M. Abdel Hamid, E. Ramadan, M. Hagar, and E. S. H. El Ashry, *Synth. Commun.*, **34**, 377 (2004).

04SL723 E. S. H. El Ashry, E. Ramadan, H. M. Abdel Hamid, and M. Hagar, *Synlett.*, 723 (2004).

05UP1 E. S. H. El Ashry, E. Ramadan, H. M. Abdel Hamid, and M. Hagar, *J. Chem. Res.* (*S*), (2005), in press.

05UP2 E. S. H. El Ashry, E. Ramadan, H. M. Abdel Hamid, and M. Hagar, *Lett. Org. Chem.*, (2005), submitted.

Organometallic Complexes of the η^2(N, C)-Coordinated Derivatives of Pyridine

ALEXANDER P. SADIMENKO

Department of Chemistry, University of Fort Hare, Alice 5701, Republic of South Africa

Abbreviations

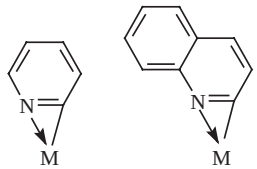
Ac	acetyl
AN	acetonitrile
Ar	aryl
Bipy	2,2′-bipyridine
Bu	butyl
Bz	benzyl
cod	cyclooctadiene-1,4
COE	cyclooctene
COT	cyclooctatetraene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
cyclen	1,4,7,10-tetraazacyclododecane
dba	dibenzylideneacetone
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppm	diphenylphosphinomethane
EBI	ethylenebis(indenyl)
en	ethylenediamine
Et	ethyl
Me	methyl
Mes	mesityl
OTf	triflate

ADVANCES IN HETEROCYCLIC CHEMISTRY
VOLUME 88 ISSN: 0065-2725 DOI: 10.1016/S0065-2725(04)88002-4

Ph	phenyl
phen	1,10-phenanthroline
PPN	bis(triphenylphosphoranylidene) ammonium
Pr	propyl
py	pyridine
solv	solvated
THF	tetrahydrofuran
TMEDA	tetramethylenediamine
tmen	tetramethylethylenediamine
Vin	vinyl

I. Introduction

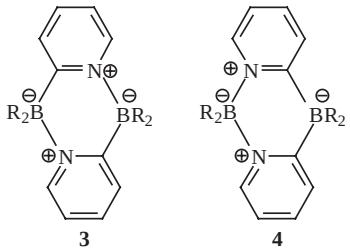
A previous chapter of our series on the organometallic chemistry of pyridines and their analogs (04AHC(86)293) embraced all the possible coordination modes but the η^2(N, C) pattern. There can be two major cases of such bonding: (i) the structures of the types **1** and **2** (90JA2814, 95P3315, 95P3335) and (ii) cyclometallation in suitably substituted pyridine ligands (96MI1). The η^2(N, C)-coordinated species of types **1** and **2** are important in solving the problem of denitrification of fuels, while the cyclometallated species present new valuable materials.



1 **2**

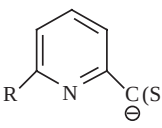
II. Non-Transition Elements

2-Lithiopyridine with bromodimethylborane gives a separable mixture of isomers **3** and **4**, where R = Me (93IC6115). The ethyl analogs of **3** and **4** exist (84H2471). The other derivatives that are mentioned in this respect are $[Me_2B(py)_2]X$ (X = Cl, Br) (74CB3104, 78JINC1289).

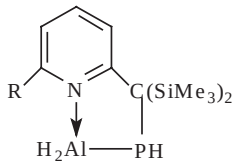


3 **4**

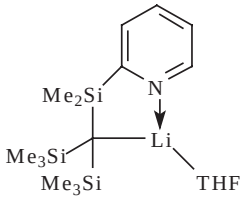
Ligands **5** (R = H, Me) are widely applied for the preparation of main group metal complexes (84P389, 90JCS(CC)1006, 91JCS(CC)1560, 93JCS(D)2653, 97JCS(CC)1183, 98JCS(CC)547, 98JCS(CC)575, 98OM779, 99OM389, 99OM4247). They easily form the PCl_2 and PH_2 complexes. The latter with AlH_3 form **6**. {Dimethyl(2-pyridyl)silyl}bis(trimethylsilyl)methyl gives a number of cyclometallated species with non-transition and transition metal compounds (00JCS(CC)691, 00OM3224). With methyl lithium in THF, **7** is the product; species **7** with potassium *t*-butylate gives **8**; lithium complex **7** with $[MgBr_2(OEt_2)_2]$ produces **9**, while with chromium(III) chloride in THF, **10** and minor amount of **11** are obtained. Manganese(II) chloride in THF reacts differently and the product is **12**. The lithium derivative **7** and cobalt(II) bromide form **13**. Species **14** follows from $[PdCl_2(PPh_3)_2]$ and the lithium salt of the ligand. In turn, $[NiCl_2(PPh_3)_2]$ gives the nickel(I) complex **15** (00JCS(CC)691). The lithium salt of the ligand and $[NiCl_2(PPh_3)_2]$ also produce **16** due to the traces of the Ni–OH compound. Complexes of similar nature are **17** and **18** (93P1613, 96P135, 98JOM(564)193, 01JCS(D)1541). $[Li(THF)\{C(SiMe_3)_2(SiMe_2C_5H_4N\text{-}2)\}]$ with $[MgBr_2(OEt)_2]$ yields **19** (67AX332, 00OM3224, 01JOM(631)76). Another representative of organomagnesium chemistry is **20** (01JOM(631)76). The anionic ligands **5** (R = H, Me) react with *n*-butyl lithium and then SiX_nCl_{4-n} (X = H, *n* = 1; X = Me, *n* = 1–3) to yield a series of species **21** (Y = Z = Cl, X = H, Me, R = H, Me; Z = Cl, X = Y = Me, R = H, Me; X = Y = Z = Me, R = H, Me) (00OM4437). The ligands with CH_2SiMe_3 substituent behave differently and in a sequence of reactions with *n*-butyl lithium and trichloromethyl- or dichlorodimethylsilane give the products **22** (X = Cl, Me; R = H, Me), where the nitrogen heteroatom does not participate in coordination. The lithium salt of $C(SiMe_3)_2(SiMe_2C_5H_4N\text{-}2)$ with MCl_2 (M = Ge, Sn, Pb) forms species **23** (M = Ge, Sn, Pb) (01OM1223). Compound **23** (M = Sn) oxidatively adds methyl iodide to yield **24**. The product reacts with silver triflate and *p*-tosylate to give **25** and **26**, respectively.



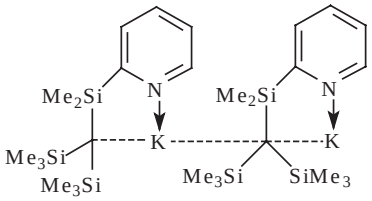
5



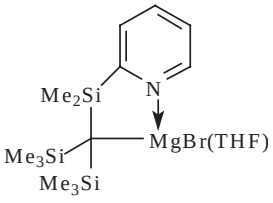
6



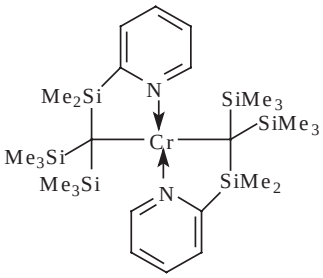
7



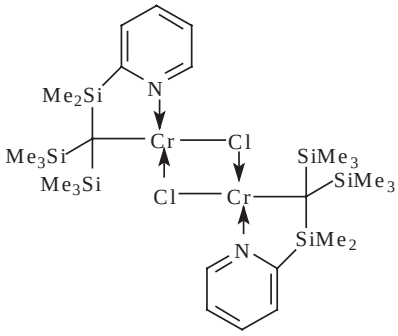
8



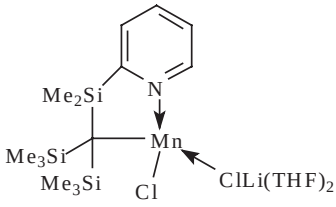
9



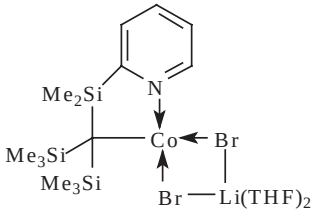
10



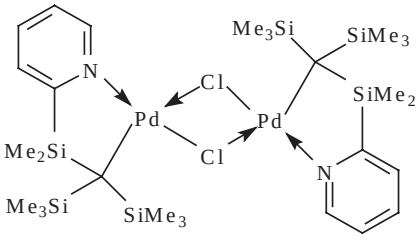
11



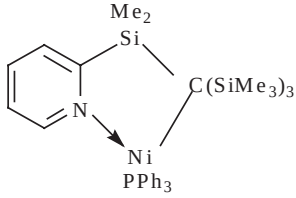
12



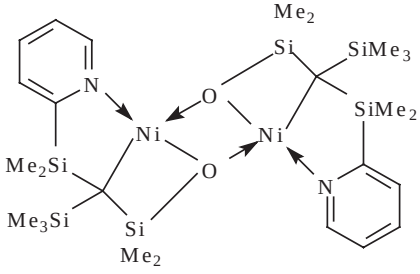
13



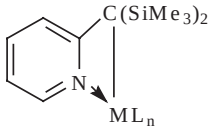
14



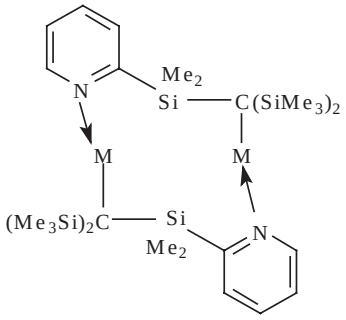
15



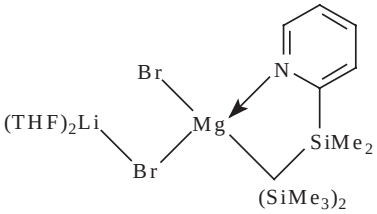
16



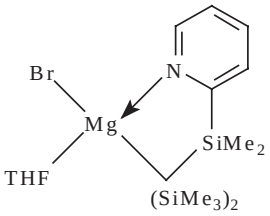
17



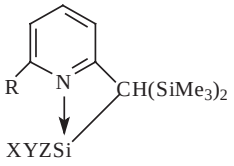
18



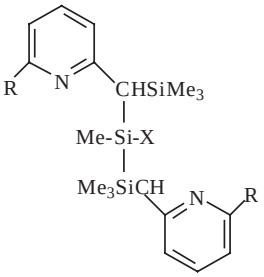
19



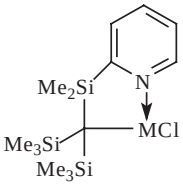
20



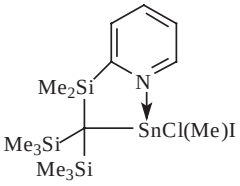
21



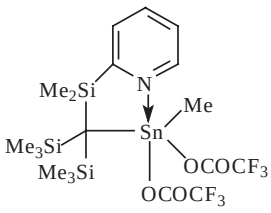
22



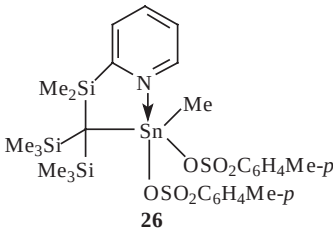
23



24

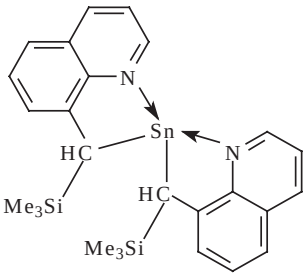


25

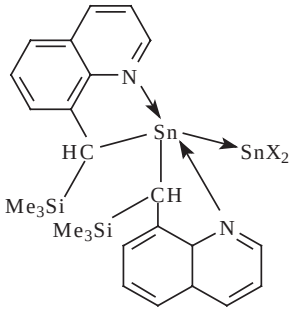


26

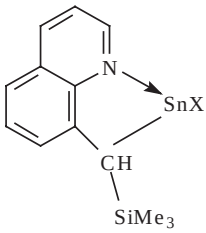
The organolithium compound [Li{CH(SiMe$_3$)C$_9$H$_6$N-8}(TMEDA)] reacts with tin(II) chloride to yield **27** (97JCS(D)4301). Reaction of the product with SnX_2 (X = Cl, Br) forms adducts **28** (X = Cl, Br) (97JA1145, 03OM1751) and prolonged reaction gives the products **29** (X = Cl, Br) (03OM1751). The same reaction but run under reflux gives **30** (X = Cl; Br), which can alternatively be the product of the reflux of **29** (X = Cl, Br) in THF, or the chlorine product may follow from [Li{CH(SiMe$_3$)C$_9$H$_6$N-8}(TMEDA)] and $SnCl_4$ in diethyl ether. A compound of a similar nature is [Sn{C(SiMe$_3$)$_2$C$_5$H$_4$N-2}X] (X = Cl, N(SiMe$_3$)$_2$) (88CB347, 91JCS(CC)1302).



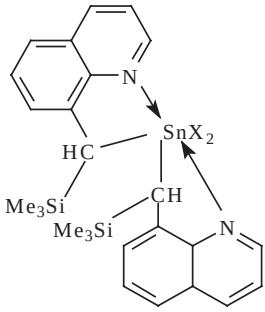
27



28

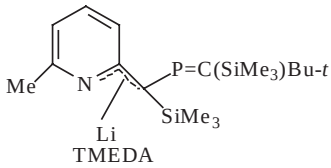


29



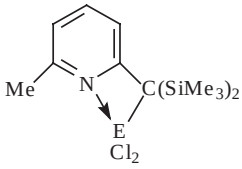
30

[LiC(SiMe$_3$)$_2$(2-NC$_5$H$_3$Me-6)] (00OM4437, 01JCS(D)996) reacts with P≡CBu-*t* in the presence of TMEDA to yield the η^3-azaallyl species **31** (02JOM(645)256). A similar mode is observed in [Li(TMEDA){C(SiMe$_3$)$_2$(2-NC$_5$H$_4$N)}] (84JCS(CC)1708, 90JCS(D)1161).

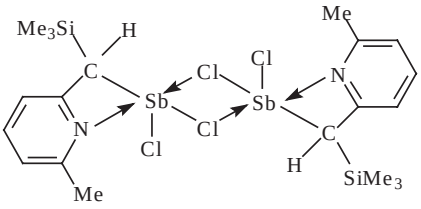


31

2-Bis(trimethylsilyl)methylpyridine and 6-methyl-2-bis(trimethylsilyl)methylpyridine (L) form η^1-alkyls $[(LiL)_2]$, ionic species $(AlL_2)^+(AlCl_4)^-$ (95JOM(500)289), chelated non-transition metal complexes (91JCS(CC)1560), and organometallic [2 + 2] cycloaddition derivatives of non-transition metals (98JCS(CC)575). Thus, with *n*-butyl lithium and then ECl_3 (E = P, As, Sb), products of the type **32** (E = P, As, Sb) are formed. 6-Methyl-2-trimethylsilylmethylpyridine with *n*-butyl lithium and then $SbCl_3$ forms **33** (00JOM(607)213).

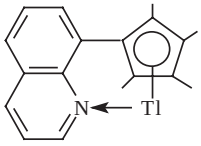


32



33

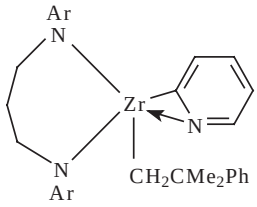
1-(8-Quinolyl)-2,3,4,5-tetramethylcyclopentadiene with thallium(I) ethoxide gives the thallium(I) species **34** with the mixed $\eta^5(C):\eta^1(N)$ mode of coordination (00EJIC1923).



34

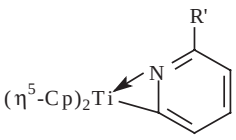
III. Titanium Group

Interaction of (2,6-methylpyridyl)methyl lithium with $[(\eta^5\text{-Cp})MCl_2]$ (M = Zr, Hf) gives complexes $[(\eta^5\text{-Cp})_2M(CH_2py\text{-}CH_2\text{-}6\text{-}Me)_2]$, where the pyridine ligands are not equivalent (87OM891). One of them is C-bonded but the other is η^2(N, C)-coordinated. Pyridine with $[(Me_2N)Zr\{N(Ar)(CH_2)_3N(Ar)\}]$ and $MeNH_2Cl$ gives the η^1(N)-coordinated $[(py)_2ZrCl_2\{N(Ar)(CH_2)_3N(Ar)\}]$, where Ar = 2, 6-*i*-$Pr_2C_6H_3$. Treatment of the product with $PhMe_2CCH_2MgCl$ gives the η^2(N, C)-coordinated species **35** (95OM5478) with the pattern similar to that in related species (87JA203, 87OM2053).

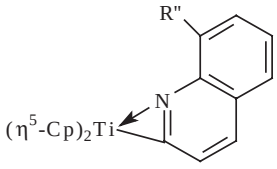


35

The reaction of $[(\eta^5\text{-Cp})_2\text{TiR}]$ (R = Me, Et, *n*-Bu) with 2-substituted pyridines, quinoline, and 8-methylquinoline gives the type of the cyclometallated structures described as the α-metallated species **36** (R′ = Me, Vin, Ph) and **37** (R″ = H, Me) (78JCS(CC)659, 81JOM(214)53). The products are paramagnetic and contain one unpaired electron.



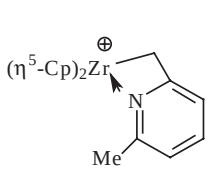
36



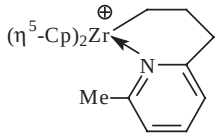
37

Insertion reactions predominate in the chemistry of $[(\eta^5\text{-Cp})_2\text{M(pyridyl)}]^+$ (M = Ti, Zr, Hf) complexes (78IC3257, 79JA3659, 81CL719, 85JOM(279)281, 85OM1006, 86TL2829, 87JA2788, 88JA2310, 88JA7128, 89JA778, 89JA2870, 89JA3336, 89JA4486, 89JA4495, 89JA9113, 89JOC2793, 89JOC3521, 89TL3495, 90JA4600, 90JA7994, 90OM524, 90OM871, 90OM1546, 90OM2116, 90OM2190, 91OM3470). A general route for the complexes $[(\eta^5\text{-Cp})_2\text{Zr(R)L}]^{n+}$ (n = 0, 1; R = alkyl; L = labile ligand) with pyridine and its derivatives is towards the η^2(N, C)-coordinated pyridyl complexes followed by the N-coordination and metallation or activation of the *o*-C–H moiety (90NJC505, 91ADOC325, 92ACR57, 93JOC5995, 94TPS158, 95MI2, 96JCS(D)255). Species **38** (90OM2116) containing a four-membered metallocycle can be prepared from $[(\eta^5\text{-Cp})\text{Zr(THF)(Me)}]$ and 2,6-lutidine (91JA1833). With ethylene it gives **39**, with $CH_2{=}CHR$ (R = Me, CH_2SiMe_3)—**40** (R = Me, CH_2SiMe_3), with trimethylsilylacetylene—**41**, dimethylacetylene—**42**, and with benzaldehyde or benzophenone—**43** (R = H, Ph), all containing six-membered chelate rings. Treatment of **38** with AN is a different reaction leading to **44**. Then on heating through the proven stage of **45**, the insertion product **46** is formed, which again contains the six-membered metallocycle. 2,6-Diethylpyridine with $[(\eta^5\text{-Cp})_2\text{Zr(Me)(THF)}](BPh_4)$ yields **47** (92JA8991), the C–H activated product (80JOM(198)41), similar to $[(\eta^5\text{-Cp})_2\text{Zr}\{\eta^2\text{-(C, N)-(CH(CH}_2\text{-6-methylpyrid-2-yl))}\}(\text{py})]^+$ (87JA4111). With carbon monoxide **47** gives **48** (92JA8991), retaining the η^2(N, C)-coordination mode (80JOM(188)245, 81IC1496, 83JCS(CC)1419, 83JOM(254)281, 84JCS(CC)1708, 86JCS(CC)672, 87AGE681, 87JCS(D)3085, 87OM2498, 88JCS(CC)336, 90JA1289). Species **47** with nitriles gives **49** (R = Me, *t*-Bu) and with $(PhCH_2)Et_3NCl$, **50**.

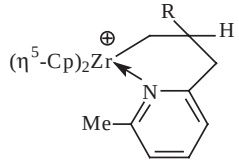
Comprehensive X-ray analysis of **50** shows that the coordination situation in such complexes is averaged between the chelated structure **50** and aza-allyl structure **51**, which can be generalized to complexes **47**, **48**, and **49** on the basis of spectral characteristics. The same reasoning follows for the structures of [(η^5-Cp)$_2$Zr{η^2-(N, C)-CH(SiMe$_3$)pyrid-2-yl}Cl] (86JCS(D)605) and [(η^2-Cp)$_2$Zr{η^2(C, N)-CH$_2$(6-methylpyrid-2-yl)}{CH$_2$(6-methylpyrid-2-yl)}] (90OM2375).



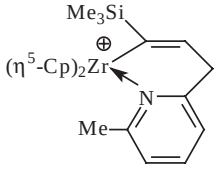
38



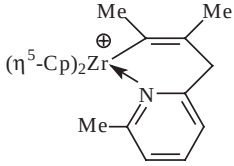
39



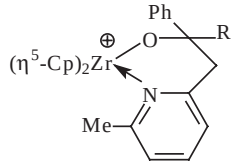
40



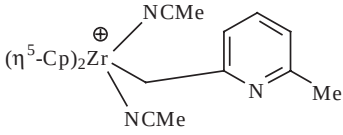
41



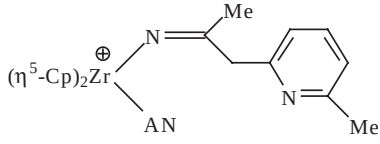
42



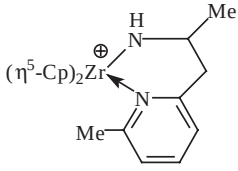
43



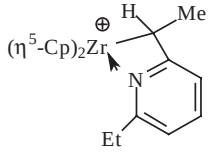
44



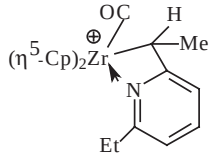
45



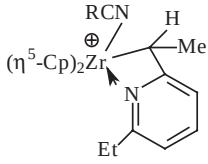
46



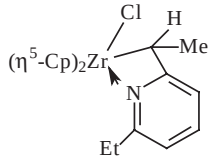
47



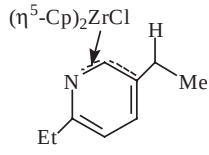
48



49

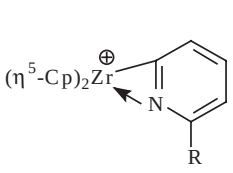


50

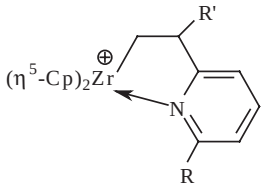


51

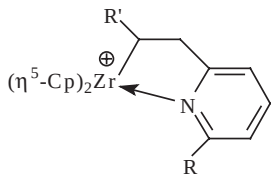
Species **52** (R = H, Me, Ph, Me_3Si) undergo insertion reactions with olefins $CH_2{=}CHR'$ (R′ = H, Me, Ph) to yield a mixture of isomers **53** and **54** (R = H, Me, Ph, Me_3Si; R′ = H, Me, Ph) (89JA778, 90OM1546, 90OM2116, 90OM2190, 91JA1833, 91OM3470, 92JOC5994). Complexes **55** ($n = 4$, 8) result from the corresponding zirconium dimethyl and 2-picoline (94JA4491). They are also able to insert $CH_2{=}CHR'$ (R = H, Me, Ph, Me_3Si) with elimination of 2-picoline to yield **56** ($R^1 = R^2 = H$, $R^3 = Me$; $R^1 = Ph$, $R^2 = R^3 = H$; $R^1 = Me_3Si$, $R^2 = R^3 = H$; $R^1 = R^2 = H$, $R^3 = Me_3Si$; $R^1 = R^2 = Me$, $R^3 = H$; $R^1 = R^3 = Me$, $R^2 = H$). Disubstituted olefins $R^2C{=}CR^3$ ($R^2 = R^3 = H$, Me) add to species **57** (R^1 = Me, Ph, H) to give **58** ($R^1 = R^2 = R^4 = Me$, $R^3 = H$; $R^1 = R^2 = R^3 = Me$, $R^4 = H$; R^1 = Ph, $R^2 = R^3 = H$, $R^4 = Me$; $R^1 = R^2 = R^4 = H$, $R^3 = Me$). Complexes **59**, **60** (89JA778) and **61** (94JA4491, 97OM5541) are catalysts of the functionalization of pyridines (99EJIC1047).



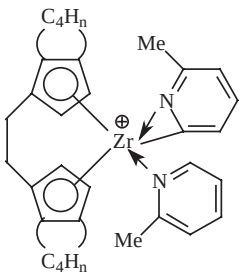
52



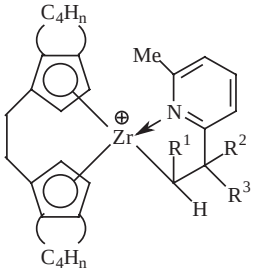
53



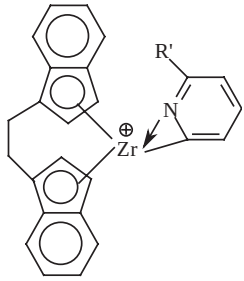
54



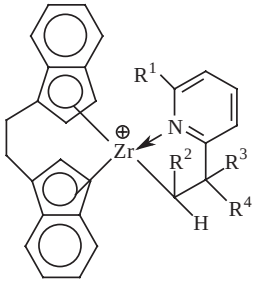
55



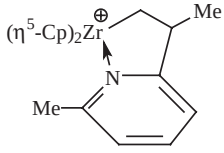
56



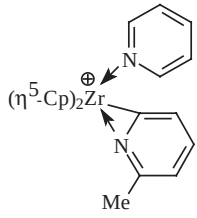
57



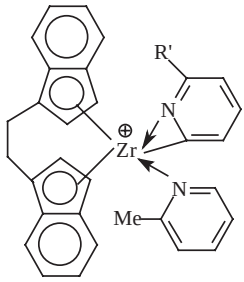
58



59



60

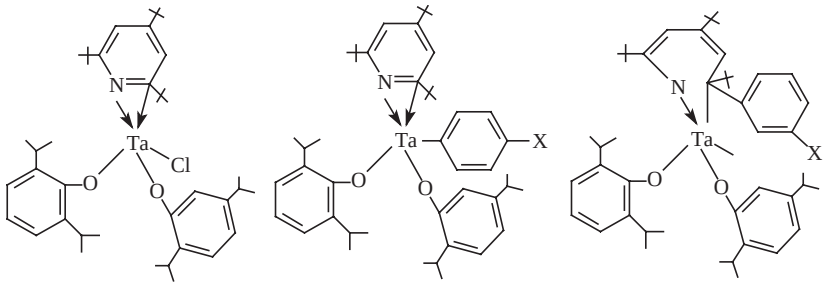


61

A series of pyridines reacts with [(EBI)$ZrMe_2$] in the presence of $B(C_6F_5)_3$ to yield the η^2(N, C)-coordinated species of composition [(EBI)Zr($R^3R^5R^6$-pyrid-2-yl)][-$MeB(C_6F_5)_3$] ($R^3 = R^5$ = H, Me, Ph, R^3 = Me, R^5 = H, R^6 = Me; R^3 = H, $R^5 = R^6$ = Me; $R^3 = R^5$ = Me, R^6 = H) (97OM5541). The products with propene form the η^2(N, C)-coordinated insertion species [(EBI)Zr{CH_2CHMe(pyrid-2-yl)}][-$MeB(C_6F_5)_3$]. Starting materials enter into insertion reactions with α-olefins (92CRV965, 94JA4491, 95AGE1143, 96AGE1263).

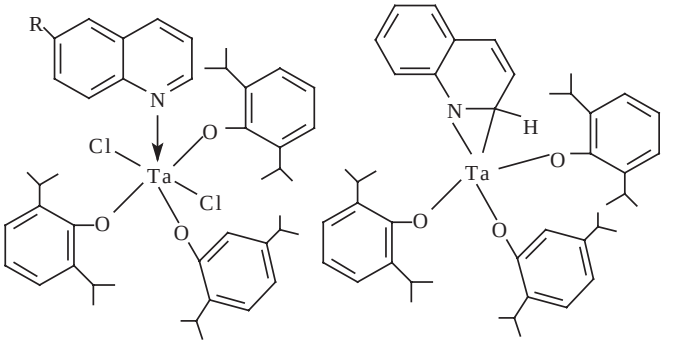
IV. Vanadium Group

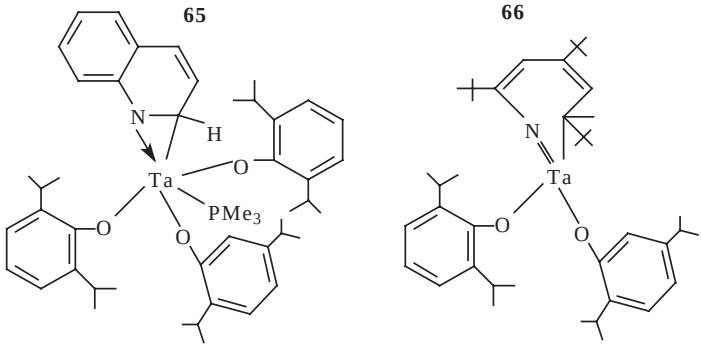
The η^2(N, C)-coordinated species **62** (92OM1275) with $LiBEt_3H$ gives the ring-opened product Ta═(NC^{t}Bu═CHC^{t}Bu═CHCH^{t}Bu)$(OAr)_2$ (81JCS(D)2088, 83JA2651, 87JA4720, 89IC3095, 92JA5462, 94PIC239, 95JA10678, 96JA5132, 97JA247, 97P3139). With phenyl lithium, the product is **63** (X = H) (95OM5588). In a similar way, species of the type **64** (X = OMe, Me, Cl, CF_3) are prepared using either 4-X-C_6H_4MgBr (X = OMe, Me, Cl) or Li-4-C_6H_4X (X = CF_3). In these species as well as in [{η^2-(C, N)-NC_5H_5}$Ta(OSi^tBu_3)_3$] (88JA4421, 91IC2494) and [{η^2-(C, N)-$NC_{10}H_9$}$Ta(OAr)_3(PMe_3)$] (92JA5462, 95P3315), the η^2-coordination causes the interruption of aromatic delocalization in the pyridine ring. Thermolysis of the complexes **63** (X = H, OMe, Me, Cl, CF_3) causes the ring opening and formation of **64** (X = H, OMe, Me, Cl, CF_3).



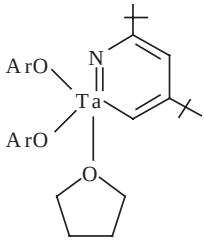
62 **63** **64**

Quinoline and 6-methylquinoline with [Ta(O-2,6-$C_6H_3Pr^i_2$)$_3$Cl$_2$] give the η^1(N)-coordinated species **65** (R = H, Me) (92JA5462). Reduction of **65** (R = H) with sodium amalgam gives the η^2(N, C)-product **66**. The starting organotantalum precursor, 6-methylquinoline, and trimethylphosphine in the presence of sodium amalgam give **67** with a metallaaziridine structure. A similar 2,4,6-tri-*tert*-butyl complex **66** (92OM1275) reacts with $LiBEt_3H$ to yield the ring-opened product **68**.



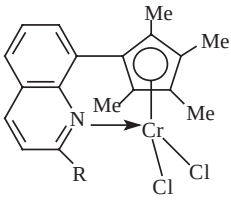


The η^2(N, C)-complex of composition [{η^2(N, C)-2,4,6-$NC_5{}^tBu_3H_2$}Ta(OAr)$_2$Me] follows from [{η^2(N, C)-2,4,6-$NC_5{}^tBu_3H_2$}Ta(OAr)$_2$Cl] (95JA10678). In THF it thermolyzes into the metallapyridine complex **69**, while in benzene thermolysis leads to the metallapyridine dimer [Ta(μ-NC^{t}Bu=CH^{t}Bu=CH)(OAr)$_2$]$_2$ (98OM322). Similar transformations are known (97JOM(528)225).

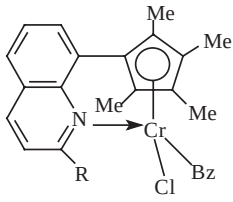


V. Chromium and Manganese Group

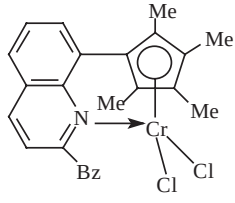
Species **70** (R = H) (01OM5005) on treatment with benzylmagnesium chloride produces a mixture of isomers **71** and **72** (03JOM(687)125). Species **70** (R = Me) gives the dinuclear product **73**. All these compounds are prospective catalysts for olefin polymerization.



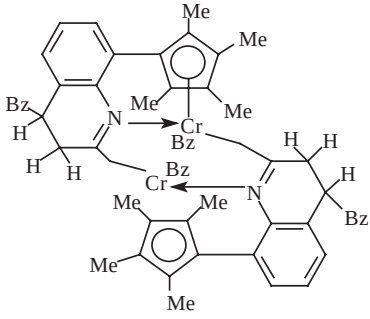
70



71

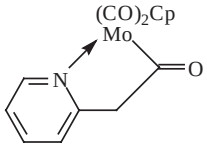


72



73

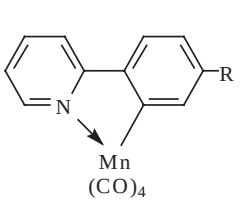
The cyclometallated product [(η^5-Cp)Mo(CO)$_2$(L)] (HL = 8-methylquinoline) follows from 8-bromomethylquinoline and Na[(η^5-Cp)Mo(CO)$_3$] (73JOM(66)219). Reaction of 2-chloromethylpyridine with Na[(η^5-Cp)Mo(CO)$_3$] gives **74** (66IC293), while interaction of this ligand with Na[(η^5-Cp)W(CO)$_3$] gives the η^1-alkyl complex [(η^5-Cp)Mo(CO)$_3$L] (L = 2-pyridylmethyl). Benzo[h]quinoline (L) and [(η^5-Cp)Mo(-CO)$_3$Me] give the cyclometallated species [(η^5-Cp)Mo(CO)$_3$L] (73JOM(60)343).



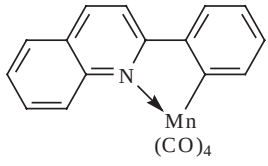
74

2-Phenylpyridine with alkylpentacarbonyl manganese species gives the cyclomanganated products (82MI1, 95MI1). Complexes **75** (R = H, Me), **76** and **77** follow from the corresponding heteroaromatic ligand and pentacarbonyl (η^1-benzyl) manganese (73JOM(60)343, 75AJC1259, 97OM5171). Interaction of **75**

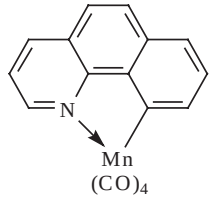
(R = H, Me) with phenyl lithium or **76** with phenyl or 2-naphthyl lithium and subsequent alkylation by methyl or ethyl triflate gives the $\eta^1 : \eta^3$ coordinated species **77**, **78** (R″ = Me, Et) and **79** (R′ = Ph, 2-$C_{10}H_7$) (97OM5171). Cyclomanganated 2-phenylpyridine (75AJC1259), 2-*p*-tolylpyridine (**75**, R = H, Me) and 2-phenylquinoline **76** (73JOM(60)343) were entered into the reaction with aryl lithiums and then quenched with alkyl triflates, ROTf, to yield the products **81** (R = H, R′ = Ph, R″ = Me, R = Me, R′ = Ph, R″ = Me, Et) and **80** (R′ = Ph, 2-$C_{10}H_7$) (97OM5171). Reaction of 2-vinylpyridine with [$Re(CO)_5Me$] gives **82**, although structure **83** could not be excluded (80JCS(D)1974). Photolysis of [$Re_2(CO)_9(py)$] gives a mixture of **84**, [$Re_2(CO)_{10}$], and [$Re(CO)_3(py)_3$][$HRe_4(CO)_{16}$]. Thermolysis of [$Re_2(CO)_8(py)_2$] gives **85** (82OM1143). Prolonged reaction leads to [$Re_2(CO)_7$ (py)(C_5H_4N)H] (83OM515).



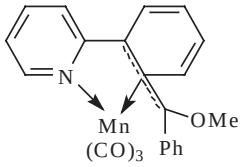
75



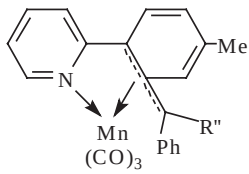
76



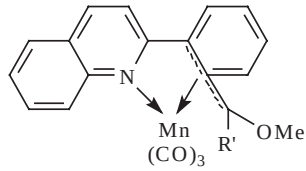
77



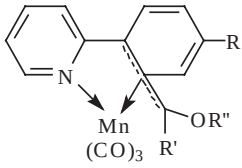
78



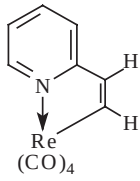
79



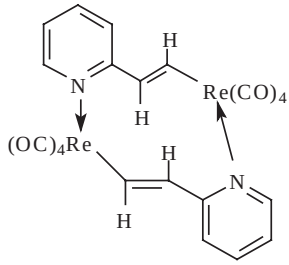
80



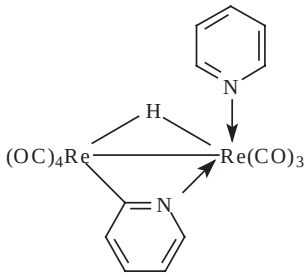
81



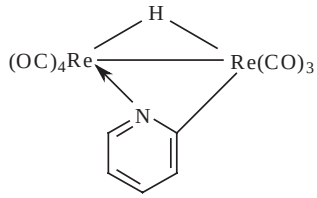
82



83

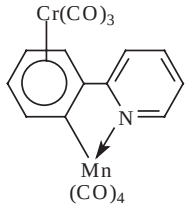


84

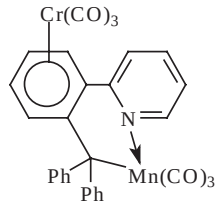


85

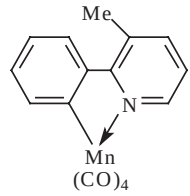
Species **86** reacts with N_2CPh_2 to yield **87** (00CEJ1064). Species **88**, which does not contain the $Cr(CO)_3$ framework, reacts with Ph_2CN_2 similarly but the product is $\eta^3 : \eta^1$(N)-coordinated, **89** (02OM3519). Species **86** and **87** with 9-diazafluorene form **90** and **91**, respectively. The same reaction route was noted for the chiral species **92** and cyclorhenated species **93**. However, in the latter case, along with the $\eta^6 : \eta^6$ product **94**, the η^2(N, C)-coordinated species **95** is obtained.



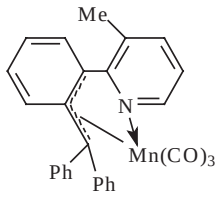
86



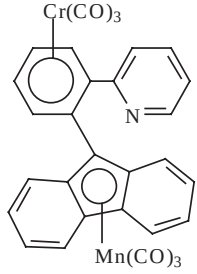
87



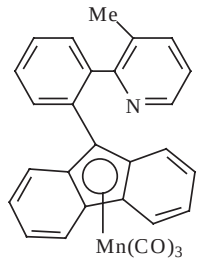
88



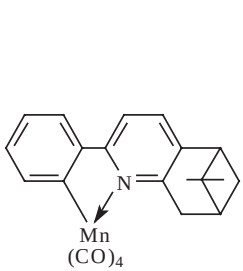
89



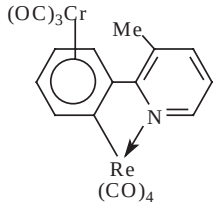
90



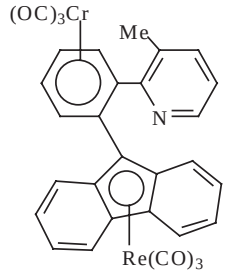
91



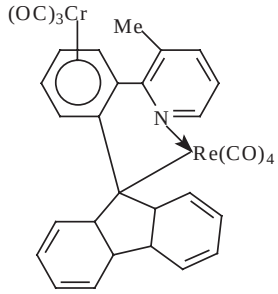
92



93

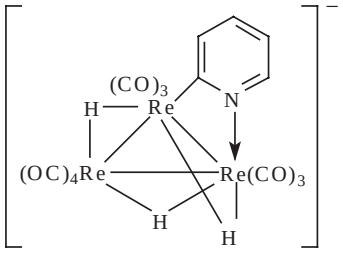


94

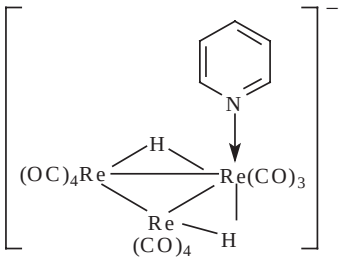


95

Pyridine with $[Re_3(\mu\text{-}H)_4(CO)_{10}]^-$ yields the η^2(C, N)-coordinated species **96** (93OM4863, 97OM2719). With carbon monoxide, the product gives $[Re_3(\mu\text{-}H)_2(CO)_{12}]^-$ with elimination of pyridine (95JOM(504)15). Similarly, $[Re_3(\mu\text{-}H)_4(CO)_{10}]^-$ is produced with hydrogen. If $[Re_3(\mu\text{-}H)_4(CO)_{10}]^-$ reacts with carbon monoxide in pyridine medium, the product is **97** with the η^1-coordination of the pyridine ligand as in $[Re_3(\mu\text{-}H)_3(CO)_{10}(py)_2]$ (80JOM(186)353), $[Re_3(\mu\text{-}H)_3(CO)_9(py)]^-$ (86JCS(D)2691).



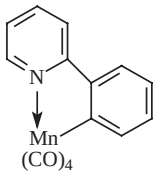
96



97

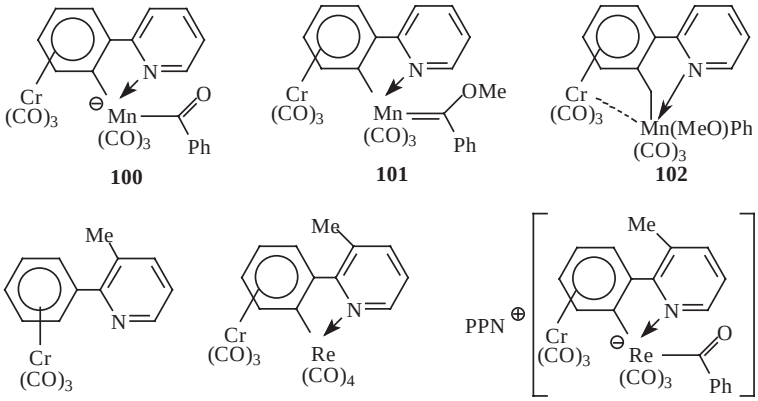
2-Phenylpyridine (68BCSJ1272, 71INCL943), 2-phenylquinoline (68BCSJ1272), and benzo[h]quinoline (71INCL943, 73JOM(60)343) are metallated at an aromatic carbon atom. 2-Vinylpyridine (69BCSJ1702), 8-methyl- and 8-ethylquinoline

(72JOM(36)389) are metallated elsewhere. 2-Phenylpyridine reacts with [MeM(CO)$_5$] (M = Mn, Re) to yield **98** (M = Mn, Re) (75AJC1259). 2-Vinylpyridine with [MeRe(CO)$_5$] is metallated via the route of vinylic elimination to yield **99**.



98 **99**

Cyclometallated complexes [(2-phenylpyridine)Re(CO)$_4$] react with nucleophiles at one of the two axial carbonyl moieties (98IC3649). Complex **100** reacts with methyl lithium to yield **101** with subsequent *cis*-migration to **102** (97OM657, 98EJIC1781, 98IC3649, 98JOM(567)65). Reaction of **103** with [PhCH$_2$Re(CO)$_5$] gives the cyclometallated product **104** (99OM2786). Application of phenyl lithium and then PPN$^+$ Cl$^-$ leads to **105**.

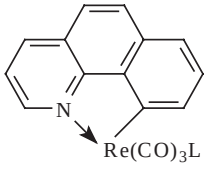


100 **101** **102**

103 **104** **105**

Species [Re(NC$_5$H$_4$CH=CH)(CO)$_4$] originating from 2-vinylpyridine contains the metallated vinyl carbon (75AJC1259).

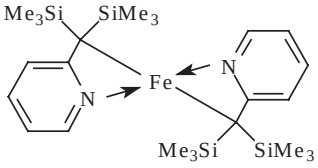
Reflux of benzo[h]quinoline and [Re(CO)$_5$Cl] gives the tetracarbonyl product **106** (L = CO) (73JOM(60)343, 93IC5633). An alternative route is the oxidative addition of benzo[b]quinoline on [Re$_2$(CO)$_{10}$] (93IC5633). With triphenylphosphine, the cyclometallated species **106** (L = CO) gives the product of the monocarbonyl substitution **106** (L = PPh$_3$).



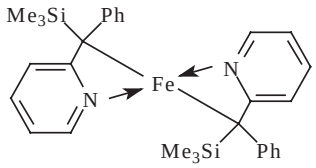
106

VI. Iron Group

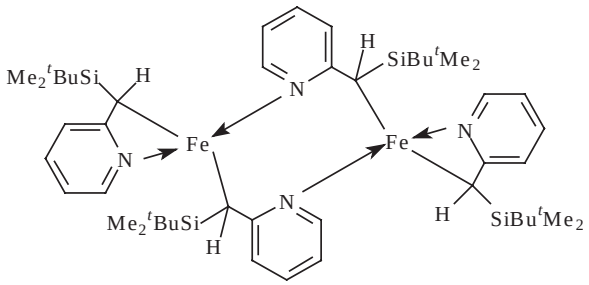
Pyridine reacts with $[FeMes]_2$ to yield $[FeMes_2(py)_2]$ (93OM2414, 94JA9123). Species $[FeL_2]$ (93JOM(443)C39) and $[CoL_2]$ (95JOM(489)C71) where $L = [C(SiMe_3)_2C_5H_5N\text{-}2]^-$ are known. The range of ligands in these species can be extended to $[CPh(SiMe_3)C_5H_4N\text{-}2]^-$, $[CH(Si^tBuMe_2)C_5H_4N\text{-}2]^-$ and $[CH(SiMe_3)_2C_9H_6N\text{-}8]^-$ (95OM4832). Corresponding lithium reagents with iron(II) chloride give rise to **107**, **108**, **109**, **110**, and **111** (96OM1785). Species $[Fe\{CPh(SiMe_3)\}(C_5H_4N\text{-}2)Cl(tmen)]$ is also $\eta^2(N,C)$-coordinated (93JOM(462)7, 95JOM(500)289).



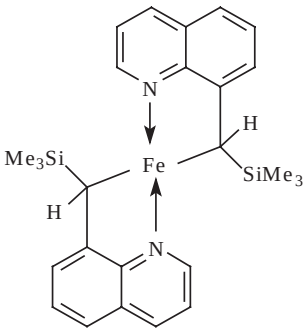
107



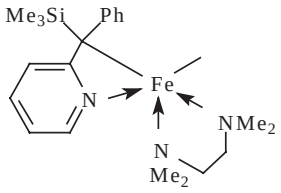
108



109

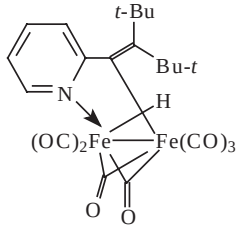


110



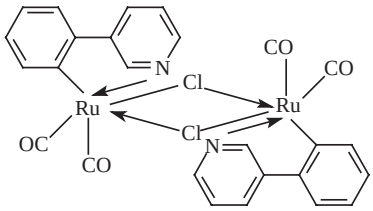
111

Pyridine with $[(t\text{-}Bu_2C{=}C{=}C)Fe_2(CO)_8]$ gives the CO-substituted product followed by the addition of the C–H bond of the pyridine framework to the allylidene double bond, **112** (87JOM(318)157).

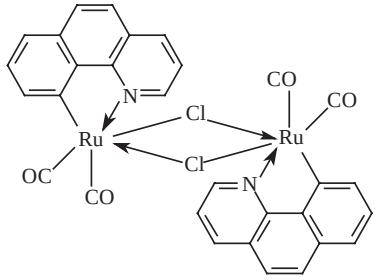


112

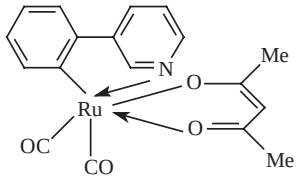
2-Phenylpyridine and benzo[h]quinoline react with a solution formed by bubbling carbon monoxide through a 2-methoxyethanol solution of $RuCl_3 \cdot 3H_2O$ to yield ruthenium(II) complexes **113** and **114** (79BCSJ1372). Thallium acetylacetonate and triphenylphosphine cleave the μ-Cl groups in **113** and **114** and give rise to the mononuclear species **115, 116, 117,** and **118**. 4-Methylpyridine reacts similarly.



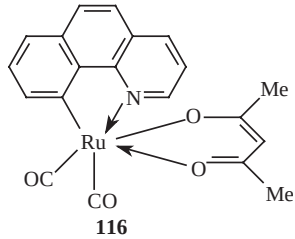
113



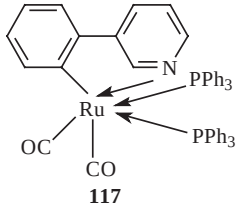
114



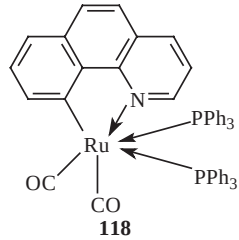
115



116

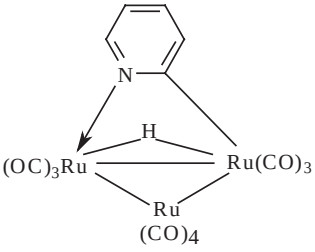


117

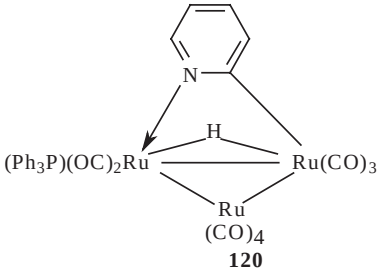


118

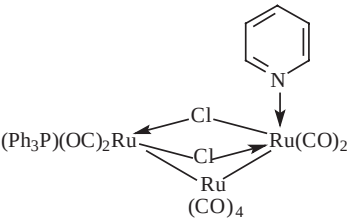
UV-photolysis of pyridine with $[Ru(CO)_5]$ gives the monosubstituted product $[Ru(CO)_4(py)]$ (97JCS(D)2997), which has an iron analog (74JA3438). As the UV source is removed, the product is gradually converted into the cluster $[Ru_3H(CO)_{10}(C_5H_4N)]$ (97JCS(D)2997) with the η^2(N, C)-coordination mode of 2-pyridyl (85JOM(296)147). Reaction of pyridine with $[Ru_3(CO)_{12}]$ gives the well-established cluster with the (C, N)-coordination of the heterocycle, **119** (86JOM(314)311, 91P227). The same product follows from pyridine and $[Ru_3(CO)_{10}(AN)_2]$ (85JOM(296)147). With $[Ru_3(\mu\text{-AuPPh}_3)(\mu\text{-Cl})(CO)_{10}]$, a mixture of numerous products is formed, most of them being non-pyridine-containing; among them are **119**, **120**, **121**,and **122** (94JOM(466)211). The only other example of pure η^1(N) coordination of the pyridine ring in ruthenium clusters is $[Ru_3(\mu\text{-H})(\mu\text{-CNMe}_2)(CO)_4(py)]$ (85OM1867). 2-, 3-, and 4-Methylpyridines give products similar to **119** (85JOM(294)123). Quinoline and $[Ru_3(CO)_{10}(AN)_2]$ form **123**, while isoquinoline under these conditions gives a mixture of isomers **124** and **125**.



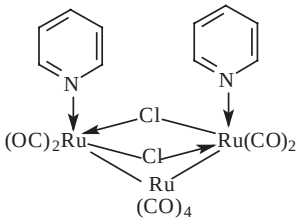
119



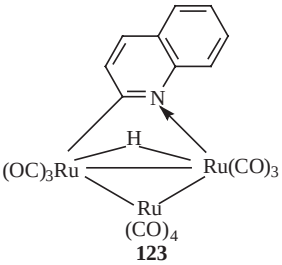
120



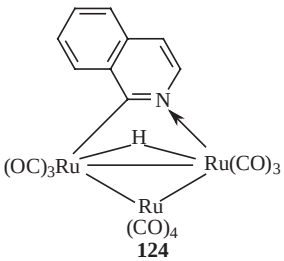
121



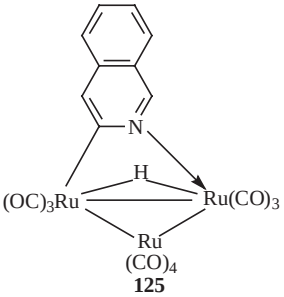
122



123

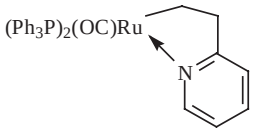


124



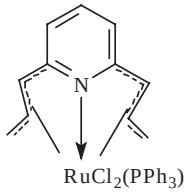
125

2-Vinylpyridine is inserted into the Ru–H bond of $[Ru(Cl)(H)(CO)(PPh_3)_2L]$ [L = 2-(2-pyridylethyl)], **126** (80CL449).



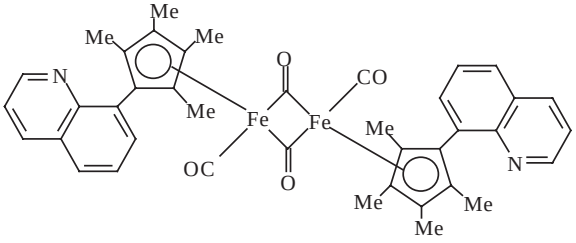
126

2,6-Diallylpyridine with $[RuCl_2(PPh_3)_3]$ gives the product **127** (87JOM(336)429), which with carbon monoxide forms $[RuCl_2(CO)_2(PPh_3)_2]$.

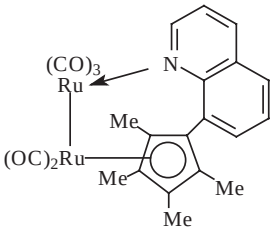


127

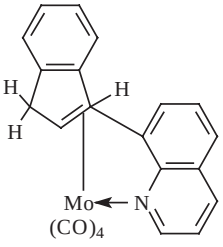
Cyclopentadiene derivatives of quinoline with $[Fe(CO)_5]$ give species of the type **128**. $[Ru_3(CO)_{12}]$ forms the derivative **129** with a combination of η^1(N) and $\eta^5(\pi)$-coordination as well as cyclometallation at the cyclopentadienyl ring (02JOM(641)81). Indene derivatives of quinoline lead to the η^1(N):η^2(indene) complexes **130** and **131** on reaction with $[Mo(CO)_6]$ and $[Rh(CO)_2Cl]_2$, respectively. The latter gives rise to the same coordination mode on reaction with the cyclopentadiene derivative of quinoline, and the product is described by structure **132**.



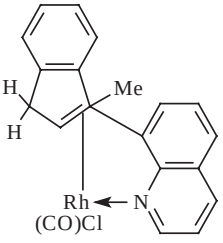
128



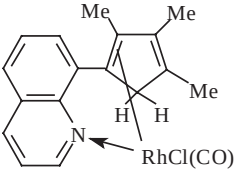
129



130

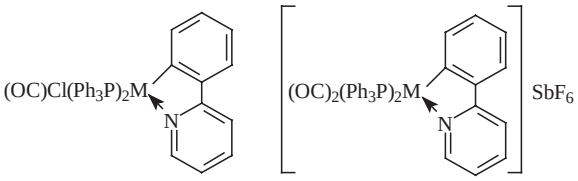


131



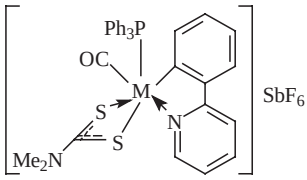
132

Cyclometallation of 2-phenylpyridine usually goes to the *o*-position (88IC3464, 89IC309, 89JA3855, 90CCR(97)193, 90JOM(395)359, 91ICA(182)93). $[Hg(pyPh)_2]$ reacts with $[MHCl(CO)(PPh_3)_3]$ (M = Ru, Os) to yield species **133** (M = Ru, Os) (99OM2813). With sodium iodide, the cyclometallated derivative with $(CO)I(Ph_3P)_2M$ (M = Ru, Os) moiety results. Carbonylation in the presence of $AgSbF_6$ gives **134** (M = Ru, Os), and the reaction with NaS_2CNMe_2 yields **135** (M = Ru, Os). Starting complexes with $Cu(NO_3)_2$ in acetic anhydride initially give **136** (M = Ru, Os) and then later **137** (M = Ru, Os). Bromination of the phenyl ring is achieved by $PyH^+Br_3^-$ to yield **138** (M = Ru, Os), and for M = Os in excess of brominating agent—**139**. $[Os(\eta^2\text{-8-quinolyl})Cl(CO)(PPh_3)_2]$ contains a four-membered chelate ring (97JOM(545)619, 98OM4535). Interaction of $[RuLCl_3]$ (L = 2,2′:6′,2″-terpyridine) with 2-phenylpyridine and thallium hexafluorophosphate gives the cyclometallated $[Ru(2\text{-}Phpy)(L)Cl]^+$ (86JOM(301)203, 02IC6521). By reaction with AN in the presence of Tl^+, the product is converted into $[Ru(2\text{-}Phpy)(L)(AN)]^{2+}$ (02IC6521). Further substitution with $NO^\bullet$ radical gives the nitrosyl complex $[Ru(2\text{-}Phpy)(L)(NO)]^{2+}$.

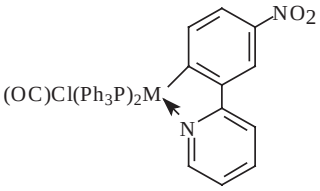


133

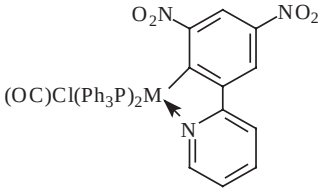
134



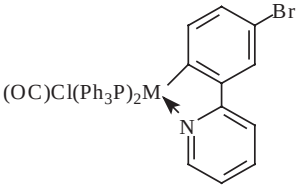
135



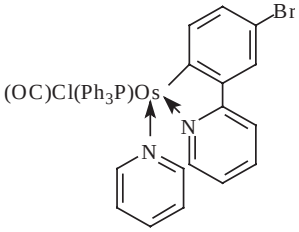
136



137



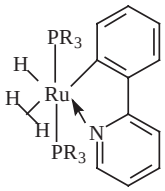
138



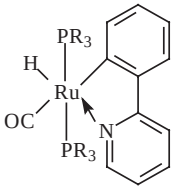
139

The reaction of 2-phenylpyridine with $[(Cy_3P)_2RuH_2(\eta^2\text{-}H_2)]$ gives the cyclometallated product **140** (R = Cy) (98JA4228). A similar compound, **140** (R = *i*-Pr),

follows from [(η^4-cod)Ru(COT)], molecular hydrogen, tri(*iso*-propyl)phosphine, and 2-phenylpyridine. The latter on carbonylation gives **141** (R = *i*-Pr).

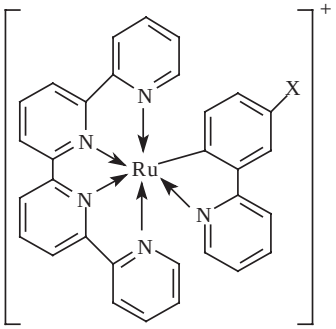


140



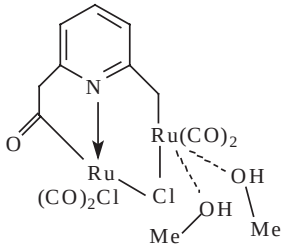
141

Cyclometallated cationic ruthenium(II) complexes **142** (X = H, Br, C≡CH) are building blocks for the constitution of molecular wires (90JOM(381)203, 98JCS(CC)663, 98TL7873, 00EJIC1581, 01JOM(624)388).

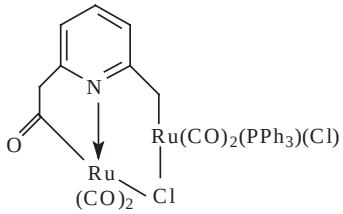


142

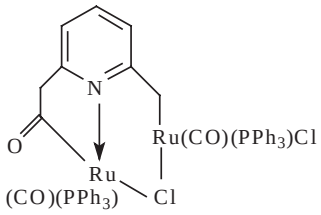
2-Chloromethylpyridine with [$Ru_3(CO)_{12}$] yields a mononuclear cycloruthenated pyrid-2-yl methyl carbonyl species (97P577). 2,6-Bis(chloromethyl)pyridine under these conditions gives the dinuclear Ru(II) species, where the role of the bridge belongs to the pyridine-2,6-diyl-2-methylcarbonyl-6-methyl framework (96CL773). 2,6-Bis(chloromethyl)pyridine with [$Ru_3(CO)_{12}$] in methanol gives **143** and then in the presence of triphenylphosphine—**144**, and further—**145** (96CL773).



143

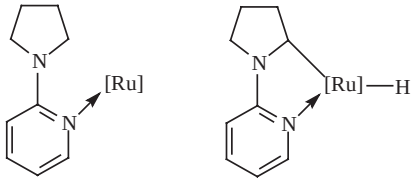


144



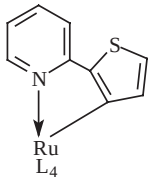
145

$[Ru_3(CO)_{12}]$ catalyzes alkylation of 2-(1-pyrrolidinyl)pyridine and the process is believed to occur through the stages of the formation of the η^1(N)-complex **146** and then C–H activation to yield the η^2(N, C)-cyclometallated structure **147**, where the nature of [Ru] has not been identified (01JA10935).



146 **147**

Reaction of 2-thienylpyridine with $[RuCl_2(CO)_3]_2$ gives the chlorine-bridged dimer $[Ru(CO)_2L(\mu\text{-}Cl)]_2$ (HL = 2-thienylpyridine), which can be converted into mononuclear complexes of the type **148** (L = py, *n*-Bu_3P) when treated with pyridine or tri-*n*-butylphosphine (81TMC163).

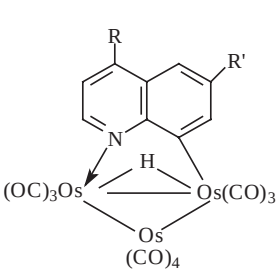


148

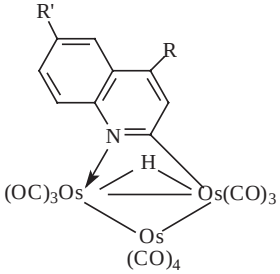
For the osmium clusters, the typical coordination situation of pyridine and its substituted derivatives is the η^2(C, N) mode (82JOM(233)C55, 90JPC5208). Complex $[HOs_3(CO)_{10}(\eta^2\text{-C, N-py})]$ can be prepared by the reaction of pyridine with $[Os_3(CO)_{10}(COE)_2]$ or $[Os_3(CO)_{10}(AN)_2]$ (77JOM(124)C19). In this situation the pyridine derivatives, 4-methylpyridine and 4-vinylpyridine, become *ortho*-metallated (75JCS(D)2091, 84P1175). Pyridine and $[Os_3(CO)_{11}(AN)]$ at room temperature give, however, the η^1(N)-coordinated substitution product $[Os_3(CO)_{11}(py)]$ (81JCS(D)407). Thermolysis leads to the *ortho*-metallated product (82JCS(D)2099). With $[Os_6(CO)_{18}]$, the only pyridine-containing product, $[Os_6(CO)_{17}(py)]$, is η^1(N)-coordinated and present in minor amounts (84JCS(CC)1089). Pyridine and $[Os_5H_2(CO)_{15}]$ give rise to the species $[Os_5H_3(CO)_{14}\{(\eta^2\text{-C,N-py}\}]$,

$[Os_5H_2(CO)_{14}\{\eta^1\text{-N})\text{-py}\}]$ and $\{Os_5H_2(CO)_{15}\{(\eta^1\text{-N})\text{-py}\}\}$ (87JCS(D)327). 2-Vinylpyridine with $[Os_3H_2(CO)_{10}]$ gives $[Os_3H(CO)_{10}(NC_5H_4CH{=}CH)]$, where the coordination is via the heteroatom, vinylic carbon, and vinylic C=C bond (85JCS(D)85). Pyridine and 2-alkyl- (aryl-) pyridines give $[Os_3H(CO)_{10}(\mu\text{-L})]$, where the pyridine ligand (L) performs the bridging C, N function and is metallated at position 2 of the heteroring (82JCS(D)787).

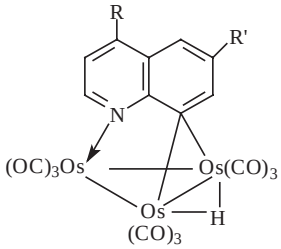
Quinoline and tetrahydroquinoline react with $[M_3(CO)_{12}]$ (M = Ru, Os) to give $[(\mu\text{-H})(\mu\text{-}\eta^2\text{-}C_9H_6N)M_3(CO)_{10}]$ (M = Ru, Os) (85OM2033, 86OM2193, 87NJC543, 90MI1), the product of the oxidative addition of the C(2)–H bond of the quinoline ring to $[M_3(CO)_{12}]$. The same type of products, **149** (R = R′ = H; R = Me, R′ = H; R = H, R′ = Me), results from the derivatives of quinoline and $[Os_3(CO)_{10}(AN)_2]$ (95OM3611, 02OM1508), but products **150** (R = R′ = H; R = Me, R′ = H; R = H, R′ = Me) are also formed in minor amounts. At elevated temperatures, decarbonylation of **149** (R = R′ = H; R = Me, R′ = H; R = H, R′ = Me) takes place, and the result is the formation of **151** (R = R′ = H; R = Me, R′ = H; R = H, R′ = Me); the process is reversible. Complexes **151** (R = R′ = H; R = Me, R′ = H; R = H, R′ = Me) undergo hydrogenation with $LiEt_3BH$ to give **152** (R = R′ = H; R = Me, R′ = H; R = H, R′ = Me). Protonation of **152** (R = R′ = H; R = Me, R′ = H; R = H, R′ = Me) by triflic acid gives **153** (R = R′ = H; R = Me, R′ = H; R = H, R′ = Me), and further hydrogenation/protonation sequence gives **154** (R = Me, R′ = H).



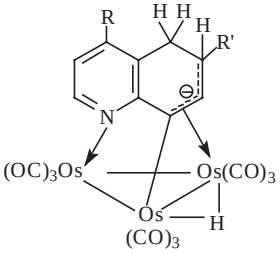
149



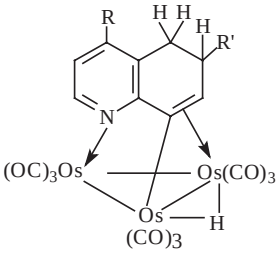
150



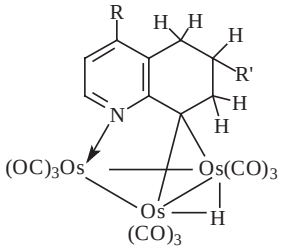
151



152



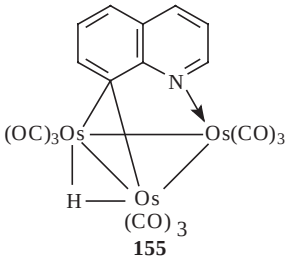
153



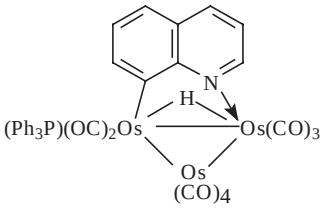
154

Quinoline with $[Os_3(CO)_{10}(AN)_2]$ gives cluster **155** on thermolysis or photolysis (95OM3611, 96OM1979, 98OM415, 99CCR(190)175, 00ICA(300)769). With triphenylphosphine, the substitution product **156** is formed. Hydrides and carbanions

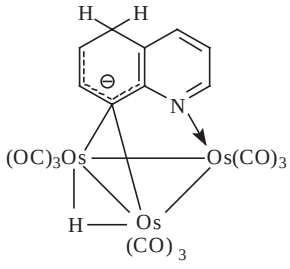
give the products of the nucleophilic attack at position 5 of the heteroring, which can be protonated to give **157** and **158** and deprotonated to restore **155**. With amines ($L = NH_3$, $EtNH_2$, Et_2NH, *t*-$BuNH_2$, *i*-$BuNH_2$, *n*-$BuNH_2$, $CyNH_2$), the substitution products **159** follow (98P2975). With trifluoroacetic acid, also the product of ligand substitution results, **160**, which is, however, in equilibrium with species **161** ($X = CF_3COO$). Complex **161** is a mere product of interaction of **155** with tetrafluoroboric acid ($X = BF_4$). The 3-aminoquinoline analog of **156** enters the reactions of CO ligand substitution to yield, for example, $[Os_3(CO)_9(\mu\text{-}\eta^2\text{-L-H})(\mu\text{-H})L']$ (L = 3-aminoquinoline, $L' = Na_3(P(C_6H_4SO_3)_3)$ (03JOM(668)51).



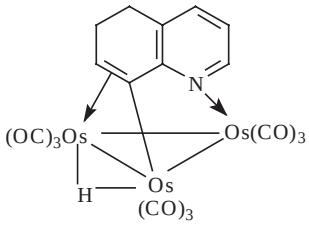
155



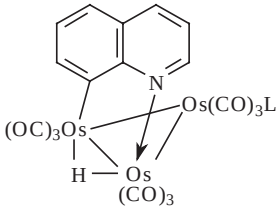
156



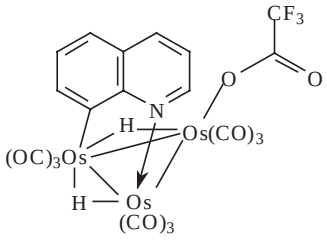
157



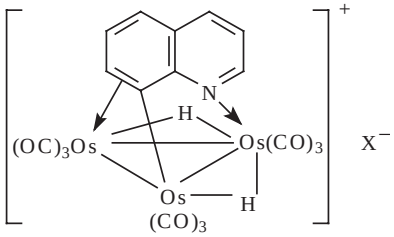
158



159



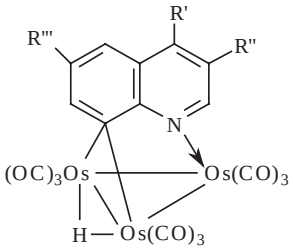
160



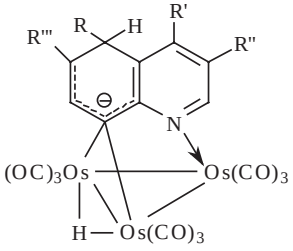
161

Although quinoline is preferably η^1(N)-coordinated (94OM4523), the μ_3-η^2(N, C)-coordinated species become typical in organoosmium chemistry (95OM3611, 98OM415, 98P2975). These possess interesting reactivity pattern (95MI3) in contrast to that of free quinolines, whose site for nucleophilic attack is position 2, or if position 2 is blocked, position 4 is engaged (77MI1). Thus, complex **162** ($R' = R'' = R''' = H$) when reacted with hydride anions gives **163** ($R = R' = R'' = R''' = H$) and on further protonation—**164** ($R = R' = R'' = R''' = H$). A similar process occurs when **162** ($R' = R'' = R''' = H$)

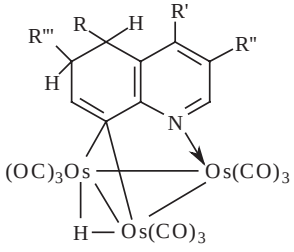
interacts with RLi [R = Me, *n*-Bu, *t*-Bu, Bz, Ph, Vin, $C_2(CH_2)_3Me$, CH_2CN, CMe_2CN, $CHS(CH_2)_2S$, CH_2COOBu-*t*] or RMgBr (R = Me, $CH_2{=}CHCH_2MgBr$) to yield **163** [R = Me, *n*-Bu, *t*-Bu, Bz, Ph, Vin, $CH_2{=}CHCH_2$, $C_2(CH_2)_3Me$, CH_2CN, $CHS(CH_2)_2S$, CH_2COOBu-*t*, R′ = R″ = R‴ = H] and on protonation—**164** with the same set of substituents as in **163** (98JA12818, 00JOM(593)226). The same reaction course can be noted for the derivatives of quinoline when the final products are **164** (R′ = Cl, R″ = R‴ = H, R = CMe_2CN, CH_2COOBu-*t*; R′ = Cl, R″ = R‴ = H, R = CH_2COOBu-*t*; R″ = R‴ = H, R″ = NH_2, R = CMe_2CN; R′ = R″ = H, R‴ = Cl, R = CMe_2CN).



162

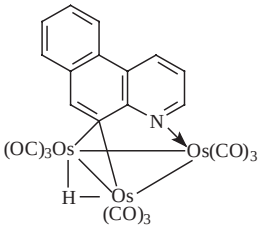


163

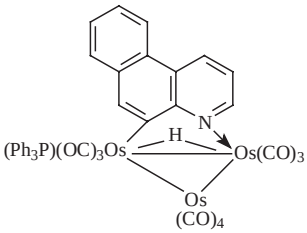


164

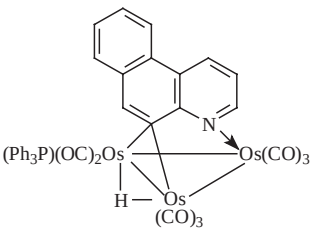
5,6-Benzoquinoline complex **165** is reactive with respect to triphenylphosphine to yield **166** (98OM415, 99OM3519). Thermolysis of **166** gives **167**. Complex **165** with $LiEt_3BH$ and then CF_3COOH gives **168** and with $LiMe_2CCN/CF_3COOH$—**169**. With *n*-butyl lithium/CF_3COOH, a mixture of products is obtained, **170**, **171**, and **172**.



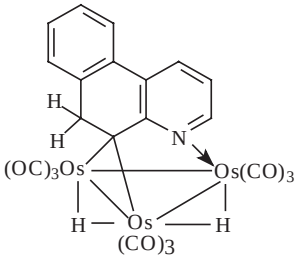
165



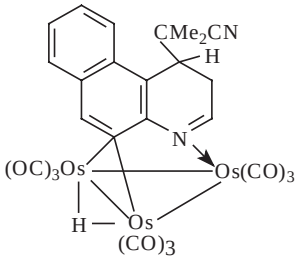
166



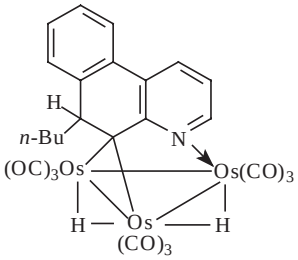
167



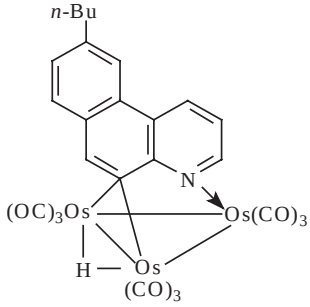
168



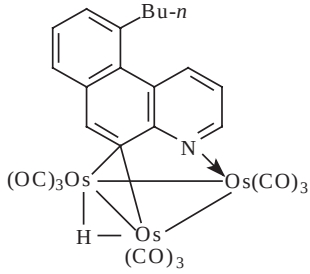
169



170

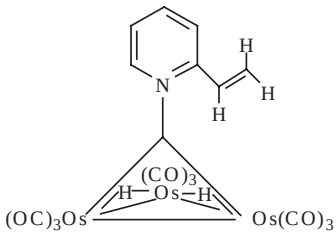


171

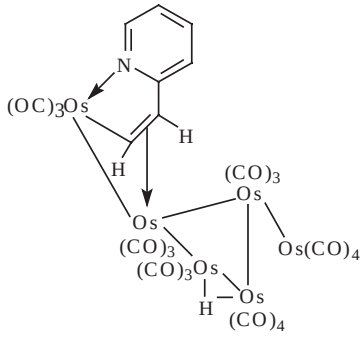


172

Cluster **173** (94JOM(474)C30) upon thermolysis in the presence of $[Os_3(CO)_{10}(AN)_2]$ rearranges into **174** (96JOM(513)27) containing along with the N-coordination , the η^2-coordination via the vinyl group. 2-Vinylpyridine and $[Os_3(CO)_{10}(AN)_2]$ in the presence of L (CO, PMe_2Ph) interact followed by the cleavage of the CH_2 proton of the vinyl group to yield the open structure of composition $[HOs_3(CO)_9L(NC_5H_4CH{=}CH)]$ (L = CO, PMe_2Ph) (85JCS(D)85).

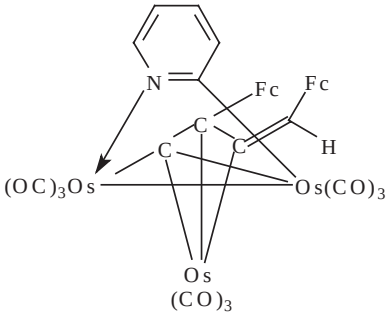


173

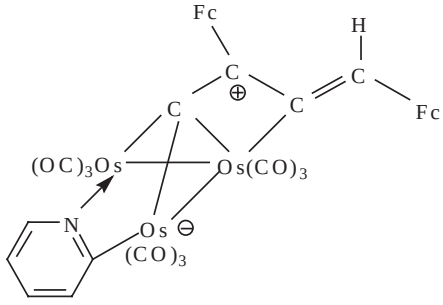


174

Cluster $[Os_3(CO)_{10}(\mu\text{-}\eta^2\text{-}2\text{-}C_5H_4N)(\mu\text{-}H)]$ (81JCS(D)407) reacts with 1,4-bis(ferrocenyl)butadiyne to yield isomers **175** and **176** (01JOM(637)514).



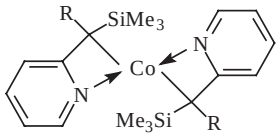
175



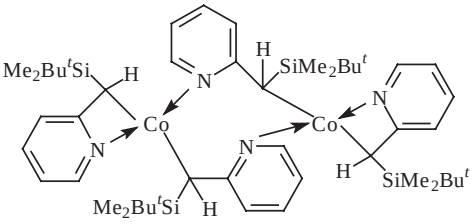
176

VII. Cobalt Group

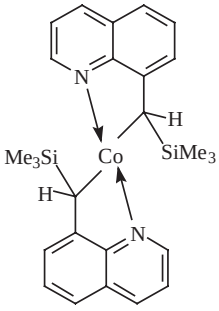
Reaction of $[Li\{C(SiMe_3)_2(C_5H_4N\text{-}2)\}]_2$, $[Li\{CH(SiMe_3)_2(C_5H_4N\text{-}2)\}(tmen)]$, $[Li\{CH(SiMe_3)(C_9H_8N\text{-}8)\}(tmen)]$, and $[Li\{CH(SiBu^tMe_2)(C_5H_4N\text{-}2)\}(tmen)]_2$ with cobalt(II) chloride gives the η^2(N, C)-coordinated products **178** (R = $SiMe_3$, Ph), **179** and **180** (97JCS(D)779), respectively.



178

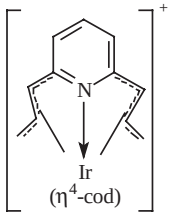


179



180

2,6-Diallylpyridine (L) with the dimer $[(\eta^4\text{-cod})IrCl]_2$ forms $[(\eta^4\text{-cod})IrL][[(\eta^4\text{-cod})IrCl_2]$, where the ligand fulfils the tridentate ligand function, **181** (87JOM(336)429). If the reaction occurs in the presence of silver perchlorate, the composition of the product is $[(\eta^4\text{-cod})IrL](ClO_4)$. With $[(\eta^2\text{-COE})IrCl]_2$, the neutral complex [IrClL] is formed, which reacts with carbon monoxide to yield [IrCl(CO)L].

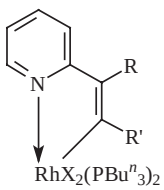


181

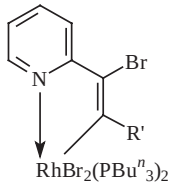
2-Phenylpyridine is a popular ligand for the cyclometallated complexes (70ACR139, 76CCR(18)327, 77AGE73, 79CRV287, 80CCR(32)325, 01IC1704,

01JA4304). In the synthesis of the cyclometallated species $[Ir(2\text{-}Phpy)_2Cl]_2$, the side product is *fac*-$[Ir(2\text{-}Phpy)_3]$ (84JA6647, 85JA1431). The latter found application as a luminescent oxygen sensor (94BSCB207, 01ACA(445)177). Other sensors are based on the mixed-ligand complex $[Ir(2\text{-}Phpy)_2(2\text{-}Vinpy)Cl]$ and some derivatives, where the vinylpyridine framework is not cyclometallated (03IC4864). More efficient preparative approaches for *fac*-$[M(2\text{-}Phpy)_3]$ (M = Rh, Ir) and $[Ir\{2\text{-}(2\text{-thienyl})pyridine\}_3]$ exist (91IC1685, 94IC545, 01JCS(CC)1494). The adducts of the cyclometallated complexes $[M\{2\text{-}(2\text{-thienyl})pyridine\}_2L]^+$ (L = bipy, en; M = Rh^{3+} and Ir^{3+}) are worth mentioning (90JA4581, 91JL549, 93IC3081). Iridium(III) complexes of 2-phenylpyridine and derivatives are interesting as strong photoreducing agents (87JA1589, 90IC582). Dimeric species $[Ir(2\text{-}Phpy)_2Cl]_2$ (74BCSJ767, 74JOM(82)271) in solutions of DMF, DMSO, and AN can be solvated to yield monomeric species $[Ir(2\text{-}Phpy)_2Cl(solv)]$ (94IC9) but the equilibrium of this reversible process is strongly shifted to the dimer. To ensure that the equilibrium is shifted towards monomer, $[Ir(2\text{-}Phpy)_2Cl]_2$ and $[Ir\{2\text{-}p\text{-tolyl})py\}_2Cl]_2$ were reacted with silver triflate in different media to yield $[IrL_2(solv)_2](OTf)$ [L = 2-phenylpyridine, 2-(*p*-tolyl)pyridine; solv = H_2O, AN]. The products with solv = H_2O react with NaOR (R = Me, Et) to yield $[IrL_2(OH)]_2$ [L = 2-phenylpyridine, 2-(*p*-tolyl)pyridine].

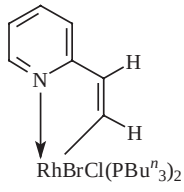
A series of 2-vinylpyridines reacts with $[Rh_2X_6(P^nBu_3)_4]$ (X = Cl, Br) to yield the cyclometallated species **182** (X = Cl, R = R′ = H; X = Br, R = R′ = H; R = H, R′ = Me; R = R′ = Me (73JCS(CC)838, 79JCS(D)295). On reaction of **182** with bromine, products **183** (R′ = H, Me) can be obtained. In excess lithium bromide, one of the representatives of **182** gives **184**. A related complex is that of benzo[h]quinoline (75JOM(92)89).



182

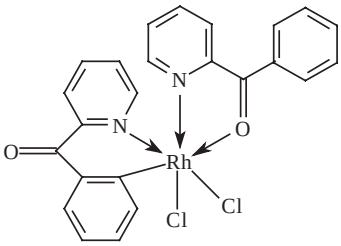


183

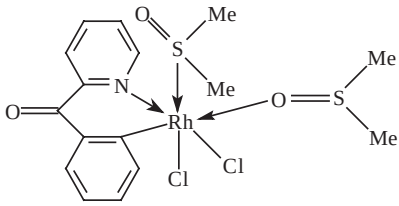


184

The vinyl carbon of 2-vinylpyridine is metallated in $[RhCl_2(NC_5H_4CH{=}CH)(P^nBu_3)_2]$ (73JCS(CC)838). 2-Phenyl- and 2-benzoylpyridine are the typical ligands in cyclometallation reactions (82BCSJ955, 84JOM(268)85, 87JOM(327)101, 89JMC(49)271, 90JOM(382)455, 91JOM(408)395, 92HCA1320, 93MRC529). Thus, 2-phenylpyridine (L) with rhodium(III) chloride gives the η^2(N, C)-coordinated species of composition $[L_2Rh(\mu\text{-}Cl)_2RhL_2]$ (91JOM(408)395). Two equivalents of 2-benzoylpyridine with rhodium(III) chloride in 2-methoxyethanol gives the cyclometallated species **185**, where one of the ligands is η^2(N, C)-cyclometallated and the other is η^2(N, O)-coordinated (95AJC1573). In DMSO, species **185** gradually transforms to **186**.

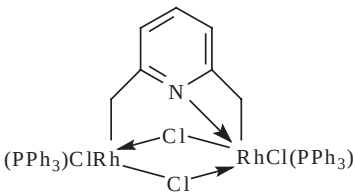


185

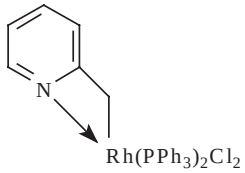


186

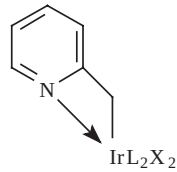
2,6-Bis(chloromethyl)pyridine with $[RhCl(PPh_3)_3]$ gives a mixture of a dinuclear Rh(III) species **187** and the mononuclear complex **188** (94RE14, 95BCSJ183). 2,6-Bis(chloromethyl)pyridine and 2,6-bis(bromomethyl)pyridine react with $[IrCl(PPh_3)_3]$ and $[IrBr(PPh_3)_3]$, respectively, to give **189** (X = Cl, Br; L = PPh_3) (97BCSJ2155). 2,6-Bis(chloromethyl)pyridine with $[\{(\eta^4\text{-cod})IrCl\}_2]$ gives **189** (X = Cl, $L_2 = \eta^4$-cod). Complex **189** (X = Cl, L = PPh_3) further reacts with $[RhCl(PPh_3)_3]$ to yield the iridium(III)–rhodium (III) heterodinuclear species **190**, which on thermolysis gives **191**.



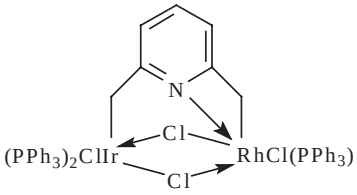
187



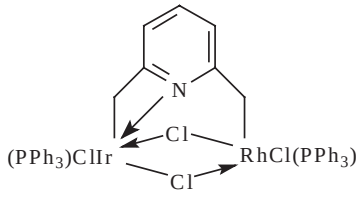
188



189

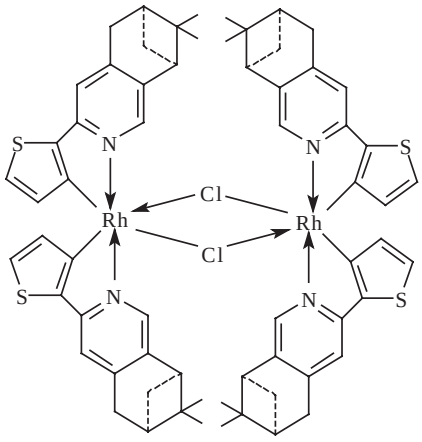


190

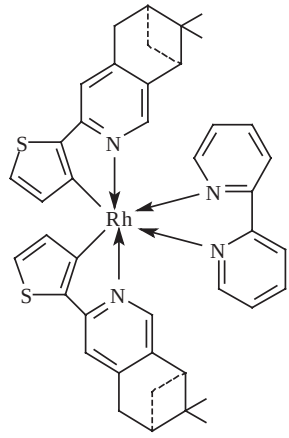


191

The thienyl-4,5-pienepyridine cyclometallated complex **192** (99EJIC1271) further reacts with diimine ligands and forms various products, e.g. **193** (01EJIC993).

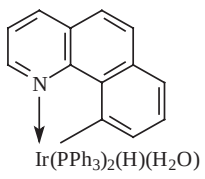


192

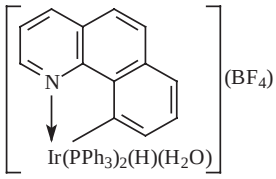


193

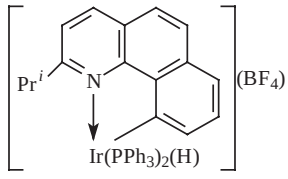
Cyclometallation of 7,8-benzoquinoline occurs during the reaction of the ligand with $[(\eta^4\text{-cod})Ir(PPh_3)_2]^+$ (87JOM(324)57). The product **194** reacts with Alk_3BH^+ followed by the substitution of the water ligand by the hydride. 2-Substituted benzoquinolines (R = H, *i*-Pr, *t*-Bu) react with $[IrH_2(Me_2CO)_2(PPh_3)_2](BF_4)$ in the presence of $NaBF_4$ to yield the cyclometallated products **195**, **196**, and **197** (89OM99, 02OM575). The presence of water in **195** is ascribed to traces of water in the solvent. Species **197** is found agostic. Carbonylation of **195**, **196**, and **197** gives **198** (R = H, *i*-Pr, *t*-Bu) (02IC5561). Similar complexes are known (89IC3084). Other similar derivatives from this range are $[ClIr(L)(CO)]$, $[ClIrL_2(PPh_3)]$ (84JA6647), and $[RhL_2(phen)]^+$ (87JPC1047) where L is benzo[h]quinolyl. $[Ir_2(2\text{-}PhC_5H_3N)_4Cl_2]$ (84JA6647) with 5-isothiocyanato-1,10-phenanthroline, 5-iodo-acetamido-1,10-phenanthroline, and 5-amino-1,10-phenanthroline (LL) in the presence of KPF_6 forms the cyclometallated iridium(III) species $[Ir(2\text{-}PhC_5H_3N)_2(LL)](PF_6)$ (01OM4999).



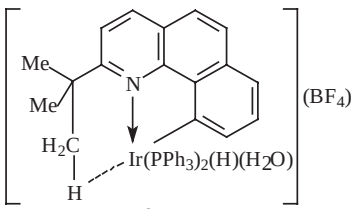
194



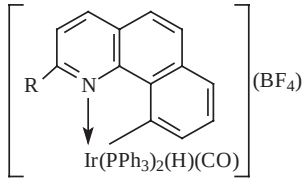
195



196

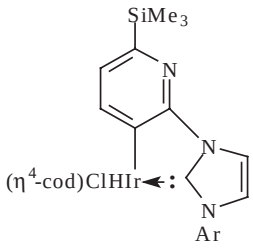


197

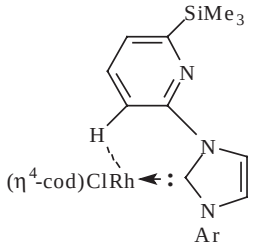


198

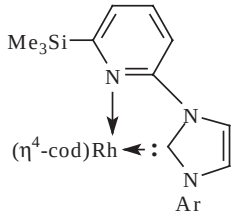
1-[2-(6-Trimethylsilyl)pyridyl]-3-[2,6-di-*iso*-propyl)-phenylimidazol-2-ylidenes with $[Ir(\eta^4\text{-}1,5\text{-cod})Cl]_2$ gives the complex **199** (02JCS(D)3090). The rhodium starting analog in the presence of $Na[B(3,5\text{-}C_6H_3(CF_3)_2]_4$ gives **200**. The latter upon heating is rearranged into **201**.



199



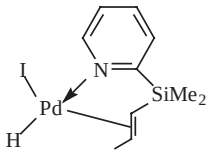
200



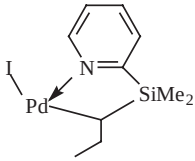
201

VIII. Nickel Group

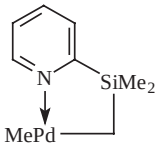
In Heck coupling of 2-pyridylvinyl(methyl)silane with phenyl iodide catalyzed by $[Pd_2(dba)_3]$ and tri-2-furylphosphine, the intermediate species are postulated to be the $\eta^1(N) : \eta^2$-coordinated complex **202** that rearranges to the cyclometallated complex **203** before forming the products (99TL5533, 99TL5537, 00JA12013, 01AGE2337, 01JA11577, 01JOC3970, 02CRV3693, 02JOM(653)105). Similarly, in the Stille coupling reactions, species **204** is postulated and it is close to the isolated species **205**. Allylic alkylation might proceed via **206** by analogy with existing **207**.



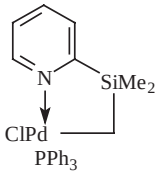
202



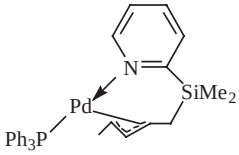
203



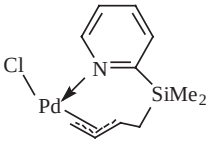
204



205



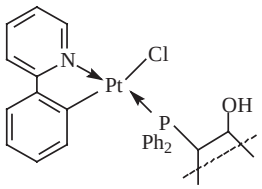
206



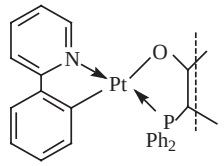
207

Some of the cyclometallated species have luminescent properties (88IC3644, 89HCA377, 95JCS(CC)509, 95JCS(CC)1787, 96JCS(CC)1039, 98JCS(CC)1127, 99CEJ2845, 99CEJ3350), e.g. $[Pt(2\text{-Phpy})L^1L^2]^z$ ($z = -1$, $L^1 = L^2 = Cl$; $z = 0$, $L^1 =$ Cl, $L^2 =$ tris(morpholino)phosphine; $z = 1$, $L^1 = L^2 =$ bipy, phen, 1,2-diaminoethane) (95ACSA313, 95ACSA335, 96ACSA1108) or $[Pt(2\text{-Phpy})_2(CH_2Cl)Cl]$ (86JA6084). 2-Phenylpyridine with $PtCl_2$ in glycerol gives the cyclometallated

derivative $[Pt(2\text{-}Phpy)Cl]_2$, which interacts with methyl-4,6-benzylidene-*n*-deoxy-*n*-(diphenylphosphine)-α-D-altropyranozide ($n = 2$, 3) to yield **208** and then with sodium methoxide in methanol, **209** results (00JCS(D)3128).



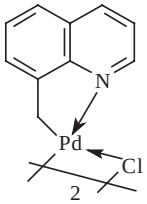
208



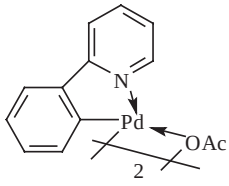
209

Cyclometallation reactions of halopyridines proceed via the oxidative addition route (84P1037, 86CRV451, 86JOML1). Thus, 2-chloromethylpyridine oxidatively adds to $[Pd(PPh_3)_4]$ to give a dinuclear species $[\{PdCl(\mu\text{-}CH_2py\text{-}CH_2\text{-}C,N)(PPh_3)\}_2]$ (80JOM(188)245, 81ICA(54)L69, 89BCSJ1802), and a similar reaction proceeds with 2-chloropyridine (80CL913, 86BCSJ2141). 2,6-Bis(chloromethyl)pyridine under these conditions gives a mixture of tetranuclear, $[\{Pd_2Cl(\mu\text{-}Cl)(\mu\text{-}CH_2pyCH_2\text{-}C,N,C')(PPh_3)_2\}_2]$, and dinuclear, $[\{PdCl(ClCH_2pyCH_2)(PPh_3)\}_2]$, species (93JCS(D)3075).

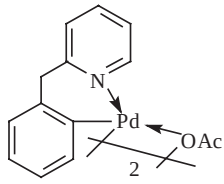
The cyclometallated complexes **210** (70JCS(D)912), **211** (68BCSJ1272), **212** (81IC4316), **213** (99JOM(579)97) and 2-(2-pyridyloxy)naphthalene analogs (99ICC10, 03OM1281), **214** (91MK45), **215** (92IC3083), and **216** (70JCS(D)912) are efficient catalysts in Heck arylation of olefins (01JOM(622)89). Reaction of [Pd(L)(L′)Cl] (HL = 8-methylquinoline, L′ = PPh_2Me, 4-Mepy, CO) with $Na[(\eta^5\text{-}Cp)Mo(CO)_3]$ gives the heterobimetallic Mo–Pd products **217** (81IC4426).



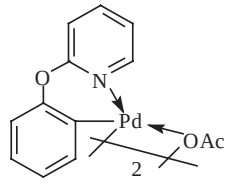
210



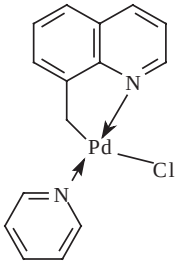
211



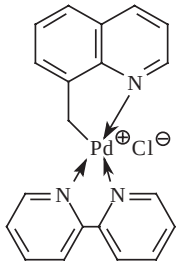
212



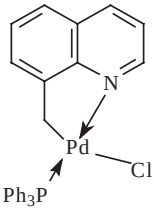
213



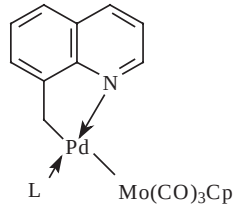
214



215

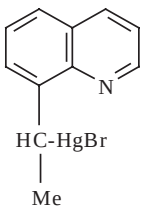


216

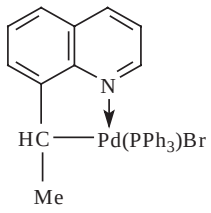


217

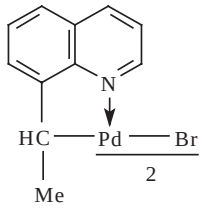
8-Ethylquinoline reacts with *N*-bromosuccinimide and then metallic mercury (53DAN479, 76ICA(18)L10) to provide the optical isomer **218** (82JOM(225)57) after some manipulations. The product with $[Pd^0(PPh_3)_4]$ gives the cyclopalladated species **219**. With (dibenzylideneacetone)dipalladium, **220** results. This approach to the cyclopalladated species proved useful as compared to the more traditional ways (72JOM(36)389, 76DAN367).



218

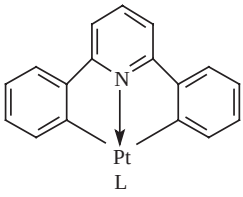


219

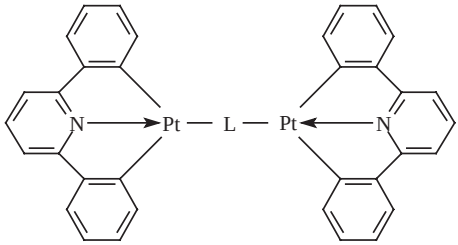


220

The cyclometallated species **221** (L = DMSO) (99OM1801, 00OM1355) react with 4-*t*-butylpyridine, 1-methyl-4,4′-bipyridinium hexafluorophosphate, 2,6-dimethylphenyl isocyanine, tricyclohexyl phosphine, and triphenylphosphine (L) to yield species **221** (01OM2477). The same starting material with pyrazine, bis(dicyclohexylphosphino)methane and bis(diphenylphosphino)methane (L) gives complexes of the type **222**. Similar cycloaurated complexes are known (98OM3505).

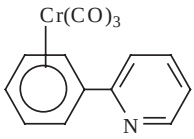


221

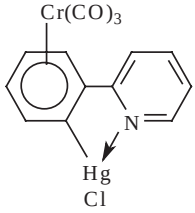


222

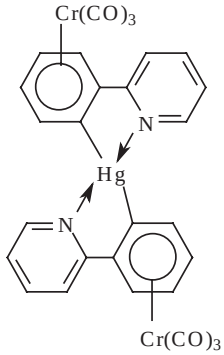
Complex **223** (98JOM(567)65) with mercury(II) acetate and then calcium chloride gives the cyclometallated complex **224** (01OM3230). With tetramethylammonium chloride, **224** gives species **225**. The latter with $[PdCl_2(AN)_2]$ or $[(\eta^2\text{-}C_2H_4)PdCl]_2$ and pyridine (95JCS(D)999) gives the cyclometallated species **226** (01OM3230) along with a minor amount of **227** known before (72JOM(39)413, 73IC1215, 81JOM(222)155, 88HCA134). Reaction of $K[Fe(CO)_3(dppm)\{Si(OMe)_3\}]$ with [Pd(8-methylquinoline)(μ-Cl)]$_2$ (81JOM(205)117) containing a chelating quinoline derivative gives product **228** with the iron–palladium bond (99JCS(D)4175).



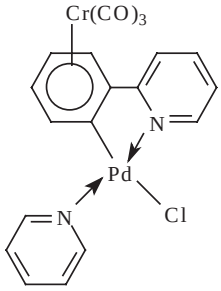
223



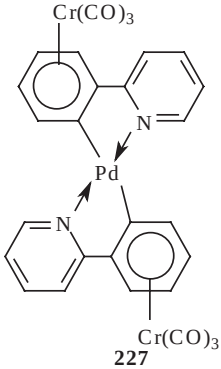
224



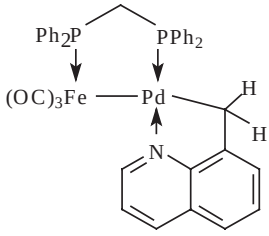
225



226

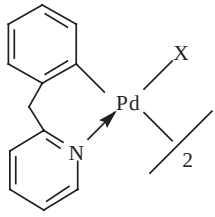


227



228

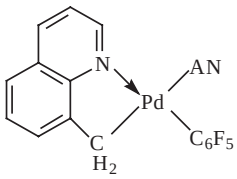
The ligand-exchange reaction of 2-benzylpyridine with $[PdCl(C_6H_4CH_2NMe_2)]_2$ yields the cyclopalladated species **229** (84IC789, 84JOM(268)85, 85KK1532, 86JCS(D)1785, 86JOM(307)C44, 87IC1252).



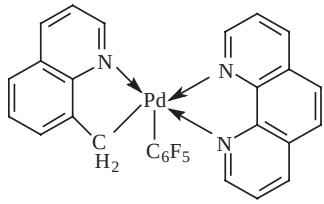
229

8-Methylquinoline is often applied as the cyclometallating ligand (84P1037, 86CRV451, 86JOML1, 89CCR(93)155). Complex **230** (91JOM(408)425) reacts with 1,10-phenanthroline to give the mononuclear product **231** (90OM2422, 93IC3675). Further addition of 1,10-phenanthroline gives the dinuclear complex **232** with the bridging 8-methylquinolinato moiety. Reaction of **230** with 2,2′-bipyridine proceeds differently. Exclusively the dinuclear product **233** is formed, where 2,2′-bipyridine performs the bridging function. The reactivity of [Pd(8-quinolylmethyl)(C_6F_5)(AN)] with respect to neutral phosphines or aromatic halides reduces not only to the

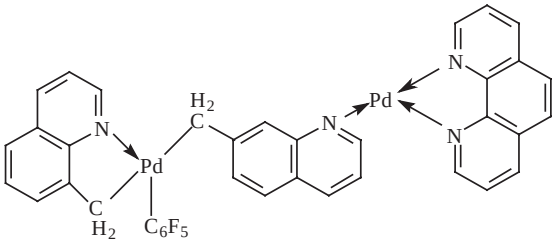
displacement of the labile acetonitrile ligand but to the opportunity of preparation of the dinuclear species $(NBu^n_4)[\{Pd(8\text{-quinolylmethyl})(C_6F_5)\}_2(\mu\text{-X})]$. With 2,2′-bipyridine, irrespectively of the ratio of reactants, $[Pd\{8\text{-quinolylmethyl})(C_6F_5)\}_2(\mu\text{-bipy})]$ is eventually formed, while 1,10-phenanthroline taken in equimolar amount produces mononuclear $[Pd(8\text{-quinolylmethyl})(C_6F_5)(phen)]$ as the normal substitution product (93IC3675). If the molar ratio of the palladium precursor and 1,10-phenanthroline is 2:1, the product is $[(C_6F_5)(8\text{-quinolylmethyl})Pd(\mu\text{-}8\text{-quinolylmethyl})Pf(C_6F_5)(phen)]$.



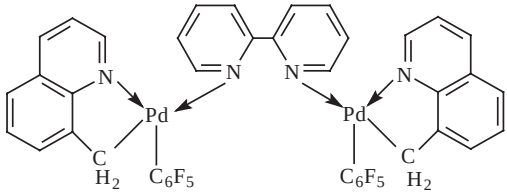
230



231



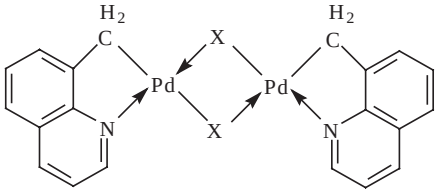
232



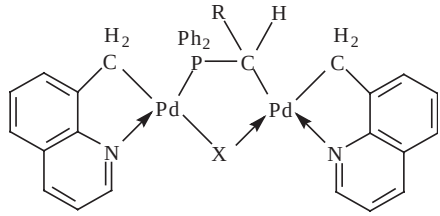
233

The *ortho*-metallated palladium complexes of 8-methylquinoline **234** (X = Cl, Br) (81JOM(205)117) possess an interesting reactivity pattern. They further react with carbanionic phosphines $[Ph_2PCHR]^-$ (R = CN, COOEt) with the replacement of one of the bridging groups X (X = Cl, Br) to yield **235** (X = Cl, Br; R = CN, COOEt) by the new (P, C)-bridge (81JA5115). Under alternative circumstances, however, the carbanion coordinates as the (P, O)-chelate (not the bridge), as in **236**. Interaction of the complex **235** (X = Br, R = COOEt) with $AgPF_6$ in methylene chloride gives species **237**, the trinuclear species containing the carbanionic $\mu_3(P, O, C)$-ligand and the $\mu(OH)$ group, both per all three palladium atoms (84JA410). The latter may be a result of the synthetic conditions (water in silica gel in

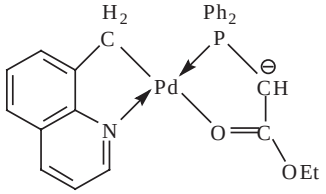
the process of filtration). Another coordination situation is realized in **238**, where the phosphine is coordinated monodentately. Complex **238** results from Ph_2PCH_2COOEt and dimer **234** (X = Br). Complex **234** (X = Cl) reacts with $Na[Mo(CO)_3(\eta^5\text{-Cp})]$ to yield the double-bridged species **239** containing, moreover, the semi-bridged carbonyl groups. The latter interacts with silver tetrafluoroborate or hexafluorophosphate to yield the tetranuclear species **240** (A = BF_4, PF_6) of the same structural pattern. Complexes $[PdL(PMe_2Ph)\{Mo(CO)_3(\eta^5\text{-Cp})\}]$ and $[Pd(L)(C_{10}H_6OMe)]$ (83JOM(250)537) may also be mentioned in discussing the *ortho*-metallation ability of 8-methylquinoline (HL).



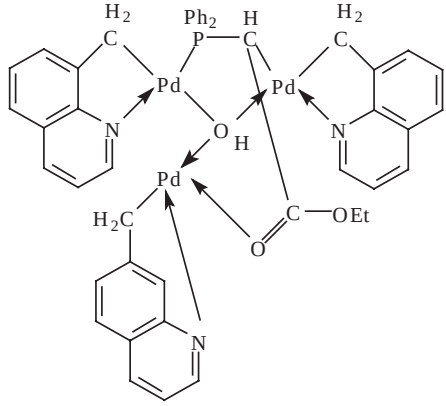
234



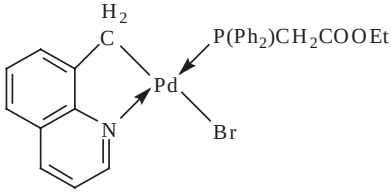
235



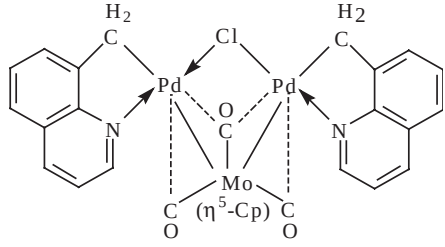
236



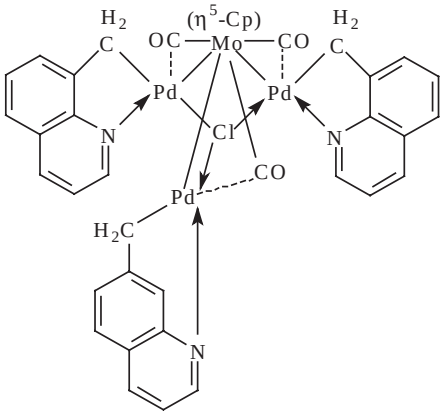
237



238

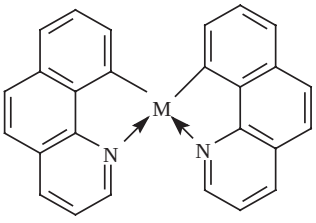


239

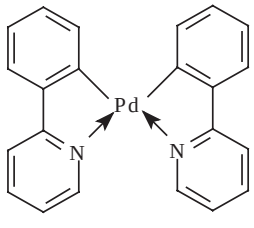


240

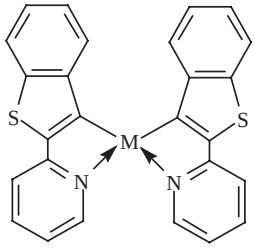
The general approach to the cyclometallated palladium(II) and platinum(II) complexes of benzo[h]quinoline **241** (M = Pt, Pd), 2-phenylpyridine **242**, 2-(2′-benzothienyl)pyridine **243** (M = Pt, Pd), 2-(2′-thienyl)quinoline **244**, and 2-(2′-thienyl)pyridine **245** is the metal-exchange reaction of the lithiated ligand with $[M(Et_2S)_2Cl_2]$ (M = Pt, Pd) (73JCS(D)404, 84IC4249, 86HCA1855, 87IC2814, 88HCA130, 90JCS(CC)121, 93ZK297, 96IC4883, 97AX(C)562, 00RJGC163). Some mixed-ligand complexes of palladium(II), **246**, **247**, and **248** , were obtained using a multistep synthetic strategy. Interaction of the platinum analogs of **242** (84IC4249, 87IC3354) and **245** (87IC2814) with $[Cd(cyclen)(MeOH)_2](ClO_4)_2$ gives the corresponding complexes with the platinum–cadmium bond, $[(PtI_2)\{Cd(cyclen)\}](ClO_4)_2 \cdot C_3H_6O$ (99JA7405) with retention of the cyclometallated pattern. The cyclometallated complexes of platinum(II) containing two ligands like 2-phenylpyridine, 2-(2′-thienyl)pyridine, or 2,6-diphenylpyridine undergo thermal and photochemical oxidative addition reactions with dihalogens and alkyl halides to yield platinum(IV) products. Thus, the platinum analogs of **245** with RX (R = Et, *n*-Pr, *n*-Bu, CH_2Br, X = Br; R = $C_6H_5CH_2$, X = Br; R = Ph_2CH, X = Br; R = PhC(CO), X = Cl; and others) give the group of oxidative addition products **249** (93IC4585). The platinum(II) complex[Pt{2-(2′-thienyl)pyridine}{H-2-(2′-thienyl)pyridine)]I contains one cyclometallated and one η^1(N)-coordinated ligand (75IC1629).



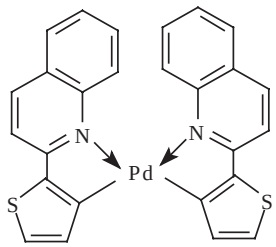
241



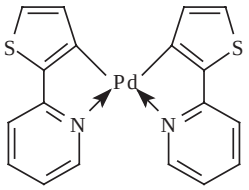
242



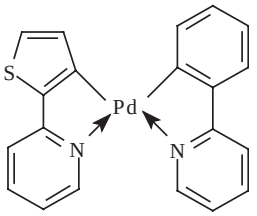
243



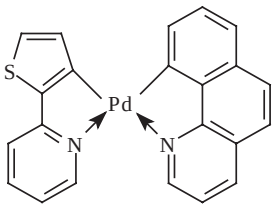
244



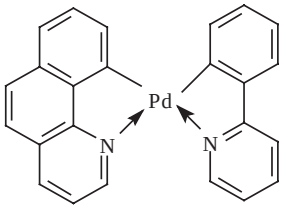
245



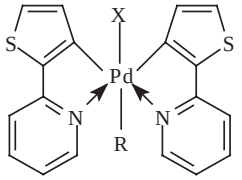
246



247

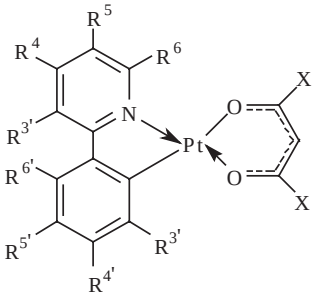


248

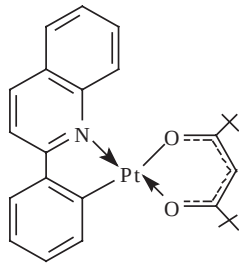


249

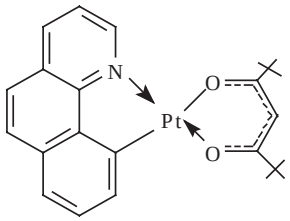
A group of cyclometallated platinum(II) complexes has interesting photochemical properties. They are based on 2-arylpyridines or 2-thienylpyridine and include homoleptic [(C^N)Pt(C^N)] (84IC4249, 85CPL375, 87IC2814, 95JPC13385, 96IC4883, 99IC5820, 00CP301), heteroleptic [$(C^N)_1$Pt$(C^N)_2$] (89HCA377), mixed ligand [(C^N)Pt(L)] (L is a non-cyclometallating ancillary ligand) (95ACSA335, 95IC2334, 97CCR(159)109, 00IC1955), or bridged (65JA3272, 76TMC10, 91IC859, 91JOM(418)249, 00OM1355) species. Reaction of $K_2[PtCl_4]$ with 2-arylpyridines, benzoquinoline, 2-phenylquinoline, 2-thienyl-, and 2-pyrrolylpyridine give dimers [(C^N)Pt$(\mu$-Cl$)_2$Pt(C^N)] (02IC3055). The latter reacts with acetylacetonate or dipivaloylmethane to yield derivatives that may be grouped into structures **250** (all R and R^1 are H, X = Me, *t*-Bu; $R^{3'}$ = Me, all the rest R and R′ are H, X = Me; $R^{5'}$ = Me, all the rest R and R′ are H, X = Me; $R^{4'}$ = MeO, all the rest R and R′ are H, X = *t*-Bu; $R^{5'}$ = MeO, all the rest R and R′ are H, X = *t*-Bu; $R^{6'}$ = F, CF_3, all the rest R and R′ are H, X = *t*-Bu; $R^{4'} = R^{6'}$ = F, all the rest R and R′ are H, X = Me; $R^{4'} = R^{6'}$ = F, all the rest R and R′ are H, X = Me, *t*-Bu; $R^{4'} = R^{6'}$ = F, R^3, or R^4, or R^5, or R^6 = Me, all the rest R and R′ are H, X = *t*-Bu; $R^{4'} = R^{6'}$ = F, R^4 = MeO, all the rest R and R′ are H, X = *t*-Bu; $R^4 = R^6$ = F, $R^4 = NMe_2$, all the rest R and R′ are H, X = *t*-Bu), **251**, **252**, and **253** (A = S, R = H; A = NMe, R = Me). Other complexes of photochemical interest include [Pt(2-thienylpyridine)(CO)Cl] (02IC4915) and [Pt(2-phenylpyridine)(CO)Cl] (98JL611, 01TCC81). Complex [Pt(L)$(\mu$-Cl$)]_2$ (L = benzo[h]quinoline) (91JOM(418)249) reacts with LiC≡CR (R = *t*-Bu, $SiMe_3$, Ph, *p*-Tol, $C_6H_4CF_3$-4, C_5H_4N-2, C_6H_4≡CPh) to produce the monoanionic species **254** (R = *t*-Bu, $SiMe_3$, Ph, *p*-Tol, $C_6H_4CF_3$-4, C_5H_4N-2, C_6H_4≡CPh) (03JCS(D)822).



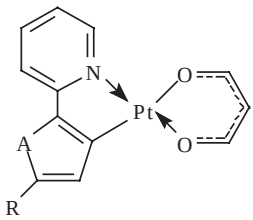
250



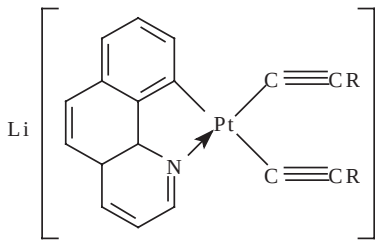
251



252

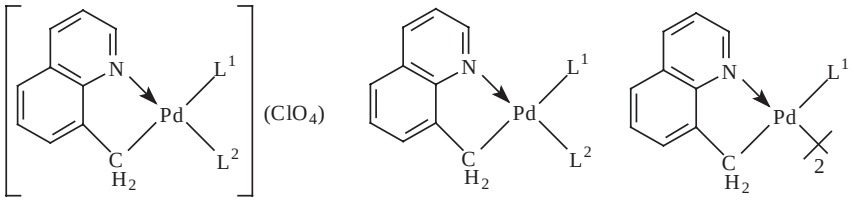


253



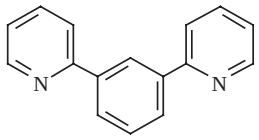
254

The cyclometallated palladium(II) derivatives of 8-methylquinoline (L) include $[Pd(L)(AN)_2](ClO_4)$, $[Pd(L)(ClO_4)(SPPh_3)]$, $[Pd(L)(\mu\text{-}SPMe_2Ph)]_2(ClO_4)_2$, $[Pd(L)(OCMe_2)_x]$ (88P2659, 90ICA(168)201), and $[Pd(L)(\mu\text{-}Cl)]_2$ (81JOM(205)117). The cyclometallated cationic species **255** ($L^1 = L^2 = OCMe_2$) on carbonylation yields the neutral complex **256** (97P1963) similar to the other palladium carbonyl cyclometallated derivatives (81IC4426, 89JOM(363)401). It has a rather branched reactivity pattern (97P1963). Thus, a labile perchlorate ligand is easily replaceable by halides originating from organic halide salts to yield **256** (L^1 = Cl, Br, I; L^2 = CO). The latter can be decarbonylated to yield the dinuclear products **257** (L^1 = Cl, Br, I) but this process is reversible. A similar platinum species $[Pt(CO)(py)X_2]$ (X = Cl, Br, I) may be mentioned at this point (58JCS2283). The starting cationic species **255** ($L^1 = L^2 = Me_2CO$) also reacts with Ph_3PS to yield **256** ($L^1 = OClO_3$, $L^2 = SPPh_3$), which can be carbonylated to give **255** ($L^1 = SPPh_3$, L^2 = CO) (97P1963). The other route to the latter derivative is the reaction of **256** ($L^1 = OClO_3$, L^2 = CO) with Ph_3PS or Me_2PhPS to yield **255** ($L^1 = SPPh_3$, $SPMe_2Ph$, L^2 = CO).

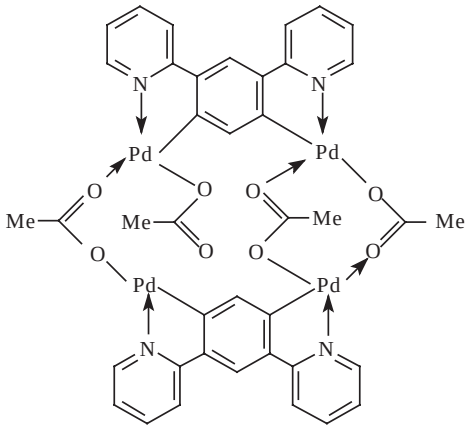


255 256 257

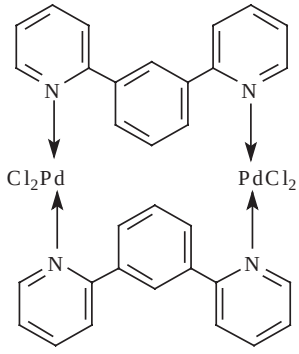
Ligand **258** reveals a versatile cyclometallation chemistry (78JCS(CC)1061, 80JCS(D)1992, 83JCS(D)1483, 94OM882, 95OM4427). Thus, with palladium(II) acetate, it gives dimer **259** (99OM3337). With $Li_2[PdCl_4]$ in the presence of acetic acid, **260** is the product, and with $K_2[PtCl_4]/CH_3COOH$, the monomeric cyclometallated complex **261** is formed. Cyclometallation of 2,6-diarylpyridines occurs at C_4 position of the pyridine ring (98AGE3270).



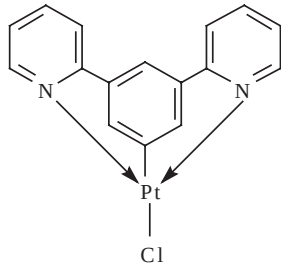
258



259

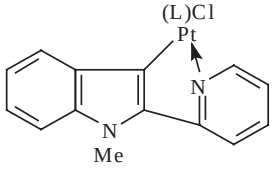


260

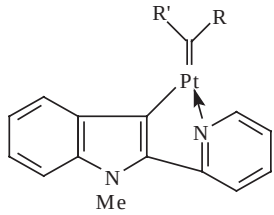


261

1-Methyl-2-(2′-pyridinyl)-1*H*-indole enters the cyclometallation reaction with $[Pt(DMSO)_2Cl_2]$ in the presence of sodium acetate to give **262** (L = DMSO) (00JOM(608)34). DMSO is easily replaceable by the other ligands, and the ligand-substitution products are formulated as **262** (L = CO, *t*-BuNC, PhCH=CH_2, PhC≡CH) in methylene chloride. However, the reaction of **262** (L = DMSO) with phenylacetylene in CH_2Cl_2/C_2H_5OH gives the platinum(II) carbene **263** (R = Ph, R′ = Et). The whole series of carbenes **263** [R = Ph, R′ = Et, *i*-Pr, *t*-Bu; R = $(CH_2)_5Me$, $SiMe_3$, $(CH_2)_4C{\equiv}CH$, *t*-Bu, $CMeCH_2$, CMe_2OH, R′ = Et; R = $SiMe_3$, R′ = $OCH_2(CH_2)_{14}Me$] can be prepared using the same synthetic route.

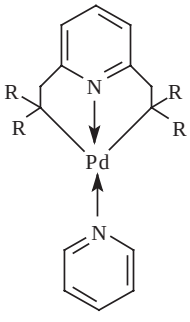


262

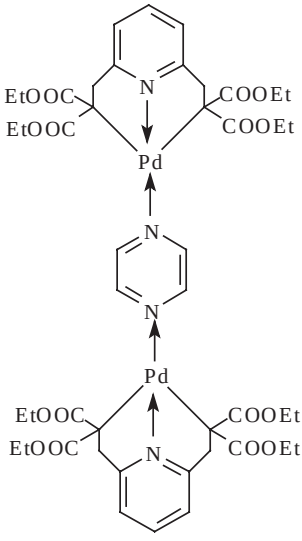


263

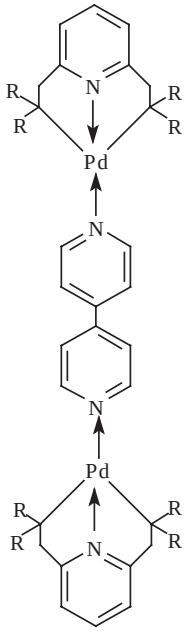
The reaction of appropriate ligands with $K_2[PdCl_4]$ and pyridine, pyrazine, 2,2′-bipyridine, 1,2-bis(4-pyridyl)ethylene, 1,2-bis(4-pyridyl)acetylene, or 1,2-bis(4-pyridyl)ethane gives complexes **264** (R = COOMe, COOEt) **265**, **266**, **267**, **268**, or **269** (in **265**, **266**, **267**, **268**, and **269**, R = COOMe, COOEt), respectively (81JA3423, 82JA994).



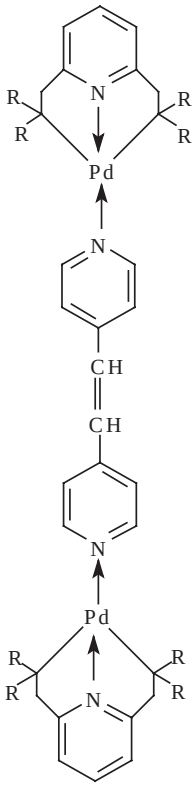
264



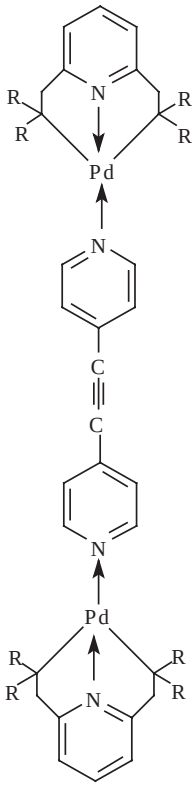
265



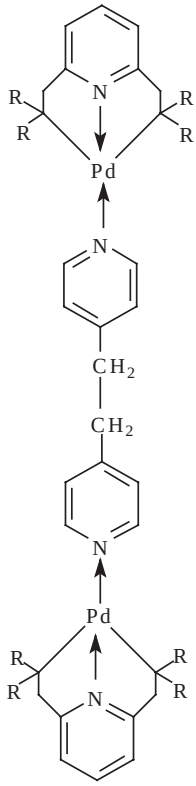
266



267

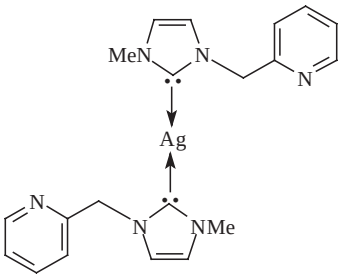


268

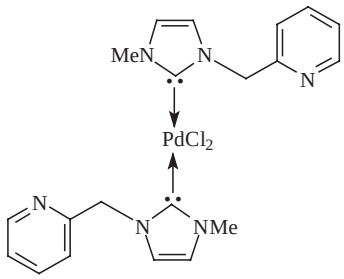


269

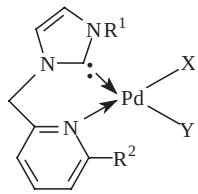
Silver carbene complexes **270** may serve as a convenient precursor for the cyclopalladated complexes. However, the reaction with $[PdCl_2(AN)_2]$ gives structure **271**, in which coordination occurs only via the carbene carbon sites (00JCS(D)4499, 00OM741, 01OM2027, 01JCS(CC)1270, 02JCS(CC)482, 02JCS(D)2163). The cyclopalladated structure **272** (X = Me, Y = Cl, R^1 = Me, R^2 = H) follows from the silver precursor and [(η^4-Pd(Me)Cl]. A wide range of analogs can be prepared using the same synthetic technique: **272** (R^2 = H, R^1 = *t*-Bu, 2,4,6-$Me_3C_6H_2$, X = Me, Y = Br, OTs, OTf, $OOCCF_3$; R^2 = H, R^1 = 2,6-$Pr^i{}_2C_6H_3$, X = Me, Y = Br, OTs; R^2 = Me, R^1 = 2,6-$Pr^i{}_2C_6H_3$, X = Me, Y = Br) (00JCS(CC)1247, 03JCS(D)699). A peculiar way of cyclopalladation is in the carbene pincer palladium complexes of the type **273** (01JCS(CC)201). Interaction of the ligand **274** with palladium(II) acetate gives products **275** (X = Cl, Br) catalytically active in Heck olefination reactions (01OM5485, 03JCS(D)831). The imidazolium salts *N*-R-N′-pyridylimidazolium bromide (R = *i*-Pr, *n*-Bu) form the partially cyclometallated complexes **276** (R = *i*-Pr, *n*-Bu) on interaction with $[Pd_2(dba)_3]$ (02JCS(D)2163). *N*-Mesityl-N′-2-pyridylimidazolium bromide gives the product **277**, where the coordination takes place via the carbene carbon.



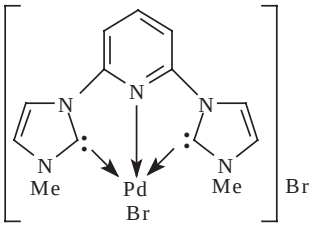
270



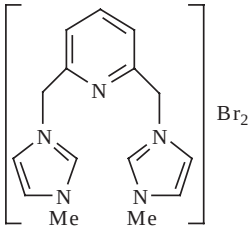
271



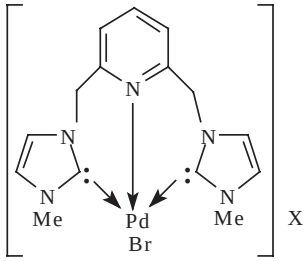
272



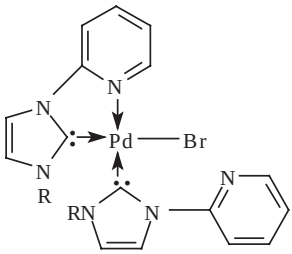
273



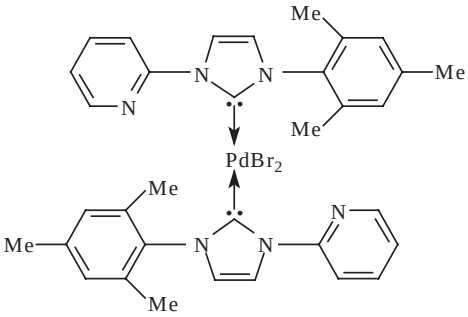
274



275



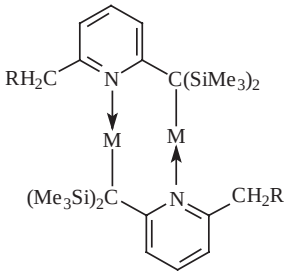
276



277

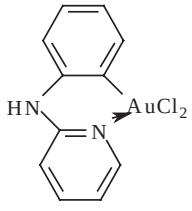
IX. Late Transition and Rare Earth Metals

2-LiC($SiMe_3$)$_2$py-6-CH_2R (R = H, Me_3Si) with [(OC)AuCl], CuCl or $AgNO_3$ gives the dinuclear cluster **278** (01JCS(D)3069). Complexes of a similar nature include [Au_2(μ-2-C(Me_3Si)$_2$py)$_2$] (87JCS(D)3085) and [Cu_2(μ-2-C($SiMe_3$)$_2$py)$_2$] (83JCS(CC)1419).

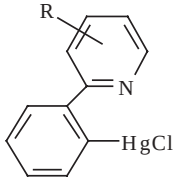


278

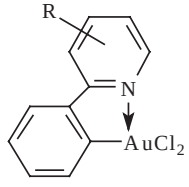
2-Anilinopyridine can be cyclopalladated (82TMC(L)281) or cycloaurated to yield **279** (95JCS(D)2865, 97P4039). The latter follows from the ligand and sodium tetrachloroaurate (97P4039). Cyclometallation of 2-phenylpyridine and related ligands gives the five- or six-membered C, *N*-chelates (89JOM(363)277, 89JOM(363)419, 92JCS(D)2251, 96JCS(D)69, 96JCS(D)4217, 98JCS(D)791, 98JCS(D)4095, 98JOM(560)233, 99P749, 00JCS(D)735). 2-Phenylpyridines with mercury(II) acetate in the presence of lithium chloride give species **280** (R = H, 3-Me, 3,5-Me_2, 4-*n*-Pr, 4-*t*-Bu) (88JCS(D)2863, 93AJC1323), and further with $Na[AuCl_4] \cdot 2H_2O$, the cycloaurated derivatives **281** (R = H, 3-Me, 3,5-Me_2, 4-*n*-Pr, 4-*t*-Bu) can be prepared (00JOM(596)165). With silver acetate, **281** (R = 3-Me, 3,5-Me_2, 4-*t*-Bu) give the substitution products containing $Au(OAc)_2$ moiety. The $Au(OAc)_2$ derivatives with pyridine perchlorate give the cationic complexes **282** (R = 3-Me, 3,5-Me_2, 4-*t*-Bu). Various other reactions are possible (00JOM(596)165). 2-Phenyl-4-(methylcarboxylato)quinoline undergoes a similar set of mercuration/cycloauration reactions to yield **283** and **284**. Cycloaurated species **285** reveal complicated electrochemical properties (01JOM(622)47). Complexes of the type **279** as well as those of 2-benzylpyridine react with catechol, tetrachlorocatechol, and other derivatives to give stable combined cyclometallated–chelated derivatives promising in medicinal chemistry (03JOM(679)194). Complexes $[AuCl_2L]$ (L = deprotonated 2-phenylpyridine) (89JOM(363)419) react with C_{10}-$C_6S_8(CH_2CH_2COOEt)_2$ in the presence of sodium to give $[AuL(C_{10}$-$C_6S_8)]$ (03JOM(669)141).



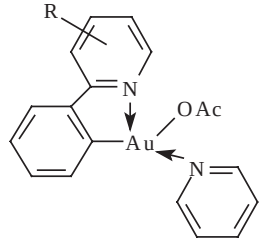
279



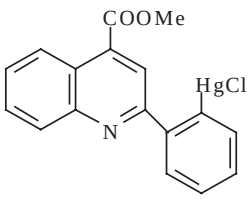
280



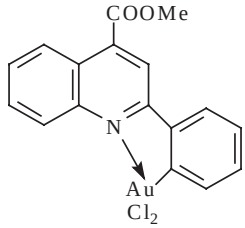
281



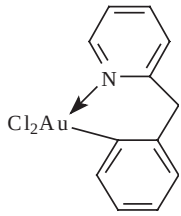
282



283

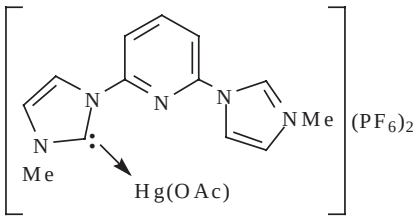


284

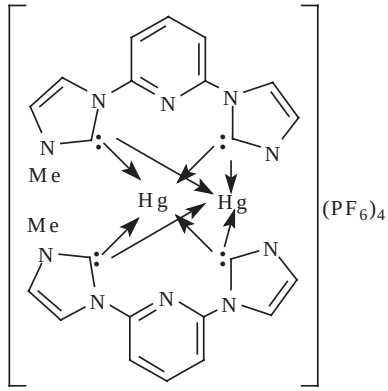


285

2,6-Bis(1-methylimidazolium-3-yl)pyridine bis(hexafluorophosphate) with mercury(II) acetate does not form any cyclometallated products, but only those with C-coordination, **286** and **287** (00JCS(D)839). Two mercury(II) sites in **287** are bridged by the carbene ligands, and the helical structure is formed.

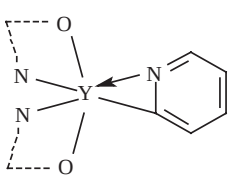


286

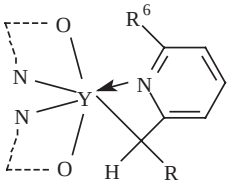


287

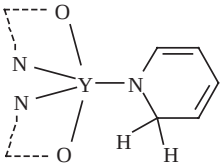
Organolanthanide compounds containing pyridyl and 2,6-dimethylpyridyl moieties are normally η^2(C,N)-coordinated, e.g. [$(\eta^5$-Cp$^*)_2$Ln{η^2(C,N)-2-C_5H_4N}] (Ln = Sc, Y, Lu) (83JCS(CC)276, 84PAC1, 87JA203, 87OM2053, 93OM3531, 94OM3881). Pyridine, 2-methyl-, 2,6-dimethyl, and 2-ethylpyridine with [{Me_2Si(NBu^t)(OBu^t)}$_2$YCH(SiMe$_3$)$_2$] give the product of *ortho*-metallation **288** in case of the unsubstituted heterocycle and metallation via the 2 substituent, **289** R = H, Me, R^6 = H; R = H, R^6 = Me), otherwise (97OM5506). The same products follow much more easily from the corresponding lithium pyridyls and [{Me_2Si(NBu^t)(OBu^t)}$_2$YCl · THF]. Species **288** is hydrogenated to give **290**, which on heating undergoes rearrangement to **291**. Further hydrogenation of **291** gives **292**. The vanadium analog of **292** exists (94JCS(CC)2419). With ethane, complex **288** forms the insertion product **289** (R = Me); with phenylacetylene, the alkynyl species **293**; with acetonitrile, the insertion product **294** (R = Me) and by 1,3-H shift the final product **295**; and with benzonitrile—**294** (R = Ph) only (96OM2291, 97OM5506, 02CRV1851). Complex **289** (R = R^6 = H) with nitriles also gives the insertion products **296** (R = Me, Ph) with subsequent 1,3-H shift to generate **297** (R = Me, Ph). Finally, reaction of **288** with carbon monoxide gives **298** through the stage of insertion, **299**.



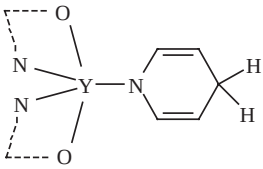
288



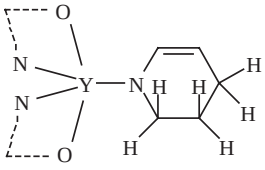
289



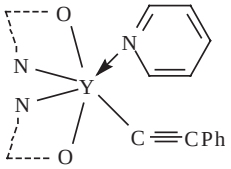
290



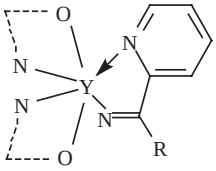
291



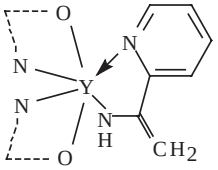
292



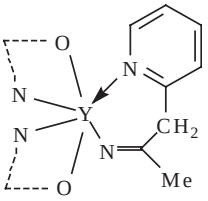
293



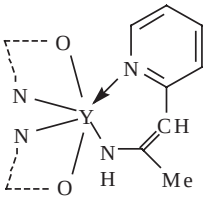
294



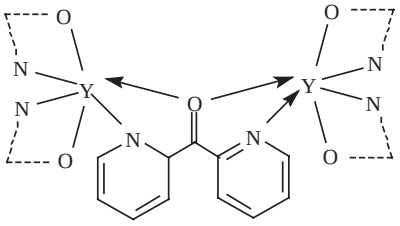
295



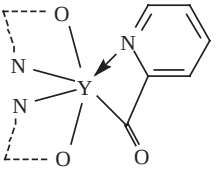
296



297

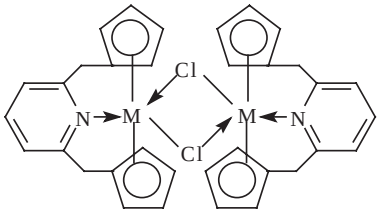


298

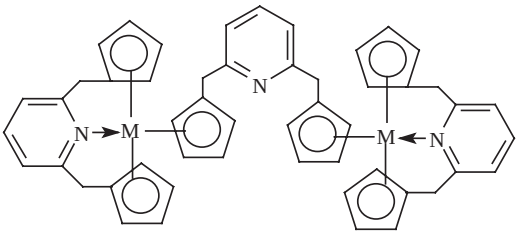


299

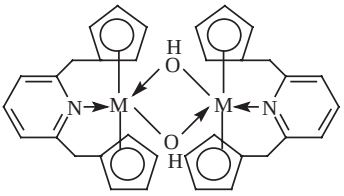
A pyridine ligand, containing 2,6-methylenecyclopentadienyl substituents (89CSB1788, 91OM1746), form an uranium(IV) complex of composition [{2,6-$C_5H_3N(CH_2C_5H_4)$}$_2UCl_2$] (91JOM(412)327). The product of interaction of disodium 2,6-methylenecyclopentadienyl pyridine with lanthanide(III) chloride is **300** (M = Y, Pr, Nd, Sm, Dy, Er, Yb, Lu) (94JOM(471)97). With $PrCl_3 \cdot 3THF$, however, the dianionic ligand forms complex **301**. The disodium salt of $[C_5H_4(CH_2)_2C_5H_4N]^{2-}$ (L^{2-}) when reacted with $[Y(OTf)_3]$ gives $[YL(\mu\text{-}OTf)]_2$ (98ICC424). Excess Na_2L gives $[(YL)_2ML]$, which readily hydrolyzes to **302**.



300



301



302

X. Conclusion

1. Non-transition elements rarely form η^2(N, C) species within the heterocycle but mainly the complexes with (N,C)-coordination via the heteroatom and the carbon atom of the 2-substituent, e.g. $C(SiMe_3)_2$, $Me_2SiC(SiMe_3)_2$, or Me_3SiH.
2. Titanium and zirconium precursors give rise predominantly to the α-metallated species, al though the substituted pyridines provide the *ortho*-C-atom of the substituent for coordination. The latter complexes enter a variety of insertion reactions.
3. Tantalum precursors on the formation of the α -metallated complexes cause the interruption of the aromatic delocalization in the heteroring, and often the ring-opening reactions occur.
4. The representatives of the chromium, manganese, iron, cobalt, and nickel groups are in the center of the cyclometallation chemistry of the pyridine ligands. Along with the classical cases of the exocyclic and endocyclic η^2(C, N)-coordination, there are cases of cluster formation, espe cially in rhenium, ruthenium and osmium chemistry; complexation with the pincer-type ligands, especially for the imidazol-1-ylidene pyridine-containing ligands. Osmium clusters of the pyridine and benzannulated pyridine derivatives traditionally serve as good models for the studies of reactivity of the coordinated heteroaromatic ligands. Representatives of the iron and cobalt groups are known as catalysts, molecular wires and luminescent materials.
5. Along with traditional coordination situations, late transition and rare earth metals often form dimeric structures and are prone to the insertion reactions.

REFERENCES

53DAN479 O. A. Reutov, A. N. Nesmeyanov, and S. S. Poddubnaya, *Dokl. Akad. Nauk SSSR*, **88**, 479 (1953).

58JCS2283 R. J. Irving and E. A. Magnusson, *J. Chem. Soc.*, 2283 (1958).

65JA3272 A. C. Cope and R. W. Siekman, *J. Am. Chem. Soc.*, **87**, 3272 (1965).

66IC293 R. B. King and M. B. Bisnette, *Inorg. Chem.*, **5**, 293 (1966).

67AX332 H. Schibilla and M. T. Le Bihan, *Acta Cryst.*, **23**, 332 (1967).

68BCSJ1272 A. Kasahara, *Bull. Chem. Soc. Jap.*, **41**, 1272 (1968).

69BCSJ1702 A. Kasahara, K. Tanaka, and T. Izumi, *Bull. Chem. Soc. Jap.*, **42**, 1702 (1969).

70ACR139 G. W. Parshall, *Acc. Chem. Res.*, **3**, 139 (1970).

70JCS(D)912 G. E. Hartwell, R. W. Lawrence, and M. J. Smas, *J. Chem. Soc. D*, 912 (1970).

71INCL943 M. Nonoyama and K. Yamasaki, *Inorg. Nucl. Chem. Lett.*, **7**, 943 (1971).

72JOM(36)389 V. I. Sokolov, T. A. Sorokina, L. L. Troitskaya, L. L. Solovieva, and O. A. Reutov, *J. Organomet. Chem.*, **36**, 389 (1972).

72JOM(39)413 G. Longoni, P. Fantucci, P. Chini, and F. Canciani, *J. Organomet. Chem.*, **39**, 413 (1972).

73IC1215 S. Trofimenko, *Inorg. Chem.*, **12**, 1215 (1973).

73JCS(CC)838 R. J. Foot and B. T. Heaton, *J. Chem. Soc., Chem. Commun.*, 838 (1973).

73JCS(D)404 B. N. Cockburn, D. V. Howe, T. Keating, B. F. G. Johnson, and J. Lewis, *J. Chem. Soc., Dalton Trans.*, 404 (1973).

73JOM(60)343 M. I. Bruce, B. Goodall, and F. G. A. Stone, *J. Organomet. Chem.*, **60**, 343 (1973).

73JOM(66)219 A. R. Garber, P. E. Garrou, G. E. Hartwell, M. J. Smas, J. R. Wilkinson, and L. J. Todd, *J. Organomet. Chem.*, **66**, 219 (1973).

74BCSJ767 M. Nonoyama, *Bull. Chem. Soc. Jap.*, **47**, 767 (1974).

74CB3104 H. Noth and U. Schuehardt, *Chem. Ber.*, **107**, 3104 (1974).

74JA3438 F. A. Cotton and J. M. Troup, *J. Am. Chem. Soc.*, **96**, 3438 (1974).

74JOM(82)271 M. Nonoyama, *J. Organomet. Chem.*, **82**, 271 (1974).

75AJC1259 M. I. Bruce, B. L. Goodall, and I. Matsuda, *Aust. J. Chem.*, **28**, 1259 (1975).

75IC1629 T. Giordano and P. G. Rasmussen, *Inorg. Chem.*, **14**, 1629 (1975).

75JCS(D)2091 C. C. Yin and A. J. Deeming, *J. Chem. Soc., Dalton Trans.*, 2091 (1975).

75JOM(92)89 M. Nonoyama, *J. Organomet. Chem.*, **92**, 89 (1975).

76CCR(18)327 J. Dehand and M. Pfeffer, *Coord. Chem. Rev.*, **18**, 327 (1976).

76DAN367 L. L. Troitskaya, V. I. Sokolov, A. I. Grandberg, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **228**, 367 (1976).

76ICA(18)L10 V. I. Sokolov, *Inorg. Chim. Acta*, **18**, L10 (1976).

76TMC10 M. Nonoyama and H. Takayanagi, *Transit. Met. Chem.*, **1**, 10 (1976).

77AGE73 M. I. Bruce, *Angew. Chem., Int. Ed. Engl.*, **16**, 73 (1977).

77JOM(124)C19 M. Tachikawa and J. R. Shapley, *J. Organomet. Chem.*, **124**, C19 (1977).

77MI1 G. Jones, in *"Quinolines"* (G. Jones ed.), Wiley, London (1977).

78IC3257 J. Mattia, M. B. Humphrey, R. D. Rogers, J. L. Atwood, and M. D. Rausch, *Inorg. Chem.*, **17**, 3257 (1978).

78JCS(CC)659 E. Klei and J. H. Teuben, *J. Chem. Soc., Chem. Commun.*, 659 (1978).

78JCS(CC)1061 A. G. Constable, W. S. McDonald, L. C. Sawkins, and B. L. Shaw, *J. Chem. Soc., Chem. Commun.*, 1061 (1978).

78JINC1289 D. R. Martin and P. H. Nguyen, *J. Inorg. Nucl. Chem.*, **40**, 1289 (1978).

79BCSJ1372 K. Hiraki, Y. Obayashi, and Y. Oki, *Bull. Chem. Soc. Jap.*, **52**, 1372 (1979).

79CRV287 I. Onae, *Chem. Rev.*, **79**, 287 (1979).

79JA3659 G. Erker and K. Knopp, *J. Am. Chem. Soc.*, **101**, 3659 (1979).

79JCS(D)295 R. J. Foot and B. T. Heaton, *J. Chem. Soc., Dalton Trans.*, **295** (1979).

80CCR(32)325 I. Onae, *Coord. Chem. Rev.*, **32**, 325 (1980).

80CL449 K. Hiraki, Y. Sasada, and T. Kitamura, *Chem. Lett.*, 449 (1980).

80CL913 K. Nakatsu, K. Kinoshita, H. Kanda, K. Isobe, Y. Nakamura, and S. Kawaguchi, *Chem. Lett.*, 913 (1980).

80JCS(D)1974 A. J. Deeming, I. P. Rothwell, M. B. Hursthouse, and K. M. A. Malik, *J. Chem. Soc., Dalton Trans.*, 1974 (1980).

80JCS(D)1992 A. G. Constable, W. S. McDonald, L. C. Sawkins, and B. L. Shaw, *J. Chem. Soc., Dalton Trans.*, 1992 (1980).

80JOM(186)353 G. Ciani, G. D'Alfonso, M. Freni, P. Romiti, and A. Sironi, *J. Organomet. Chem.*, **186**, 353 (1980).

80JOM(188)245 M. Onishi, K. Hiraki, K. Maeda, and T. Itoh, *J. Organomet. Chem.*, **188**, 245 (1980).

80JOM(198)41 M. Calhorda and A. R. Dias, *J. Organomet. Chem.*, **198**, 41 (1980).

81CL719 H. Yasuda, Y. Kajihara, K. Nagasuma, K. Mashima, and A. Nakamura, *Chem. Lett.*, 719 (1981).

81IC1496 M. H. Chisholm, K. Folting, J. C. Huffman, and I. P. Rothwell, *Inorg. Chem.*, **20**, 1496 (1981).

81IC4316 K. Hiraki, Y. Fuchita, and K. Takechi, *Inorg. Chem.*, **20**, 4316 (1981).

81IC4426 M. Pfeffer, D. Grandjean, and G. Borgne, *Inorg. Chem.*, **20**, 4426 (1981).

81ICA(54)L69 M. Nakatsu, K. Kafuku, Y. Yamaoka, K. Isobe, Y. Nakamura, and S. Kawaguchi, *Inorg. Chim. Acta*, **54**, L69 (1981).

81JA3423 G. R. Newkome, T. Kawato, D. K. Kohli, W. Puckett, B. D. Olivier, G. Chiari, F. R. Fronczek, and W. A. Deutsch, *J. Am. Chem. Soc.*, **103**, 3423 (1981).

81JA5115 P. Braunstein, D. Matt, Y. Dusausoy, J. Fischer, A. Mitschler, and L. Ricard, *J. Am. Chem. Soc.*, **103**, 5115 (1981).

81JCS(D)407 B. F. G. Johnson, J. Lewis, and D. A. Pippard, *J. Chem. Soc., Dalton Trans.*, 407 (1981).

81JCS(D)2088 K. W. Chiu, R. A. Jones, G. Wilkinson, A. M. R. Galas, and M. B. Hursthouse, *J. Chem. Soc., Dalton Trans.*, 2088 (1981).

81JOM(205)117 A. J. Deeming and I. P. Rothwell, *J. Organomet. Chem.*, **205**, 117 (1981).

81JOM(214)53 E. Klei and J. H. Teuben, *J. Organomet. Chem.*, **214**, 53 (1981).

81JOM(222)155 A. F. M. van der Ploeg, G. van Koten, and K. J. Vrieze, *J. Organomet. Chem.*, **222**, 155 (1981).

81TMC163 M. Nonoyama and S. Kajita, *Transit. Met. Chem.*, **6**, 163 (1981).

82BCSJ955 Y. Fuchita, K. Hiraki, and Y. Kage, *Bull. Chem. Soc. Jap.*, **55**, 955 (1982).

82JA994 G. R. Newkome, D. K. Kohli, and F. R. Fronczek, *J. Am. Chem. Soc.*, **104**, 994 (1982).

82JCS(D)787 A. J. Deeming, R. Peters, M. B. Hursthouse, and J. D. J. Baker-Dicks, *J. Chem. Soc., Dalton Trans.*, 787 (1982).

82JCS(D)2099 P. F. Jackson, B. F. G. Johnson, J. Lewis, W. J. H. Nelson, and M. McPartlin, *J. Chem. Soc., Dalton Trans.*, 2099 (1982).

82JOM(225)57 V. I. Sokolov, V. V. Bashilov, A. A. Musaev, and O. A. Reutov, *J. Organomet. Chem.*, **225**, 57 (1982).

82JOM(233)C55 K. Burgess, B. F. G. Johnson, and J. Lewis, *J. Organomet. Chem.*, **233**, C55 (1982).

82MI1 P. M. Treichel, in "*Comprehensive Organometallic Chemistry*" (E. W. Abel, F. G. A. Stone, and G. Wilkinson, eds.), Vol. 4, p. 1, Pergamon, Oxford (1982).
82OM1143 D. R. Gard and T. L. Brown, *Organometallics*, **1**, 1143 (1982).
82TMC(L)281 M. Nonoyama, *Transit. Met. Chem. (London)*, **7**, 281 (1982).
83JA2651 J. M. Mayer, C. J. Curtis, and J. E. Bercaw, *J. Am. Chem. Soc.*, **105**, 2651 (1983).
83JCS(CC)276 P. L. Watson, *J. Chem. Soc., Chem. Commun.*, 276 (1983).
83JCS(CC)1419 R. I. Papasergio, C. L. Raston, and A. H. White, *J. Chem. Soc., Chem. Commun.*, 1419 (1983).
83JCS(D)1483 E. Galli, F. Gasparrini, L. Maresca, G. Natile, and G. Palmieri, *J. Chem. Soc., Dalton Trans.*, 1483 (1983).
83JOM(250)537 J. Dehand, A. Mauro, H. Ossor, M. Pfeffer, R. H. A. Santos, and J. R. Lechat, *J. Organomet. Chem.*, **250**, 537 (1983).
83JOM(254)281 M. Onishi, K. Hiraki, T. Itoh, and Y. Ohama, *J. Organomet. Chem.*, **254**, 281 (1983).
83OM515 P. O. Nubel, S. R. Wilson, and T. L. Brown, *Organometallics*, **2**, 515 (1983).
84H2471 M. Ishikara, T. Mano, I. Oda, and M. Terashima, *Heterocycles*, **22**, 2471 (1984).
84IC789 A. D. Ryabov and A. K. Yatsimirskii, *Inorg. Chem.*, **23**, 789 (1984).
84IC4249 L. Chassot, E. Mueller, and A. Zelewsky, *Inorg. Chem.*, **23**, 4249 (1984).
84JA410 P. Braunstein, J. Fischer, D. Matt, and M. Pfeffer, *J. Am. Chem. Soc.*, **106**, 410 (1984).
84JA6647 S. Sprouse, K. A. King, P. J. Spellane, and R. J. Watts, *J. Am. Chem. Soc.*, **106**, 6647 (1984).
84JCS(CC)1089 B. F. G. Johnson, J. Lewis, M. McPartlin, M. A. Pearsall, and A. Sironi, *J. Chem. Soc., Chem. Commun.*, 1089 (1984).
84JCS(CC)1708 D. Cogan, R. I. Papasergio, C. L. Raston, and A. H. White, *J. Chem. Soc., Chem. Commun.*, 1708 (1984).
84JOM(268)85 A. D. Ryabov and G. M. Kazankov, *J. Organomet. Chem.*, **268**, 85 (1984).
84P389 A. H. Cowley, *Polyhedron*, **3**, 389 (1984).
84P1037 E. C. Constable, *Polyhedron*, **3**, 1037 (1984).
84P1175 K. Burgess, *Polyhedron*, **3**, 1175 (1984).
84PAC1 M. E. Thompson and J. E. Bercaw, *Pure Appl. Chem.*, **56**, 1 (1984).
85CPL375 M. Maestri, D. Dandrini, V. Balzani, and A. Zelewsky, *Chem. Phys. Lett.*, **122**, 375 (1985).
85JA1431 K. A. King, P. J. Spellane, and R. J. Watts, *J. Am. Chem. Soc.*, **107**, 1431 (1985).
85JCS(D)85 K. Burgess, H. D. Holden, B. F. G. Johnson, J. Lewis, M. B. Hursthouse, N. P. C. Walker, A. J. Deeming, P. J. Manning, and B. Peters, *J. Chem. Soc., Dalton Trans.*, 85 (1985).
85JOM(279)281 C. McDade and J. E. Bercaw, *J. Organomet. Chem.*, **279**, 281 (1985).
85JOM(294)123 G. A. Foulds, B. F. G. Johnson, and J. Lewis, *J. Organomet. Chem.*, **294**, 123 (1985).
85JOM(296)147 G. A. Foulds, B. F. G. Johnson, and J. Lewis, *J. Organomet. Chem.*, **296**, 147 (1985).
85KK1532 A. D. Ryabov, *Koord. Khim.*, **11**, 1532 (1985).
85OM1006 S. A. Cohen and E. Bercaw, *Organometallics*, **4**, 1006 (1985).
85OM1867 M. R. Churchill, J. C. Fettinger, and J. B. Keister, *Organometallics*, **4**, 1867 (1985).

85OM2033 A. Eisenstadt, C. M. Giandomenico, M. F. Frederick, and R. M. Laine, *Organometallics*, **4**, 2033 (1985).

86BCSJ2141 K. Isobe, K. Nanjo, Y. Nakamura, and S. Kawaguchi, *Bull. Chem. Soc. Jap.*, **59**, 2141 (1986).

86CRV451 G. R. Newkome, W. E. Puckett, V. K. Gupta, and G. E. Kiefer, *Chem. Rev.*, **86**, 451 (1986).

86HCA1855 L. Chassot and A. Zelewsky, *Helv. Chim. Acta*, **59**, 1855 (1986).

86JA6084 L. Chassot, A. Zelewsky, D. Sandrini, M. Maestri, and V. Balzani, *J. Am. Chem. Soc.*, **108**, 6084 (1986).

86JCS(CC)672 M. J. Henderson, R. I. Papasergio, C. L. Raston, A. H. White, and M. F. Lappert, *J. Chem. Soc., Chem. Commun.*, 672 (1986).

86JCS(D)605 S. I. Bailey, D. Colgan, L. M. Engelhardt, W. P. Leung, R. I. Papasergio, C. L. Raston, and A. H. White, *J. Chem. Soc., Dalton Trans.*, 605 (1986).

86JCS(D)1785 J. Granell, D. Sainz, J. Sales, X. Solans, and M. Font, *J. Chem. Soc., Dalton Trans.*, 1785 (1986).

86JCS(D)2691 T. Beringhelli, G. D'Alfonso, M. Freni, G. Ciani, A. Sironi, and H. Molinari, *J. Chem. Soc., Dalton Trans.*, 2691 (1986).

86JOM(301)203 E. C. Constable and J. M. Holmes, *J. Organomet. Chem.*, **301**, 203 (1986).

86JOM(307)C44 R. M. Ceder, J. Granell, and J. Sales, *J. Organomet. Chem.*, **307**, C44 (1986).

86JOM(314)311 M. I. Bruce, M. G. Humphrey, B. W. Skelton, and A. H. White, *J. Organomet. Chem.*, **314**, 311 (1986).

86JOML1 I. Omae, *J. Organomet. Chem. Libr.*, **18**, 1 (1986).

86OM2193 R. H. Fish, J. J. Kim, J. L. Steward, J. H. Bushweller, R. K. Rosen, and J. W. Dupon, *Organometallics*, **5**, 2193 (1986).

86TL2829 E. Negishi, D. R. Swanson, F. E. Cederbaum, and T. Takahashi, *Tetrahedron Lett.*, 2829 (1986).

87AGE681 L. M. Engelhardt, U. Kynast, C. L. Raston, and A. H. White, *Angew. Chem., Int. Ed. Engl.*, **26**, 681 (1987).

87IC1252 A. D. Ryabov, *Inorg. Chem.*, **26**, 1252 (1987).

87IC2814 L. Chassot and A. Zelewsky, *Inorg. Chem.*, **26**, 2814 (1987).

87IC3354 C. Cornioley-Deuschel and A. Zelewsky, *Inorg. Chem.*, **26**, 3354 (1987).

87JA203 M. E. Thompson, S. M. Baxter, A. R. Bulls, B. J. Burger, M. C. Nolan, B. D. Santarsiero, W. P. Schaefer, and J. E. Bercaw, *J. Am. Chem. Soc.*, **109**, 203 (1987).

87JA1589 K. A. King and R. J. Watts, *J. Am. Chem. Soc.*, **109**, 1589 (1987).

87JA2788 W. A. Nugent, D. L. Thorn, and R. L. Harlow, *J. Am. Chem. Soc.*, **109**, 2788 (1987).

87JA4111 R. F. Jordan, E. E. LaPointe, C. S. Bajgur, S. F. Echols, and R. D. Willett, *J. Am. Chem. Soc.*, **109**, 4111 (1987).

87JA4720 L. D. Durfree, P. E. Fanwick, I. P. Rothwell, K. Freting, and J. C. Huffmann, *J. Am. Chem. Soc.*, **109**, 4720 (1987).

87JCS(D)327 B. F. G. Johnson, J. Lewis, W. J. H. Nelson, M. A. Pearsall, P. R. Raithby, M. J. Rosales, M. McPartlin, and A. Sironi, *J. Chem. Soc., Dalton Trans.*, 327 (1987).

87JCS(D)3085 R. I. Papasergio, C. L. Raston, and A. H. White, *J. Chem. Soc., Dalton Trans.*, 3085 (1987).

87JOM(318)157 R. C. Kerber, *J. Organomet. Chem.*, **318**, 157 (1987).

87JOM(324)57 J. T. Mague, *J. Organomet. Chem.*, **324**, 57 (1987).

87JOM(327)101 P. J. Steel and G. B. Caygill, *J. Organomet. Chem.*, **327**, 101 (1987).

87JOM(336)429 G. Vasapollo, C. F. Nobile, M. Latronico, M. Lanfranchi, and M. A. Pellinghelli, *J. Organomet. Chem.*, **336**, 429 (1987).
87JPC1047 Y. Ohsawa, S. Sprouse, K. A. King, M. K. DeAmond, K. W. Hanck, and R. J. Watts, *J. Phys. Chem.*, **91**, 1047 (1987).
87NJC543 R. M. Laine, *New J. Chem.*, **11**, 543 (1987).
87OM891 S. M. Beshouri, P. E. Fanwick, I. P. Rothwell, and J. C. Huffman, *Organometallics*, **6**, 891 (1987).
87OM2053 K. H. den Haan, Y. Wielstra, and J. H. Teuben, *Organometallics*, **6**, 2053 (1987).
87OM2498 S. M. Beshouri, P. E. Fanwick, and I. P. Rothwell, *Organometallics*, **6**, 2498 (1987).
88CB347 M. Veith, M. Jarczyk, and V. Huch, *Chem. Ber.*, **121**, 347 (1988).
88HCA130 C. Cornioley-Deuschel, T. Ward, and A. Zelewsky, *Helv. Chim. Acta*, **71**, 130 (1988).
88HCA134 M. Maestri, D. Sandrini, V. Balzani, A. Zelewsky, and P. Jouliet, *Helv. Chim. Acta*, **71**, 134 (1988).
88IC3464 F. O. Garces, K. A. King, and R. J. Watts, *Inorg. Chem.*, **27**, 3464 (1988).
88IC3644 F. Barigeletti, D. Sandrini, M. Maestri, V. Balzani, A. Zelewsky, L. Chassot, P. Joulliet, and U. Maeder, *Inorg. Chem.*, **27**, 3644 (1988).
88JA2310 P. J. Fagan and W. A. Nugent, *J. Am. Chem. Soc.*, **110**, 2310 (1988).
88JA4421 D. R. Neithamer, L. Parkanyi, J. P. Mitchell, and P. Wolczanski, *J. Am. Chem. Soc.*, **110**, 4421 (1988).
88JA7128 T. V. R. Babu, W. A. Nugent, D. F. Taber, and P. J. Fagan, *J. Am. Chem. Soc.*, **110**, 7128 (1988).
88JCS(CC)336 L. M. Engelhardt, B. S. Jolly, M. F. Lappert, C. L. Raston, and A. H. White, *J. Chem. Soc., Chem. Commun.*, 336 (1988).
88JCS(D)2863 N. Al-Salim, A. A. West, W. R. McWhinnie, and T. A. Hamor, *J. Chem. Soc., Dalton Trans.*, 2863 (1988).
88P2659 J. Fornies, R. Navarro, and V. Sicilia, *Polyhedron*, **7**, 2659 (1988).
89BCSJ1802 K. Isobe, Y. Nakamura, and S. Kawaguchi, *Bull. Chem. Soc. Jap.*, **62**, 1802 (1989).
89CCR(93)155 D. W. Evans, G. R. Baker, and G. R. Newkome, *Coord. Chem. Rev.*, **93**, 155 (1989).
89CSB1788 C. Ye, Y. Li, X. Yang, C. Qian, and G. Paolucci, *Chin. Sci. Bull.*, **34**, 1788 (1989).
89HCA377 C. Deuschel-Cornioley, R. Luond, and A. Zelewsky, *Helv. Chim. Acta*, **72**, 377 (1989).
89IC309 C. A. Craig and R. J. Watts, *Inorg. Chem.*, **28**, 309 (1989).
89IC3084 F. Neve, M. Ghedini, A. Tiripicchio, and F. Ugozzoli, *Inorg. Chem.*, **28**, 3084 (1989).
89IC3095 L. D. Durfree, J. E. Hill, J. L. Kerschner, P. E. Fanwick, and I. P. Rothwell, *Inorg. Chem.*, **28**, 3095 (1989).
89JA778 R. F. Jordan and D. F. Taylor, *J. Am. Chem. Soc.*, **111**, 778 (1989).
89JA2870 S. L. Buchwald and R. B. Nielsen, *J. Am. Chem. Soc.*, **111**, 2870 (1989).
89JA3336 E. Negishi, K. Akyoshi, B. O'Connor, K. Takagi, and G. Wu, *J. Am. Chem. Soc.*, **111**, 3336 (1989).
89JA3855 A. Zilian, U. Marder, A. Zelewski, and H. U. Gudel, *J. Am. Chem. Soc.*, **111**, 3855 (1989).
89JA4486 S. L. Buchwald, B. T. Watson, M. W. Wannamaker, and J. C. Dean, *J. Am. Chem. Soc.*, **111**, 4486 (1989).
89JA4495 J. Michael and T. Livinghouse, *J. Am. Chem. Soc.*, **111**, 4495 (1989).

89JA9113 S. L. Buchwald, R. T. Lum, R. A. Fisher, and W. M. Davis, *J. Am. Chem. Soc.*, **111**, 9113 (1989).

89JMC(49)271 A. Bose and C. R. Saha, *J. Mol. Catal.*, **49**, 271 (1989).

89JOC2793 S. L. Buchwald and Q. Fang, *J. Org. Chem.*, **54**, 2793 (1989).

89JOC3521 D. R. Swanson, C. J. Roosett, E. Negishi, T. Takahashi, E. Seki, T. Saburi, and Y. Uchida, *J. Org. Chem.*, **54**, 3521 (1989).

89JOM(363)277 E. C. Constable, R. G. P. Henney, and T. A. Leese, *J. Organomet. Chem.*, **363**, 277 (1989).

89JOM(363)401 M. A. Cinellu, S. Gladiali, and G. Minghetti, *J. Organomet. Chem.*, **363**, 401 (1989).

89JOM(363)419 E. C. Constable and T. A. Leese, *J. Organomet. Chem.*, **363**, 419 (1989).

89OM99 M. Lavin, E. M. Holt, and R. H. Crabtree, *Organometallics*, **8**, 99 (1989).

89TL3495 V. Wagenen, C. Bradford, and T. Livinghouse, *Tetrahedron Lett.*, **30**, 3495 (1989).

90CCR(97)193 C. A. Graig, F. O. Garces, R. J. Watts, R. Palmans, and A. J. Frank, *Coord. Chem. Rev.*, **97**, 193 (1990).

90IC582 G. O. Garces and R. J. Watts, *Inorg. Chem.*, **29**, 582 (1990).

90ICA(168)201 J. Fornies, R. Navarro, V. Sicilia, and M. Thomas, *Inorg. Chim. Acta*, **168**, 201 (1990).

90JA1289 R. F. Jordan, P. K. Bradley, N. C. Baenziger, and R. E. LaPointe, *J. Am. Chem. Soc.*, **112**, 1289 (1990).

90JA2814 J. R. Sticker, M. A. Bruck, and D. E. Wigley, *J. Am. Chem. Soc.*, **112**, 2814 (1990).

90JA4581 M. G. Colombo, A. Zilian, and H. U. Gudel, *J. Am. Chem. Soc.*, **112**, 4581 (1990).

90JA4600 S. L. Buchwald, K. A. Kreutzer, and R. A. Fisher, *J. Am. Chem. Soc.*, **112**, 4600 (1990).

90JA7994 G. A. Vaughan, G. L. Hillhouse, and A. L. Rheingold, *J. Am. Chem. Soc.*, **112**, 7994 (1990).

90JCS(CC)121 C. Cornioley-Deuschel, E. Stoeckli-Evans, and A. Zelewsky, *J. Chem. Soc., Chem. Commun.*, 121 (1990).

90JCS(CC)1006 T. R. van den Ancker, B. S. Jolly, M. F. Lappert, C. L. Raston, and A. H. White, *J. Chem. Soc., Chem. Commun.*, 1006 (1990).

90JCS(D)1161 R. I. Papasergio, B. W. Skelton, P. Twiss, and A. H. White, *J. Chem. Soc., Dalton Trans.*, 1161 (1990).

90JOM(381)203 E. C. Constable and J. M. Holmes, *J. Organomet. Chem.*, **381**, 203 (1990).

90JOM(382)455 G. B. Caygill, R. M. Hartsborn, and P. J. Steel, *J. Organomet. Chem.*, **382**, 455 (1990).

90JOM(395)359 P. J. Steel and G. B. Caygill, *J. Organomet. Chem.*, **395**, 359 (1990).

90JPC5208 J. L. Coffer, H. G. Drickamer, and J. R. Shapley, *J. Phys. Chem.*, **94**, 5208 (1990).

90MI1 R. H. Fish, in "*Aspects of Homogeneous Catalysis*" (R. Ugo, ed.), p. 65, Kluwer, Dodrecht (1990).

90NJC505 R. F. Jordan, P. K. Bradley, R. E. Lapointe, and D. F. Taylor, *New J. Chem.*, **14**, 505 (1990).

90OM524 G. Erker, R. Zwettler, C. Kruger, I. Hyla-Kryspin, and R. Gleiter, *Organometallics*, **9**, 524 (1990).

90OM871 R. A. Fisher and S. L. Buchwald, *Organometallics*, **9**, 871 (1990).

90OM1546 R. F. Jordan, D. F. Taylor, and N. C. Baenziger, *Organometallics*, **9**, 1536 (1990).

90OM2116 R. F. Jordan and A. S. Guram, *Organometallics*, **9**, 2116 (1990).

90OM2190 A. S. Guram and R. F. Jordan, *Organometallics*, **9**, 2190 (1990).
90OM2375 S. M. Beshouri, D. E. Chebi, P. E. Fanwick, and I. P. Rothwell, *Organometallics*, **9**, 2375 (1990).
90OM2422 J. Fornies, R. Navarro, V. Sicilla, and M. Tomas, *Organometallics*, **9**, 2422 (1990).
91ADOC325 R. F. Jordan, *Adv. Organomet. Chem.*, **32**, 325 (1991).
91IC859 K. P. Balashev, J. Simon, and P. C. Ford, *Inorg. Chem.*, **30**, 859 (1991).
91IC1685 K. Dedeian, P. I. Djurovich, F. O. Garces, G. Carlson, and R. J. Watts, *Inorg. Chem.*, **30**, 1685 (1991).
91IC2494 K. J. Covert, D. R. Neithamer, R. E. LaPointe, C. P. Schaller, and P. T. Wolczanski, *Inorg. Chem.*, **30**, 2494 (1991).
91ICA(182)93 E. C. Constable, A. M. W. Cargil-Thompson, T. A. Leese, D. G. F. Reese, and D. A. Tocher, *Inorg. Chim. Acta*, **182**, 93 (1991).
91JA1833 A. S. Guram, R. F. Jordan, and D. F. Taylor, *J. Am. Chem. Soc.*, **113**, 1833 (1991).
91JCS(CC)1302 R. W. Horley, P. B. Hitchcock, B. S. Jolly, M. F. Lappert, and G. A. Lawless, *J. Chem. Soc., Chem. Commun.*, 1302 (1991).
91JCS(CC)1560 C. Jones, L. M. Engelhardt, P. C. Junk, D. S. Hutchings, W. C. Patalinghug, C. L. Raston, and A. H. White, *J. Chem. Soc., Chem. Commun.*, 1560 (1991).
91JL549 M. G. Colombo, A. Zilian, and H. U. Gudel, *J. Lumin.*, **48–49**, 549 (1991).
91JOM(408)395 P. J. Steel, *J. Organomet. Chem.*, **408**, 395 (1991).
91JOM(408)425 J. Fornies, R. Navarro, V. Sicilla, F. Martinez, and A. Welch, *J. Organomet. Chem.*, **408**, 425 (1991).
91JOM(412)327 G. Paolucci, R. D. Fischer, F. Benetollo, R. Seraglia, and G. Bombieri, *J. Organomet. Chem.*, **412**, 327 (1991).
91JOM(418)249 P. S. Pregosin, F. Wombacher, and F. Lianza, *J. Organomet. Chem.*, **418**, 249 (1991).
91MK45 G. M. Kazankov, P. A. Poselenov, A. D. Ryabov, and A. K. Yatsimirskii, *Metaloorg. Khim.*, **4**, 45 (1991).
91OM1746 G. Paolucci, F. Ossola, M. Bettinelli, R. Sessoli, F. Benetollo, and G. Bombieri, *Organometallics*, **13**, 1746 (1991).
91OM3470 A. S. Guram and R. F. Jordan, *Organometallics*, **10**, 3470 (1991).
91P227 M. I. Bruce, M. P. Cifuentes, and M. G. Humphrey, *Polyhedron*, **10**, 227 (1991).
92ACR57 T. J. Marks, *Acc. Chem. Res.*, **25**, 57 (1992).
92CRV965 R. L. Halterman, *Chem. Rev.*, **92**, 265 (1992).
92HCA1320 U. Maeder, A. Zelewsky, and H. Stoeckli-Evans, *Helv. Chim. Acta*, **75**, 1320 (1992).
92IC3083 A. D. Ryabov, G. M. Kazankov, A. K. Yatsimirskii, L. G. Kuzmina, O. Y. Burtseva, N. V. Dvortsova, and V. A. Polyakov, *Inorg. Chem.*, **31**, 3083 (1992).
92JA5462 S. D. Gray, D. P. Smith, M. A. Bruck, and D. E. Wigley, *J. Am. Chem. Soc.*, **114**, 5462 (1992).
92JA8991 A. S. Guram, D. C. Swenson, and R. F. Jordan, *J. Am. Chem. Soc.*, **114**, 8991 (1992).
92JCS(D)2251 E. C. Constable, R. G. P. Henney, R. A. Raithby, and L. R. Sousa, *J. Chem. Soc., Dalton Trans.*, 2251 (1992).
92JOC5994 A. S. Guram and R. F. Jordan, *J. Org. Chem.*, **57**, 5994 (1992).
92OM1275 D. P. Smith, D. P. Strickler, S. D. Gray, M. A. Bruck, R. S. Holmes, and D. E. Wigley, *Organometallics*, **11**, 1275 (1992).
93AJC1323 D. S. C. Black, G. B. Deacon, G. L. Edwards, and B. M. Gatehouse, *Aust. J. Chem.*, **46**, 1323 (1993).

93IC3081 M. G. Colombo and H. U. Gudel, *Inorg. Chem.*, **32**, 3081 (1993).
93IC3675 J. Fornies, R. Navarro, V. Sicilla, and M. Tomas, *Inorg. Chem.*, **32**, 3675 (1993).
93IC4585 A. Zelewsky, A. P. Suckling, and H. Stoeckli-Evans, *Inorg. Chem.*, **32**, 4585 (1993).
93IC5633 P. J. Spellane, R. J. Watts, and A. Vogler, *Inorg. Chem.*, **32**, 5633 (1993).
93IC6115 T. G. Hodgkins, *Inorg. Chem.*, **32**, 6115 (1993).
93JCS(D)2653 L. M. Engelhardt, B. S. Jolly, M. F. Lappert, C. L. Raston, and A. H. White, *J. Chem. Soc., Dalton Trans.*, 2653 (1993).
93JCS(D)3075 K. Higashimura and Y. Nakamura, *J. Chem. Soc., Dalton Trans.*, 3075 (1993).
93JOC5995 A. S. Guram and R. F. Jordan, *J. Org. Chem.*, **58**, 5995 (1993).
93JOM(443)C39 W. P. Leung, H. K. Lee, Z. Y. Zhou, and T. C. W. Mak, *J. Organomet. Chem.*, **443**, C39 (1993).
93JOM(462)7 W. P. Leung, H. K. Lee, Z. Y. Zhou, and T. C. W. Mak, *J. Organomet. Chem.*, **462**, 7 (1993).
93MRC529 F. O. Garces and R. J. Watts, *Magn. Reson. Chem.*, **31**, 529 (1993).
93OM2414 A. Klose, E. Solari, R. Ferguson, C. Floriani, A. Chiesi-Villa, and C. Rizzoli, *Organometallics*, **12**, 2414 (1993).
93OM3531 M. Booij, B. J. Deelman, R. Duchateau, D. S. Postma, A. Meetsma, and J. H. Teuben, *Organometallics*, **12**, 3531 (1993).
93OM4863 T. Beringhelli, G. D'Alfonso, G. Ciani, D. M. Prosperio, and A. Sironi, *Organometallics*, **12**, 4863 (1993).
93P1613 K. J. Izod and P. Thornton, *Polyhedron*, **12**, 1613 (1993).
93ZK297 A. C. Strickl, U. Klement, and K. J. Range, *Z. Kristallogr.*, **208**, 297 (1993).
94BSCB207 E. van der Donckt, B. Camerman, F. Hendrick, R. Herne, and R. Vandeloise, *Bull. Soc. Chim. Belg.*, **103**, 207 (1994).
94IC9 B. Schmid, F. O. Graces, and R. J. Watts, *Inorg. Chem.*, **33**, 9 (1994).
94IC545 M. G. Colombo, T. C. Brunold, T. Riedner, H. Gudel, M. Fortsch, and H. B. Burgi, *Inorg. Chem.*, **33**, 545 (1994).
94JA4491 S. Rodewald and R. F. Jordan, *J. Am. Chem. Soc.*, **116**, 4491 (1994).
94JA9123 A. Klose, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, and N. Re, *J. Am. Chem. Soc.*, **116**, 9123 (1994).
94JCS(CC)2419 P. Berno and S. Gambarotta, *J. Chem. Soc., Chem. Commun.*, 2419 (1994).
94JOM(466)211 M. P. Cifuentes, M. G. Humphrey, B. W. Skelton, and A. H. White, *J. Organomet. Chem.*, **466**, 211 (1994).
94JOM(471)97 G. Paolucci, R. D'Ippolito, C. Ye, C. Qian, J. Graper, and R. D. Fischer, *J. Organomet. Chem.*, **471**, 97 (1994).
94JOM(474)C30 S. Chan, W. Y. Wong, and W. T. Wong, *J. Organomet. Chem.*, **474**, C30 (1994).
94OM882 D. J. Cardenas, A. M. Echavarren, and A. Vegas, *Organometallics*, **13**, 882 (1994).
94OM3881 B. J. Deelman, W. Stevels, M. T. Lakin, A. L. Spek, and J. H. Teuben, *Organometallics*, **13**, 3881 (1994).
94OM4523 J. A. Gladysz, G. A. Stark, and A. M. Arif, *Organometallics*, **13**, 4523 (1994).
94PIC239 D. E. Wigley, *Progr. Inorg. Chem.*, **42**, 239 (1994).
94RE14 Y. Nakamura and N. Shinkawa, *Rhodium Ex.*, **6**, 14 (1994).
94TPS158 A. D. Horton, *Trends Polym. Sci.*, **2**, 158 (1994).
95ACSA313 P. I. Kvam and J. Songstad, *Acta Chem. Scand.*, **A49**, 313 (1995).

95ACSA335 P. I. Kvam, M. V. Puzyk, K. P. Balashev, and J. Songstad, *Acta Chem. Scand.*, **A49**, 335 (1995).
95AGE1143 H. H. Brintzinger, D. Fischer, R. Mulhaupt, B. Rieger, and R. M. Waymouth, *Angew. Chem., Int. Ed. Engl.*, **34**, 1143 (1995).
95AJC1573 D. J. de Geest and P. J. Steel, *Aust. J. Chem.*, **48**, 1573 (1995).
95BCSJ183 N. Shinkawa, A. Sato, J. Shinya, Y. Nakamura, and S. Okeya, *Bull. Chem. Soc. Jap.*, **68**, 183 (1995).
95IC2334 M. M. Mdeleni, J. S. Bridgewater, R. J. Watts, and P. C. Ford, *Inorg. Chem.*, **34**, 2334 (1995).
95JA10678 S. D. Gray, K. J. Weller, M. A. Bruck, P. M. Briggs, and D. E. Wigley, *J. Am. Chem. Soc.*, **117**, 10678 (1995).
95JCS(CC)509 H. Q. Liu, S. M. Peng, and C. M. Che, *J. Chem. Soc., Chem.Commun.*, 509 (1995).
95JCS(CC)1787 H. Q. Liu, T. C. Cheung, S. M. Peng, and C. M. Che, *J. Chem. Soc., Chem. Commun.*, 1787 (1995).
95JCS(D)999 A. D. Ryabov, L. G. Kuzmina, V. A. Polyakov, G. M. Kazankov, E. S. Ryabova, M. Pfeffer, and R. van Eldik, *J. Chem. Soc., Dalton Trans.*, 999 (1995).
95JCS(D)2865 M. A. Cinellu, A. Zucca, S. Stoccoro, G. Minghetti, M. Manassero, and M. Samsoni, *J. Chem. Soc., Dalton Trans.*, 2865 (1995).
95JOM(489)C71 H. K. Lee, B. S. Luo, T. C. W. Mak, and W. P. Leung, *J. Organomet. Chem.*, **489**, C71 (1995).
95JOM(500)289 T. R. van den Ankler and C. L. Raston, *J. Organomet. Chem.*, **500**, 289 (1995).
95JOM(504)15 T. Beringhelli, L. Carlucci, G. D'Alfonso, G. Ciani, and D. M. Prosperio, *J. Organomet. Chem.*, **504**, 15 (1995).
95JPC13385 H. Wiedenhofer, S. Schutzenmeier, A. Zelewski, and H. Yersin, *J. Phys. Chem.*, **99**, 13385 (1995).
95OM3611 S. E. Kabir, D. S. Kolwaite, E. Rosenberg, K. Hardcastle, W. Cresswell, and J. Grindstaff, *Organometallics*, **14**, 3611 (1995).
95OM4427 D. J. Cardenas and A. M. Echavarren, *Organometallics*, **14**, 4427 (1995).
95OM4832 W. P. Leung, L. H. Weng, Z. Y. Zhou, and T. C. W. Mak, *Organometallics*, **14**, 4832 (1995).
95OM5478 J. D. Scollard, D. H. McConville, and J. J. Vittal, *Organometallics*, **14**, 5478 (1995).
95OM5588 K. J. Weller, S. D. Gray, P. M. Briggs, and D. E. Wigley, *Organometallics*, **14**, 5588 (1995).
95P3315 K. D. Allen, M. A. Bruck, S. D. Gray, R. P. Kingsborough, D. P. Smith, K. J. Weller, and D. E. Wigley, *Polyhedron*, **14**, 3315 (1995).
95P3335 P. T. Wolzanski, *Polyhedron*, **14**, 3335 (1995).
95MI1 T. C. Flood, in "*Comprehensive Organometallic Chemistry II*" (E. W. Abel, F. G. A. Stone, and G. Wilkinson, eds.), Vol. 6, p. 21, Pergamon Press, Oxford (1995).
95MI2 A. S. Guram and R. F. Jordan, in "*Comprehensive Organometallic Chemistry II*" (E. W. Abel, F. G. A. Stone, and G. Wilkinson, eds.), Vol. 4, p. 589, Pergamon Press, Oxford (1995).
95MI3 M. F. Semmelblack, in "*Comprehensive Organometallic Chemistry II*" (F. G. A. Stone, E. W. Abel, and G. Wilkinson, eds.), Vol. 12, Chapter 9.1, p. 979, Pergamon Press, Oxford (1995).
96ACSA1108 K. P. Balashev, T. Engebresten, P. I. Kvam, K. Maartmann-Moe, M. V. Puzyk, and J. Songstad, *Acta Chem. Scand.*, **A50**, 1108 (1996).
96AGE1263 A. H. Hoveyda and J. P. Morken, *Angew. Chem. Int. Ed. Engl.*, **35**, 1263 (1996).

96CL773 M. Shimizu, Y. Nakamura, and M. Tadokoro, *Chem. Lett.*, 773 (1996).
96IC4883 P. Jolliet, M. Gianini, A. Zelewsky, G. Bernardinelli, and H. Stoeckli-Evans, *Inorg. Chem.*, **35**, 4883 (1996).
96JA5132 J. B. Bonanno, T. P. Henry, D. R. Neithamer, P. T. Wolczanski, and E. B. Lobkovsky, *J. Am. Chem. Soc.*, **118**, 5132 (1996).
96JCS(CC)1039 H. Q. Liu, T. C. Cheung, and C. M. Che, *J. Chem. Soc., Chem. Commun.*, 1039 (1996).
96JCS(D)69 R. V. Parish, J. Mack, L. Hargreaves, J. P. Wright, R. G. Buckley, A. M. Elsome, S. P. Fricker, and B. R. C. Theobald, *J. Chem. Soc., Dalton Trans.*, 69 (1996).
96JCS(D)255 M. Bochmann, *J. Chem. Soc., Dalton Trans.*, 255 (1996).
96JCS(D)4217 M. A. Cinellu, A. Zucca, S. Stoccoro, G. Minghetti, M. Manassero, and M. Samson, *J. Chem. Soc., Dalton Trans.*, 4251 (1996).
96JOM(513)27 W. Y. Wong and W. T. Wong, *J. Organomet. Chem.*, **513**, 27 (1996).
96MI1 E. C. Constable, Metals and Ligand Reactivity, Wiley, VCH, Weinheim (1996).
96OM1785 W. P. Leung, H. K. Lee, L. H. Weng, B. S. Luo, Z. Y. Zhou, and T. C. W. Mak, *Organometallics*, **15**, 1785 (1996).
96OM1979 E. Rosenberg, D. S. Kolwaite, S. E. Kabir, K. I. Hardcastle, T. McPhillips, R. Duque, and M. Day, *Organometallics*, **15**, 1979 (1996).
96OM2291 R. Duchateau, C. T. van Wee, and J. H. Teuben, *Organometallics*, **15**, 2291 (1996).
96P135 M. B. Hursthouse, K. J. Izod, M. Motevalli, and P. Thornton, *Polyhedron*, **15**, 135 (1996).
97AX(C)562 J. Breu, K. J. Range, and A. Zelewsky, *Acta Cryst. C*, **53**, 562 (1997).
97BCSJ2155 K. Yamasaki, H. Saito, M. Tadokoro, S. Miyajima, and Y. Nakamura, *Bull. Chem. Soc. Jap.*, **70**, 2155 (1997).
97CCR(159)109 K. P. Balashev, M. V. Puzyk, V. S. Kotlyar, and M. V. Kulikova, *Coord. Chem. Rev.*, **159**, 109 (1997).
97JA247 T. S. Kleckley, J. L. Bennett, P. T. Wolczanski, and E. B. Lobkovsky, *J. Am. Chem. Soc.*, **119**, 247 (1997).
97JA1145 W. P. Leung, W. H. Kwok, F. Xue, and T. C. W. Mak, *J. Am. Chem. Soc.*, **119**, 1145 (1997).
97JCS(CC)1183 P. C. Andrews, C. L. Raston, B. W. Skelton, and A. H. White, *J. Chem. Soc., Chem. Commun.*, 1183 (1997).
97JCS(D)779 W. P. Leung, H. K. Lee, L. H. Weng, Z. Y. Zhou, and T. C. W. Mak, *J. Chem. Soc., Dalton Trans.*, 779 (1997).
97JCS(D)2997 G. R. Haire, N. E. Leadbeater, J. Lewis, P. R. Raithby, A. J. Edwards, and E. C. Constable, *J. Chem. Soc., Dalton Trans.*, 2997 (1997).
97JCS(D)4301 W. P. Leung, W. H. Kwok, L. H. Weng, L. T. C. Law, Z. Y. Zhou, and T. C. W. Mak, *J. Chem. Soc., Dalton Trans.*, 4301 (1997).
97JOM(528)225 K. J. Weller, I. Filippov, P. M. Briggs, and D. S. Wigley, *J. Organomet. Chem.*, **528**, 225 (1997).
97JOM(545)619 A. M. Clark, C. E. F. Rickard, W. R. Roper, and L. J. Wright, *J. Organomet. Chem.*, **545–546**, 619 (1997).
97OM657 J. P. Djukic, A. Maisse, M. Pfeffer, A. De Cian, and J. Fischer, *Organometallics*, **16**, 657 (1997).
97OM2719 T. Beringhelli, G. D'Alfonso, M. Freni, and M. Panigati, *Organometallics*, **16**, 2719 (1997).
97OM5171 J. P. Djukic, K. H. Dotz, M. Pfeffer, A. de Cian, and J. Fischer, *Organometallics*, **16**, 5171 (1997).

97OM5506 R. Duchateau, E. A. C. Brussee, A. Meetsma, and J. H. Teuben, *Organometallics*, **16**, 5506 (1997).
97OM5541 S. Dagorne, S. Rodewald, and R. F. Jordan, *Organometallics*, **16**, 5541 (1997).
97P577 M. Shimizu, Y. Nakamura, and M. Tadokoro, *Polyhedron*, **16**, 577 (1997).
97P1963 I. Ara, J. Fornies, R. Navarro, V. Sicilia, and E. P. Urroilabeitia, *Polyhedron*, **16**, 1963 (1997).
97P3139 K. J. Weller, P. A. Fox, S. D. Gray, and D. Wigley, *Polyhedron*, **16**, 3139 (1997).
97P4039 M. Nonoyama, K. Nakajima, and K. Nonoyama, *Polyhedron*, **16**, 4039 (1997).
98AGE3270 G. W. V. Cave, A. J. Hallett, W. Errington, and J. P. Rourke, *Angew. Chem., Int. Ed. Engl.*, **37**, 3270 (1998).
98EJIC1781 J. P. Djukic, A. Maisse, M. Pfeffer, K. H. Dotz, and M. Nieger, *Eur. J. Inorg. Chem.*, 1781 (1998).
98IC3649 J. P. Djukic, K. H. Dotz, M. Pfeffer, A. De Cian, and J. Fischer, *Inorg.Chem.*, **37**, 3649 (1998).
98ICC424 W. E. Damrau, G. Paolucci, J. Zamon, E. Siebel, and R. D. Fisher, *Inorg. Chem. Commun.*, **1**, 424 (1998).
98JA4228 Y. Guari, S. Sabo-Etienne, and B. Chaudret, *J. Am. Chem. Soc.*, **120**, 4228 (1998).
98JA12818 B. Bergman, R. Holmquist, R. Smith, E. Rosenberg, J. Ciurash, K. Hardcastle, and M. Visi, *J. Am. Chem. Soc.*, **120**, 12818 (1998).
98JCS(CC)547 P. C. Andrews, C. J. King, C. L. Raston, and B. A. Roberts, *J. Chem. Soc., Chem. Commun.*, 547 (1998).
98JCS(CC)575 P. C. Andrews, C. L. Raston, B. W. Skelton, V. A. Talhurst, and A. H. White, *J. Chem. Soc., Chem. Commun.*, 575 (1998).
98JCS(CC)663 C. Coudret, S. Fraysse, and J. P. Launay, *J. Chem. Soc., Chem. Commun.*, 663 (1998).
98JCS(CC)1127 L. Z. Wu, T. C. Cheung, C. M. Che, K. K. Cheung, and M. H. W. Lam, *J. Chem. Soc., Chem. Commun.*, 1127 (1998).
98JCS(D)791 Y. Fuchita, H. Ieda, Y. Tsunemune, J. Kinoshita-Nagaoka, and H. Kawano, *J. Chem. Soc., Dalton Trans.*, 791 (1998).
98JCS(D)4095 Y. Fuchita, H. Ieda, A. Kayama, J. Kinoshita-Nagaoka, H. Kawano, S. Kameda, and M. Mikuria, *J. Chem. Soc., Dalton Trans.*, 4095 (1998).
98JL611 J. Strasser, D. Donges, W. Humbs, M. V. Koulikova, K. P. Balashev, and H. Yersin, *J. Lumin.*, **76–77**, 611 (1998).
98JOM(560)233 M. B. Dinger and W. Henderson, *J. Organomet. Chem.*, **560**, 233 (1998).
98JOM(564)193 W. P. Leung, H. K. Lee, Z. Y. Zhou, and T. C. W. Mak, *J. Organomet. Chem.*, **564**, 193 (1998).
98JOM(567)65 J. P. Djukic, A. Maisse, and M. Pfeffer, *J. Organomet. Chem.*, **567**, 65 (1998).
98OM322 K. J. Weller, I. Filippov, P. M. Briggs, and D. E. Wigley, *Organometallics*, **17**, 322 (1998).
98OM415 E. Arcia, D. S. Kolwaite, E. Rosenberg, K. I. Hardcastle, J. Ciurash, R. Duque, R. Gobetto, L. Milone, D. Osella, M. Botta, W. Dastru, A. Viale, and J. Fiedler, *Organometallics*, **17**, 415 (1998).
98OM779 P. C. Andrews, C. L. Raston, B. W. Skelton, and A. H. White, *Organometallics*, **17**, 779 (1998).
98OM3505 K. H. Wong, K. K. Cheung, M. C. W. Chan, and C. M. Che, *Organometallics*, **17**, 3505 (1998).

98OM4535 A. M. Clark, C. E. F. Rickard, W. R. Roper, and L. J. Wright, *Organometallics*, **17**, 4535 (1998).
98P2975 A. B. Din, B. Bergman, E. Rosenberg, R. Smith, W. Dastru, R. Gobetto, L. Milone, and A. Viale, *Polyhedron*, **17**, 2975 (1998).
98TL7873 S. Fraysse, C. Coudret, and J. P. Launay, *Tetrahedron Lett.*, **39**, 7873 (1998).
99CCR(190)175 M. J. Abedin, B. Bergman, R. Holmquist, R. Smith, E. Rosenberg, J. Ciurash, K. I. Hardcastle, J. Roe, V. Vazquez, C. Roe, S. E. Kabir, B. Roy, S. Alam, and K. A. Azam, *Coord. Chem. Rev.*, **190–192**, 175 (1990).
99CEJ2845 K. H. Wong, M. C. W. Chan, and C. M. Che, *Chem. Eur. J.*, **5**, 2845 (1999).
99CEJ3350 C. M. Che, M. G. Yang, K. H. Wong, H. L. Chan, and W. Lam, *Chem. Eur. J.*, **5**, 3350 (1999).
99EJIC1047 Y. Guari, S. Sabo-Etienne, and B. Chaudret, *Eur. J. Inorg. Chem.*, 1047 (1999).
99EJIC1271 L. Ghizdavu, B. Kolp, A. Zelewsky, and H. Stoeckli-Evans, *Eur. J. Inorg. Chem.*, 1271 (1999).
99IC5820 H. Yersin and W. Humbs, *Inorg. Chem.*, **38**, 5820 (1999).
99ICC10 B. J. O'Keefe and P. J. Steel, *Inorg. Chem. Commun.*, **2**, 10 (1999).
99JA7405 T. Yamaguchi, F. Yamazaki, and T. Ito, *J. Am. Chem. Soc.*, **121**, 7405 (1999).
99JCS(D)4175 P. Braunstein, J. Durand, G. Kickelbick, M. Knorr, X. Morise, R. Pugin, A. Tiripicchio, and F. Ugozzoli, *J. Chem. Soc., Dalton Trans.*, 4175 (1999).
99JOM(579)97 D. J. de Geest, B. J. O'Keefe, and P. J. Steel, *J. Organomet. Chem.*, **579**, 97 (1999).
99OM389 S. Benet, C. J. Cardin, D. J. Cardin, S. P. Constantine, P. Heath, H. Rashid, S. Teixeira, J. H. Thorpe, and A. K. Todd, *Organometallics*, **18**, 389 (1999).
99OM1801 G. W. V. Cave, N. W. Alcock, and J. P. Rourke, *Organometallics*, **18**, 1801 (1999).
99OM2786 J. P. Djukic, A. Maisse, M. Pfeffer, K. H. Dotz, and M. Nieger, *Organometallics*, **18**, 2786 (1999).
99OM2813 A. M. Clark, C. E. F. Rickard, W. R. Roper, and L. J. Wright, *Organometallics*, **18**, 2813 (1999).
99OM3337 D. J. Cardenas, A. M. Echavarren, and M. C. R. de Arellano, *Organometallics*, **18**, 3337 (1999).
99OM3519 R. Smith, E. Rosenberg, K. I. Hardcastle, V. Vazques, and J. Roh, *Organometallics*, **18**, 3519 (1999).
99OM4247 P. C. Andrews, P. J. Nichols, C. L. Raston, and B. A. Roberts, *Organometallics*, **18**, 4247 (1999).
99P749 K. Ortner and U. Abram, *Polyhedron*, **18**, 749 (1999).
99TL5533 K. Itami, K. Mitsudo, and J. Yoshida, *Tetrahedron Lett.*, **40**, 5533 (1999).
99TL5537 K. Itami, T. Kamei, and J. Yoshida, *Tetrahedron Lett.*, **40**, 5537 (1999).
00CEJ1064 J. P. Djukic, C. Michon, A. Maisse-Francois, R. Allagapen, M. Pfeffer, K. Dotz, A. De Cian, and J. Fischer, *Chem. Eur. J.*, **6**, 1064 (2000).
00CP301 J. Strasser, H. H. H. Homeier, and H. Yersin, *Chem. Phys.*, **255**, 301 (2000).
00EJIC1581 S. Fraysse, C. Coudret, and J. P. Launay, *Eur. J. Inorg. Chem.*, 1581 (2000).

00EJIC1923 M. Enders, J. Fink, and H. Pritzkow, *Eur. J. Inorg. Chem.*, 1923 (2000).
00IC1955 J. DePriest, G. Y. Zheng, N. Goswamni, D. M. Eichhorn, C. Woods, and D. P. Rillema, *Inorg. Chem.*, **39**, 1955 (2000).
00ICA(300)769 E. Rosenberg, L. Milone, C. Nervi, D. Osella, J. Fiedler, M. Abedin, and D. Rokhsana, *Inorg. Chim. Acta*, **300–302**, 769 (2000).
00JA12013 K. Itami, K. Mitsudo, T. Kamei, T. Koike, T. Nokami, and J. Yoshida, *J. Am. Chem. Soc.*, **122**, 12013 (2000).
00JCS(CC)691 C. Eaborn, M. S. Hill, P. B. Hitchcock, and J. D. Smith, *J. Chem. Soc., Chem. Commun.*, 691 (2000).
00JCS(CC)1247 A. D. Tulloch, A. A. Danopoulos, R. P. Tooze, S. M. Cafferkey, S. Kleinhenz, and M. B. Hursthouse, *J. Chem. Soc., Chem. Commun.*, 1247 (2000).
00JCS(D)735 U. Abram, K. Ortner, R. Gust, and K. Sommer, *J. Chem. Soc., Dalton Trans.*, 735 (2000).
00JCS(D)839 J. C. C. Chen and I. J. B. Lin, *J. Chem. Soc., Dalton Trans.*, 839 (2000).
00JCS(D)3128 J. C. Shi, H. Y. Chao, W. F. Fu, S. M. Peng, and C. M. Chu, *J. Chem. Soc., Dalton Trans.*, 3129 (2000).
00JCS(D)4499 A. A. D. Tulloch, A. A. Danopoulos, S. Winston, S. Kleinhenz, and G. Eastham, *J. Chem. Soc., Dalton Trans.*, 4499 (2000).
00JOM(593)226 S. T. Betty, B. Bergman, E. Rosenberg, W. Dastru, R. Gobetto, L. Milone, and A. Viale, *J. Organomet. Chem.*, **593–594**, 226 (2000).
00JOM(596)165 R. V. Parish, J. P. Wright, and R. G. Pritchard, *J. Organomet. Chem.*, **596**, 165 (2000).
00JOM(607)213 T. R. van den Ancker, P. C. Andrews, S. J. King, J. E. McGrady, C. L. Raston, B. A. Roberts, B. W. Skelton, and A. H. White, *J. Organomet. Chem.*, **607**, 213 (2000).
00JOM(608)34 S. Tollari, S. Cenini, A. Penoni, G. Granata, G. Palmisano, and F. Demartin, *J. Organomet. Chem.*, **608**, 34 (2000).
00OM741 D. S. McGuiness and K. J. Cavell, *Organometallics*, **19**, 741 (2000).
00OM1355 G. W. V. Cave, F. P. Fanunzi, R. J. Deeth, W. Errington, and J. P. Rourke, *Organometallics*, **19**, 1355 (2000).
00OM3224 S. S. Al-Juaid, C. Eaborn, P. B. Hitchcock, M. S. Hill, and J. D. Smith, *Organometallics*, **19**, 3224 (2000).
00OM4437 T. R. van den Ancker, C. L. Raston, B. W. Skelton, and A. H. White, *Organometallics*, **19**, 4437 (2000).
00RJGC163 M. V. Kulikova, K. P. Balashev, P. L. Kvan, and J. Songstad, *Russ. J. Gen. Chem.*, **70**, 163 (2000).
01ACA(445)177 Y. Amao, Y. Ishikawa, and I. Okura, *Anal. Chim. Acta*, **445**, 177 (2001).
01AGE2337 K. Itami, K. Mitsudo, and J. Yoshida, *Angew. Chem., Int. Ed. Engl.*, **40**, 2337 (2001).
01EJIC993 L. Ghizdavu, A. Zelewsky, and H. Stoeckli-Evans, *Eur. J. Inorg. Chem.*, 993 (2001).
01IC1704 S. Lamanski, P. Djurovich, D. Murphy, F. Abdel-Razzaq, R. Kwong, I. Tsyba, M. Bortz, B. Mui, R. Bau, and M. E. Thompson, *Inorg. Chem.*, **40**, 1704 (2001).
01JA4304 S. Lamanski, P. Djurovich, D. Murphy, F. Abdel-Razzaq, H. E. Lee, C. Adachi, P. E. Burrows, S. R. Forrest, and M. E. Thompson, *J. Am. Chem. Soc.*, **123**, 4304 (2001).
01JA10935 N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, and S. Murai, *J. Am. Chem. Soc.*, **123**, 10935 (2001).
01JA11577 K. Itami, T. Nokami, Y. Ishimura, H. Mitsudo, T. Kamei, and J. Yoshida, *J. Am. Chem. Soc.*, **123**, 11577 (2001).

01JCS(CC)201 E. Peris, J. A. Loch, J. Mata, and R. H. Crabtree, *J. Chem. Soc., Chem. Commun.*, 201 (2001).

01JCS(CC)1270 A. A. D. Tulloch, A. A. Danopoulos, G. J. Tizzard, S. J. Coles, M. B. Hursthouse, R. S. Hay-Motherwell, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1270 (2001).

01JCS(CC)1494 V. V. Grushin, N. Herron, D. D. Le Cloux, W. J. Marshall, V. A. Petrov, and Y. Wang, *J. Chem. Soc., Chem. Commun.*, 1494 (2001).

01JCS(D)996 P. C. Andrews, D. R. Armstrong, C. L. Raston, B. A. Roberts, B. W. Skelton, and A. H. White, *J. Chem. Soc., Dalton Trans.*, 996 (2001).

01JCS(D)1541 C. Eaborn and J. D. Smith, *J. Chem. Soc., Dalton Trans.*, 1541 (2001).

01JCS(D)3069 T. R. van den Ancker, S. K. Bhargava, F. Mohr, S. Papadoupoulos, C. L. Raston, B. W. Skelton, and A. H. White, *J. Chem. Soc., Dalton Trans.*, 3069 (2001).

01JOC3970 K. Itami, T. Kamei, K. Mitsudo, T. Nokami, and J. Yoshida, *J. Org. Chem.*, **66**, 3970 (2001).

01JOM(622)47 G. Sanna, M. I. Piolo, M. Spano, G. Minghetti, M. A. Cinellu, A. Zucca, and R. Seeber, *J. Organomet. Chem.*, **622**, 47 (2001).

01JOM(622)89 I. P. Beletskaya, A. N. Kashin, N. B. Karlstedt, A. V. Mitin, A. V. Cheprakov, and G. M. Kazankov, *J. Organomet. Chem.*, **622**, 89 (2001).

01JOM(624)388 D. Monchaud, J. Lacour, C. Coudret, and S. Fraysse, *J. Organomet. Chem.*, **624**, 388 (2001).

01JOM(631)76 S. S. Al-Juaid, A. G. Avent, C. Eaborn, S. M. El-Hamruni, S. A. Hawkes, M. S. Hill, M. Hopman, P. B. Hitchcock, and J. D. Smith, *J. Organomet. Chem.*, **631**, 76 (2001).

01JOM(637)514 R. D. Adams, B. Qu, and M. D. Smith, *J. Organomet. Chem.*, **637–639**, 514 (2001).

01OM1223 S. S. Al-Juaid, A. G. Avent, C. Eaborn, M. S. Hill, P. B. Hitchcock, D. J. Patel, and J. D. Smith, *Organometallics*, **20**, 1223 (2001).

01OM2027 A. A. D. Tulloch, A. A. Danopoulos, S. Kleinhenz, M. E. Light, M. B. Hursthouse, and G. Eastham, *Organometallics*, **20**, 2027 (2001).

01OM2477 W. Lu, M. C. W. Chan, K. K. Cheung, and C. M. Che, *Organometallics*, **20**, 2477 (2001).

01OM3230 A. Berger, A. de Cian, J. P. Djukic, J. Fischer, and M. Pfeffer, *Organometallics*, **20**, 3230 (2001).

01OM4999 K. K. W. Lo, D. C. M. Ng, and C. K. Chung, *Organometallics*, **20**, 4999 (2001).

01OM5005 M. Enders, P. Fernandez, G. Ludwig, and H. Pritzkow, *Organometallics*, **20**, 5005 (2001).

01OM5485 S. Grundemann, M. Albrecht, J. A. Loch, J. W. Faller, and R. H. Crabtree, *Organometallics*, **20**, 5485 (2001).

01TCC81 H. Yersin and D. Donges, *Top. Curr. Chem.*, **214**, 81 (2001).

02CRV1851 F. T. Edelmann, D. M. M. Freckmann, and H. Schumann, *Chem. Rev.*, **102**, 1851 (2002).

02CRV3693 J. Yoshida and K. Itami, *Chem. Rev.*, **102**, 3693 (2002).

02IC3055 J. Brooks, Y. Babayan, S. Lamansky, P. I. Djurovich, I. Tsyba, R. Bau, and M. E. Thompson, *Inorg. Chem.*, **41**, 3055 (2002).

02IC4915 H. Yersin, D. Donges, W. Humbs, J. Shasser, R. Sitters, and M. Glasbeek, *Inorg. Chem.*, **41**, 4915 (2002).

02IC5561 T. Dube, J. M. Faller, and R. H. Crabtree, *Inorg. Chem.*, **41**, 5561 (2002).

02IC6521 H. Hadadzadeh, M. C. De Rosa, G. P. A. Yap, A. R. Rezwani, and R. J. Crutchley, *Inorg. Chem.*, **41**, 6521 (2002).

02JCS(CC)482 A. A. Danopoulos, S. Winston, and R. B. Tooze, *J. Chem. Soc., Chem. Commun.*, 482 (2002).

02JCS(D)2163 S. Grundemann, M. Albrecht, A. Kovacevic, J. W. Faller, and R. H. Crabtree, *J. Chem. Soc., Dalton Trans.*, 2163 (2000).
02JCS(D)3090 A. A. Danoupoulos, S. Winston, and M. B. Hursthouse, *J. Chem. Soc., Dalton Trans.*, 3090 (2002).
02JOM(641)81 M. Enders, P. Fernandez, M. Kaschke, G. Kohl, G. Ludwig, H. Pritzkow, and R. Rudolph, *J. Organomet. Chem.*, **641**, 81 (2002).
02JOM(645)256 C. Jones and A. F. Richards, *J. Organomet. Chem.*, **645**, 256 (2002).
02JOM(653)105 K. Itami, K. Mitsudo, T. Nokami, T. Kamei, T. Koike, and J. Yoshida, *J. Organomet. Chem.*, **653**, 105 (2002).
02OM575 E. Clox, O. Eisenstein, T. Dube, J. W. Faller, and R. H. Crabtree, *Organometallics*, **21**, 575 (2002).
02OM1508 B. Bergman, E. Rosenberg, R. Gobetto, S. Aime, L. Milone, and F. Reineri, *Organometallics*, **21**, 1508 (2002).
02OM3519 C. Michon, J. P. Djukic, Z. Ratkovic, J. P. Collin, M. Pfeffer, A. De Cian, J. Fischer, D. Heiser, K. H. Dotz, and M. Nieger, *Organometallics*, **21**, 3519 (2002).
03IC4864 M. C. DeRosa, P. J. Mosher, G. P. A. Yap, K. S. Foscaneanu, R. J. Crutchley, and C. E. B. Evans, *Inorg. Chem.*, **42**, 4864 (2003).
03JCS(D)699 A. A. D. Tulloch, S. Winston, A. A. Danopoulos, G. Eastham, and M. B. Hursthouse, *J. Chem. Soc., Dalton Trans.*, 699 (2003).
03JCS(D)822 S. Fernandez, J. Fornies, B. Gil, J. Gomez, and E. Lalinde, *J. Chem. Soc., Dalton Trans.*, 822 (2003).
03JCS(D)831 J. R. Miecznikowski, S. Grundemann, M. Albrecht, C. Megret, E. Clot, J. W. Faller, O. Eisenstein, and R. H. Crabtree, *J. Chem. Soc., Dalton Trans.*, 831 (2003).
03JOM(668)51 E. Rosenberg, F. Spada, K. Sugden, B. Martin, L. Milone, R. Gobetto, A. Viale, and J. Fiedler, *J. Organomet. Chem.*, **668**, 51 (2003).
03JOM(669)141 K. Kubo, M. Nakano, H. Tamura, G. Matsubayashi, and M. Nakamoto, *J. Organomet. Chem.*, **669**, 141 (2003).
03JOM(679)194 C. H. A. Goss, W. Henderson, A. L. Wilkins, and C. Evans, *J. Organomet. Chem.*, **679**, 194 (2003).
03JOM(687)125 M. Enders, P. Fernandez, S. Mihan, and H. Pritzkow, *J. Organomet. Chem.*, **687**, 125 (2003).
03OM1281 B. J. O'Keefe and P. J. Steel, *Organometallics*, **22**, 1281 (2003).
03OM1751 W. P. Leung, W. H. Kwok, Z. Y. Zhou, and T. C. W. Mak, *Organometallics*, **22**, 1751 (2003).
04AHC(86)293 A. P. Sadimenko, *Adv. Heterocycl. Chem.*, **86**, 293 (2004).

Annulated Heterocyclo-Purines II: Fused Six- and More-Membered Heterocyclo-Purinediones, -Purinones and -Purineimines

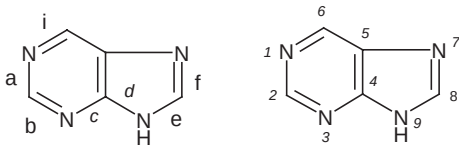
ALFONZ RYBÁR

Institute of Chemistry, Slovak Academy of Science, Bratislava 84538, Slovak Republic

I. Introduction

Efforts to obtain compounds with a greater selective efficacy without the unwanted side-effects found in the parent purines employed in medicine stimulated the study of annulated compounds. One approach fulfilling this aim employed the annulation of a heterocycle onto the purine ring.

The purine skeleton offers various geometries for ring fusion. The resultant tricyclic compounds have annulation to bonds a, b, e, f or i.



This review is a continuation of Part I published in AHC vol. 87 and presents purines annulated with six-, seven- and eight-membered rings, such as pyrido-,

ADVANCES IN HETEROCYCLIC CHEMISTRY
VOLUME 88 ISSN: 0065-2725 DOI: 10.1016/S0065-2725(04)88003-6

pyridazino-, pyrimido-, pyrazino-, oxazino-, thiazino-, azepino-, azocino-, diazepino-, diazocino-, oxazepino-, triazepino-, thiadiazepino-, oxdiazocino- and thiadiazocino-purines. Note that the numbering of the skeleton in some papers does not match that in Chemical Abstracts. Our organization includes the synthesis, the reactions of the heterocyclic system in question, the biological effects, and, if accessible, references to spectral data and X-ray analysis. Papers were abstracted up to December 2002, including vol. 137 of Chemical Abstracts.

II. Purines Fused to Six-Membered Heterocycles

A. Pyrido-Purines

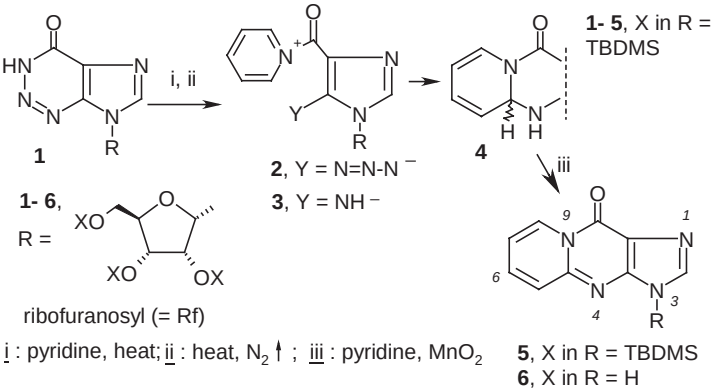
This group includes compounds with the pyridine ring annulated to the respective a, b, e, f and i positions of a purine.

1. *Pyrido[1,2-a]purines*

To date the only synthesis of the nucleoside of this heterocycle started from a ribofuranosyl derivative of imidazo[4,5-*d*][1,2,3]triazinone protected by a silyl group **1**. Heating in pyridine opened the triazine ring to the pyridinium salt **2** that lost nitrogen to give **3** followed by cyclization to **4**. Subsequent treatment with manganese dioxide gave the corresponding pyrido[1,2-*a*]purine nucleoside **5**. Deprotection of the silyl groups with tetra-*n*-butylammonium fluoride yielded **6**; its structure was demonstrated by ^{1}H- and ^{13}C-NMR (91TL5693) (Scheme 1).

2. *Pyrido[2,1-b]purines*

Two methods employing different starting materials were reported. The first used 2-aminopyridine (**7**) and sodium ethyl isonitrosocyanoacetate in boiling ethanol to



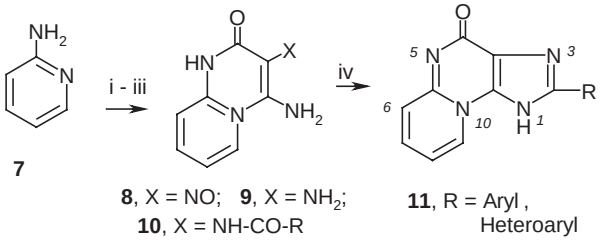
Scheme 1

give 4-amino-3-nitrosopyrido[1,2-*a*]pyrimidin-2-one **8**. Reduction of its nitroso group by sodium dithionite yielded 3,4-diamine **9** and reaction with acyl chloride produced **10**. Cyclization in alkali or heating with polyphosphoric acid gave the required pyrido[2,1-*b*]purine derivative **11** (95JHC1725).

An alternative method leading to **11** (**R** = **H**) used zinc in formic acid to reduce the 3-nitroso group of **8** to 4-amino-3-formamidopyrido[1,2-*a*]pyrimidin-2-one **10** (**R** = **H**). The third (imidazole) ring was closed with alkali or PPA (65MI1) (Scheme 2).

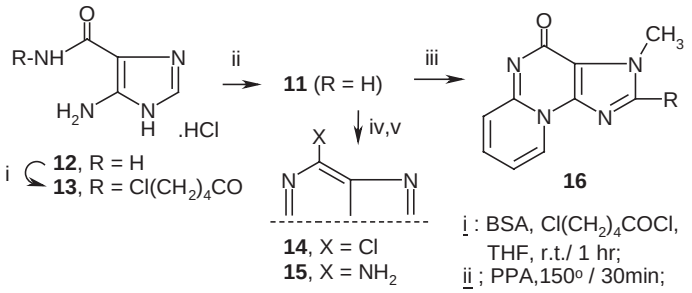
The second method started from 4-aminoimidazol-5-carboxamide hydrochloride **12** protected as its BSA (bis(trimethyl-silyl)acetamide) derivative. Treatment with 5-chlorovaleryl chloride gave 4-amino-*N*-(5-chloropentanoyl)-5-imidazol-carboxamide **13**. Its cyclization in polyphosphoric acid produced **11** (**R** = **H**) in 36% yield (93JHC593). Alkylation of the sodium salt of **11** with methyl iodide or methyl tosylate took place at *N*−3, as demonstrated by a long-range NMR decoupling experiment (93JHC593). Heating **11** in phosphoryl chloride afforded the 4-chloro **14** and the subsequent treatment with ammonia gave the 4-amino **15** (95JHC1725) (Scheme 3).

Triarylpyrido[2,1-*b*]purine-4-thiones showed herbicidal activity (00MI1).



i ; NC-C(=NOH)-CO_2Et, EtONa, EtOH, reflux; ii : $Na_2S_2O_4$, NH_4OH, 70-80°;
iii : R-CO-Cl, AcOH, AcONa; iv : MeONa, MeOH, reflux *or* PPA, 110°

Scheme 2



iii : NaH, DMF, MeI *or* TsOMe; iv : $POCl_3$, reflux; v : NH_3, MeOH

Scheme 3

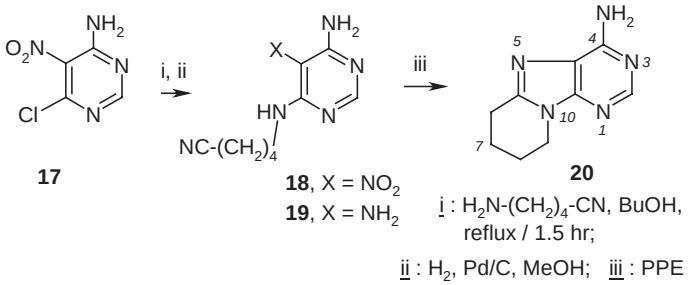
3. *Pyrido[2,1-e]purines*

The first method started from 6-amino-4-chloro-5-nitropyrimidine (**17**) and 5-aminovaleronitrile. The obtained 4-(4-cyanobutyl)amino derivative **18** was hydrogenated to the corresponding 5-amino **19** and then heated in ethyl polyphosphate (PPE, 150 °C). A double cyclization took place to form both the imidazole and pyridine rings of 6,7,8,9-tetrahydropyrido[1,2-*e*]purine-4-amine (**20**), the last step in 11% yield (90JMC2073) (Scheme 4).

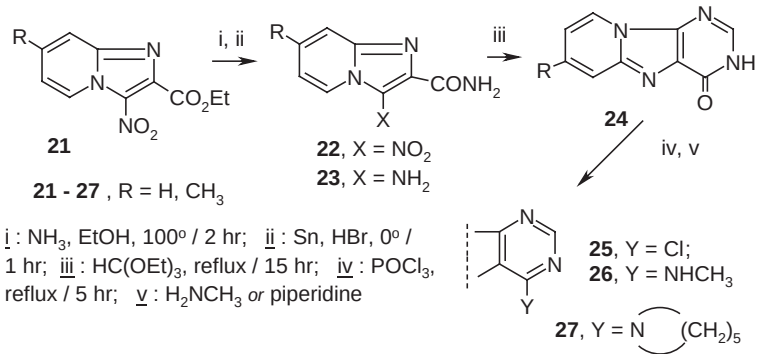
The second method utilized ethyl 3-nitroimidazo[1,2-*a*]pyridin-2-carboxylate (**21**). Aminolysis at elevated temperature yielded the amide **22**, the reduction of which with tin in hydrobromic acid gave the corresponding aminoamide **23**. Closure of the pyrimidine ring to tricyclic **24** was effected by heating with triethyl formate in acetic acid (Scheme 5).

The enol of **24** was transformed to the 4-chloro derivative **25** with phosphoryl chloride on heating. Compound **25** reacted easily with aqueous methylamine and piperidine to **26** and **27**, respectively (99PHA876).

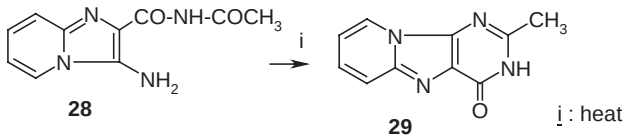
The third method used thermal cyclization of a similar imidazo[1,2-*a*]pyridine **28** to give 2-methylpyrido[1,2-*e*]purin-4(3*H*)-one **29** (96MI1) (Scheme 6).



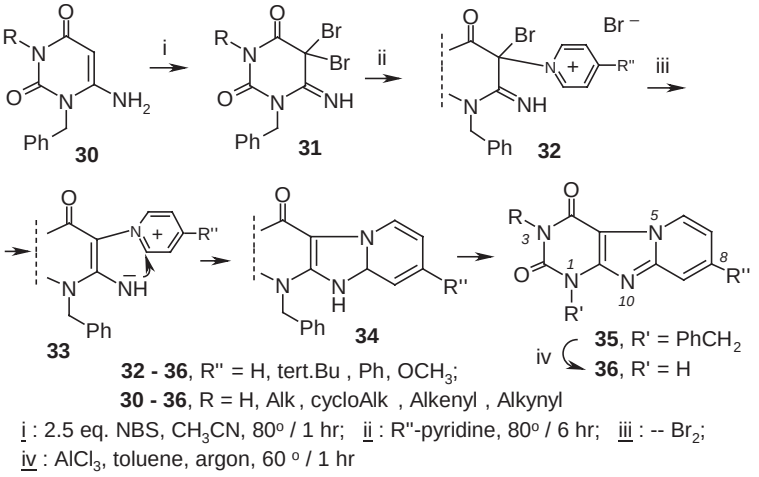
Scheme 4



Scheme 5



Scheme 6



Scheme 7

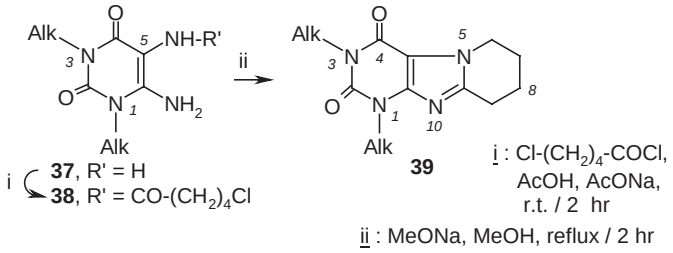
Compound **20** showed an inhibitory effect on the phosphatidinylinositol-4-kinase membrane of human erythrocytes (90JMC2073).

4. *Pyrido[2,1-f]purines*

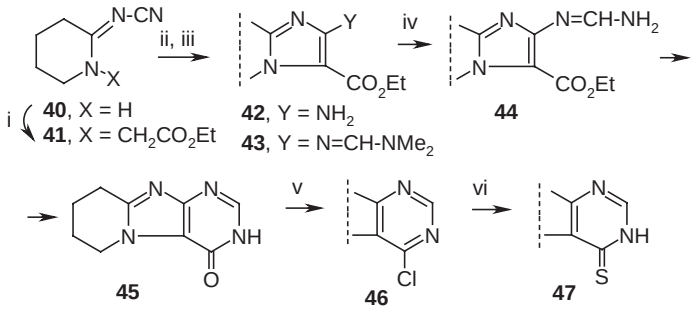
The first of the three methods involved a two-step one-pot synthesis, starting from the 6-amino-1-benzyluracil derivative **30**. Treatment with *N*-bromosuccinimide in acetonitrile gave the 5,5-dibromo-6-imino derivative **31**. The *in situ* reaction with various pyridines produces the final **35**. The mechanism of this cyclization reaction proposed by the authors is seen in Scheme 7.

The reaction started by a nucleophilic attack of pyridine on dibromo **31** to give **32**. Elimination of molecular bromine gave intermediate **33**. The positive charge on the pyridine moiety facilitated a nucleophillic attack to its α-position to yield **34**. Aromatization of the latter produced the required pyrido[2,1-*f*]purine-2,4-dione **35** (02SL155, 02JMC3337) (Scheme 7).

The second synthesis utilized 5,6-diamino-1,3-dimethyluracil **37**. The more nucleophilic 5-amino group was acylated selectively with 5-chloropentanoyl chloride to the corresponding 5-acylamino **38**. Cyclization with sodium methoxide gave the 6,7,8,9-tetrahydropyrido[2,1-*f*]purinedione **39** (60%). Derivative **38** can alternatively



Scheme 8



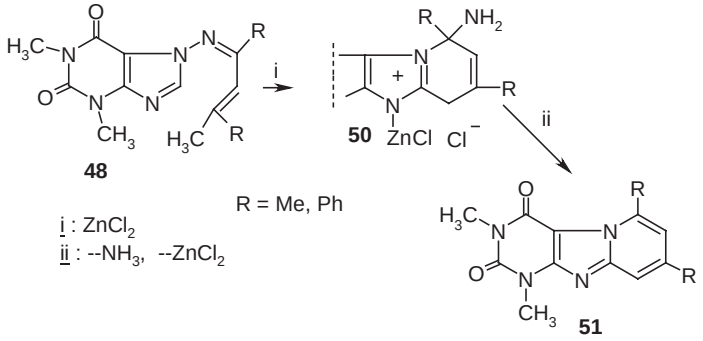
Scheme 9

be heated in diphenyl ether to give the 8-(4-hydroxybutyl)xanthine. Hydrolysis of the chlorine to a hydroxyl group resulted from the water liberated during cyclization in diphenyl ether. Heating with thionyl chloride afforded 8-(4-chlorobutyl)xanthine and cyclization with sodium methoxide gave **39** (94JHC81) (Scheme 8).

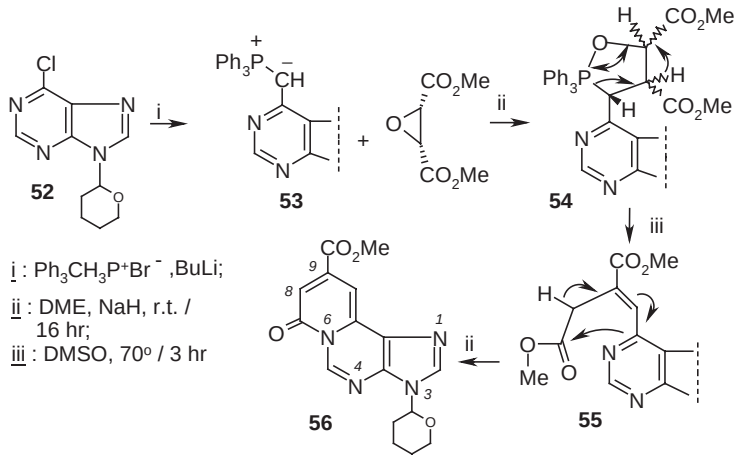
In the third method an *N*-cyanoamidine **40** was alkylated with ethyl chloroacetate to give **41**. The imidazole ring was then closed by sodium ethoxide to furnish **42**. A stepwise treatment with dimethylformamide diethyl acetal and then ammonia followed by cyclization afforded intermediates **43** and **44** and finally the 6,7,8,9-tetrahydropyrido[2,1-*f*]purine derivative **45**. The enol form of **45** reacted with phosphoryl chloride to give the chloro derivative **46** and then with thiourea to afford the 4-thione **47** through the thiuronium salt (92KFZ(9-10)63) (Scheme 9).

Another approach was demonstrated by the reaction of 7-amino-theophylline and mesityl oxide or acetophenone to give **48**, which in the presence of anhydrous zinc chloride, formed 6,8-dimethyl- or 6,8-diphenyl-pyrido[2,1-*f*]purinedione **51**. This reaction proceeded through the intermediate **50** (87KGS1551) (Scheme 10).

Alkylation of **35** (**R = H**) with alkyl-, cycloalkyl- and unsaturated alkyl bromides in the presence of diazabicycloundecene (DBU) produced a series of N(3)-substituted derivatives of **35**. Debenzylation of **35** (**R = propyl**) was effected with aluminum chloride to form **36** (02JMC3337).



Scheme 10



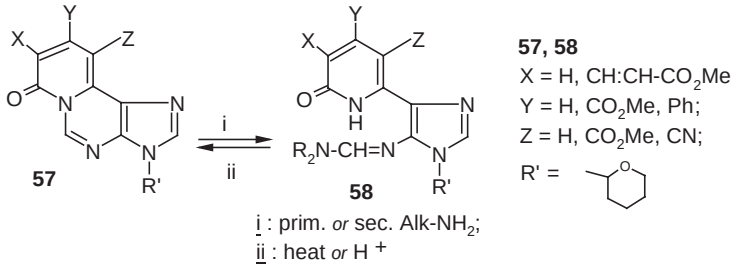
Scheme 11

The 4-thiones **47** disclosed a slight virucidal activity and moderate activity against sarcoma (92KFZ(9-10)63). Compounds **35** are highly selective and effective adenosine A_3 receptor antagonists (02JMC3337).

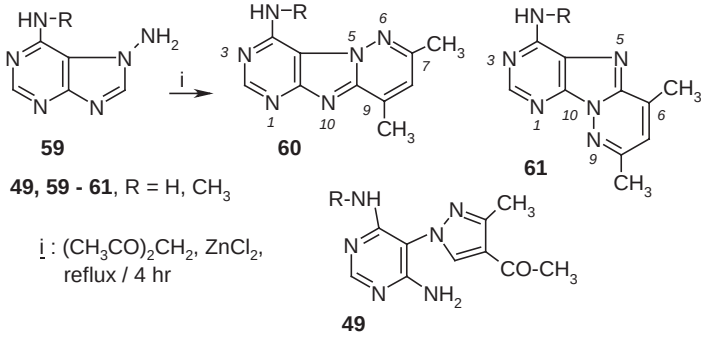
5. *Pyrido[2,1-i]purines*

To date, the only synthetic method using 9-(tetrahydro-2-pyranyl)-6-chloropurine (**52**) and methylene triphenylphosphorane (from triphenyl-phosphonium bromide and *n*-butyllitium) gave the ylide **53** which when treated with *cis*-dimethyl epoxysuccinate furnished **54**. The latter eliminated triphenylphosphine oxide on heating and originated **55** which cyclized with sodium hydride to methyl 3,7-dihydro-7-oxo-3-(tetrahydropyran-2-yl)-pyrido[2,1-*i*]purine-9-carboxylate (**56**) (80RTC20) (Scheme 11).

Compounds **57** substituted in positions 8 and 10 (CO_2Me, Ph, CN) are highly fluorescent molecules with absorption and emission in the visible region. They reacted



Scheme 12



Scheme 13

under mild conditions with primary and secondary amines cleaving the pyridine moiety to give **58** which are not fluorescent (87JCS(P2)733) (Scheme 12).

B. Pyridazino-Purines

1. *Pyridazino[6,1-f]purines*

The synthesis of this skeleton started from a 7-aminoadenine **59** and 2,4-dimethylpentanedione in the presence of anhydrous zinc chloride to yield a 4-amino-7, 9-dimethylpyridazino[6,1-*f*]purine **60** (46%). The by-product was 5-[(4-acetyl-3-methyl)pyrazol-1-yl]-4,6-diaminopyrimidine **49** (98BMC2197) (Scheme 13).

2. *Pyridazino[1,6-e]purines*

Pyridazino[1,6-*e*]purine derivative **61** can be prepared similarly from 9-aminoadenine. The by-product of the reaction with the diketone was the Schiff's base of 9-aminoadenine. The structure of both the e- and f-isomers was corroborated by ^{1}H-NMR (98BMC2197) (Scheme 13).

C. Pyrimido-Purines

The title purines belong among the most studied compounds with annulated 6-membered heterocycles. The most common are the *f*-annulated derivatives.

1. *Pyrimido[2,1-f]purines*

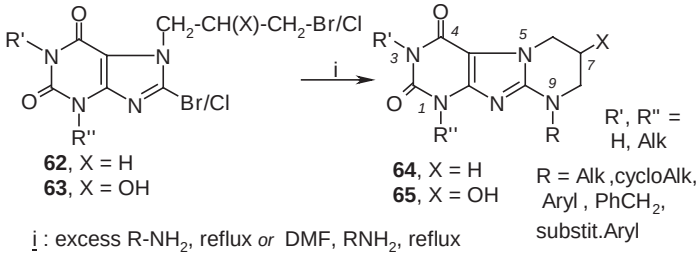
This tricyclic skeleton is accessible by five methods: the first was based upon a reaction of 8-halogeno-7-(3-halogenopropyl)- **62** or 8-halogeno-7-(3-halogeno-2-hydroxypropyl)xanthine derivative **63** with primary alkyl- and arylamines at elevated temperatures to afford 9-alkyl- or 9-aryl-6,7,8,9-tetrahydropyrimido[2,1-*f*]purine-2,4-diones **64** or their 7-hydroxy derivatives **65** (62MI1, 80FZK(4)65, 80KPS626, 81KGS1102, 94UKZ300) (Scheme 14).

Compound **64** (**R** = **H**) can be prepared from **62** by heating with saturated ethanolic ammonia under pressure (68MI1). The key materials **62** were obtained from 8-chloro- or 8-bromoxanthines by alkylation of their alkali salts with 1-chloro-3-bromopropane or, alternatively, with 3-chloro- or 3-bromopropanol and subsequent transformation of the terminal hydroxyl in the side-chain by thionyl chloride. Alkylation of 1,9-disubstituted 6,7,8,9-tetrahydropyrimido[2,1-*f*]purine-2,4(1*H*,3*H*)-dione **64** (**R′** = **H**) with glycidol or alkyl halogenoacetates afforded N(3)-substituted derivatives (94UKZ300). Also alkylation of the 7-hydroxy derivative **65** (**R′** = **H**) with alkyl halides, chloroacetone, or acrylonitrile gave the *N*(3)-substituted derivatives (86MI1).

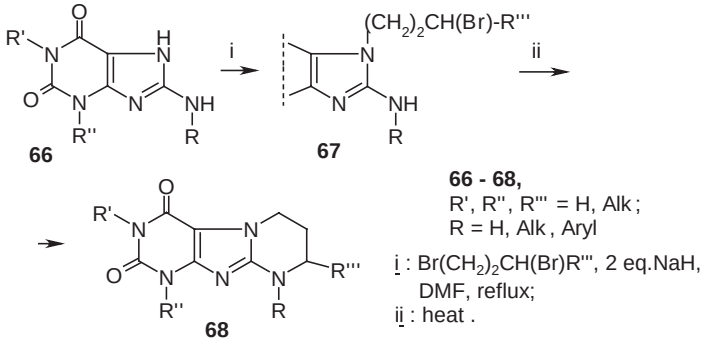
Intermediates **63** were synthesized by reaction of 8-halogenoxanthines with epichloro- or epibromohydrin. A variation used 8-aminoxanthines **66** with a 1,3-dibromoalkane in dimethylformamide in the presence of sodium hydride to produce **68** via intermediate **67** (98JHC135) (Scheme 15).

When epichlorohydrin was employed in place of a 1,3-dibromoalkane in the reaction with **66**, intermediate **69** was formed and then the third ring was closed by heating in epichlorohydrin or ethanolic sodium hydroxide to yield **65** (**R** = **H**) (80GEP(O)1, 80FRP1, 81KGS1102) (Scheme 16).

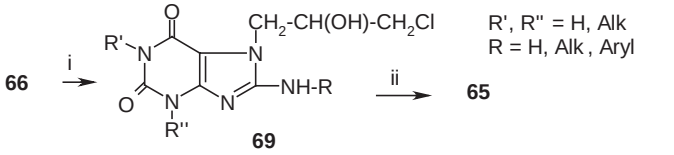
Another variation employs the alkylation of the potassium salt of 8-bromo-xanthine **70** with *N*-(3-bromopropyl)phthalimide to give **71** followed by treatment with hydrazine hydrate. The resultant 7-(3-aminopropyl)-8-bromo-xanthine **72** cyclized



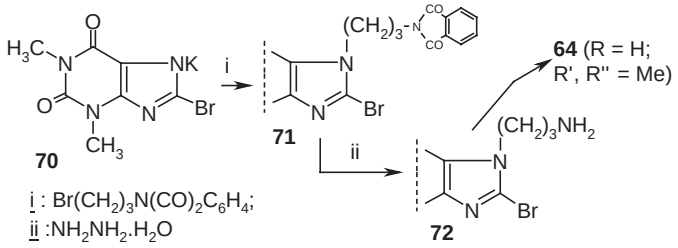
Scheme 14



Scheme 15



Scheme 16

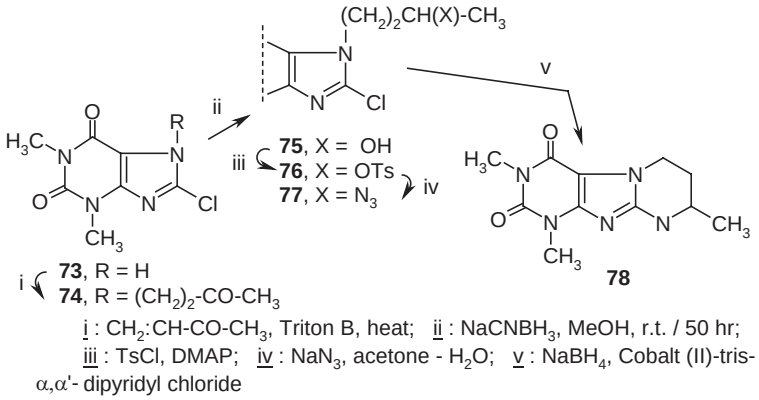


Scheme 17

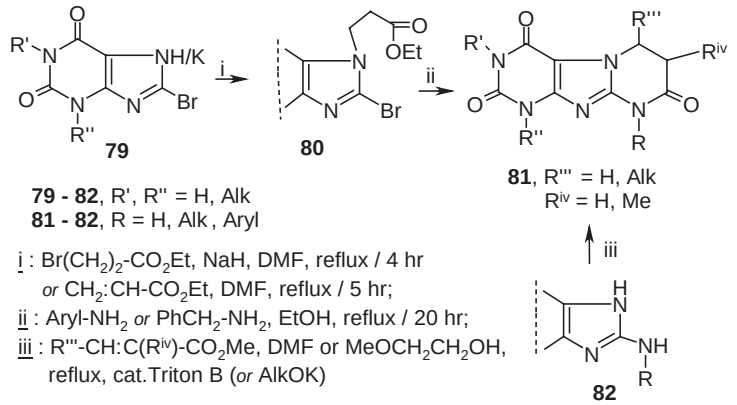
under the hydrazinolysis conditions to tricyclic **64** (**R** = **H**; **R′**, **R″** = **Me**) (73MI1) (Scheme 17).

An analogous method was based on alkali-catalyzed addition of methyl vinyl ketone to 8-chloroxanthine (**73**) affording the 7-(3-oxobutyl) derivative **74**. Its successive reduction to 7-(3-hydroxybutyl) derivative **75** followed by tosylation and nucleophilic substitution gave **76** and the 7-(3-azidobutyl) derivative **77**. Reduction of **77** through 7-(3-aminopropyl) derivative gave tricyclic **78** (86AP566) (Scheme 18).

The second synthetic method led to 6,7-dihydro-1,3-dialkylpyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-triones **81** either by alkylation of 8-bromo-xanthines **79** with halogenopropionates or by nucleophilic addition of **79** with α,β-unsaturated esters to **80** followed by treating with primary alkyl- or arylamines. Triones **81** can be prepared also by treating 8-alkylamino- or 8-arylaminoxanthines **82** with α,β-unsaturated



Scheme 18

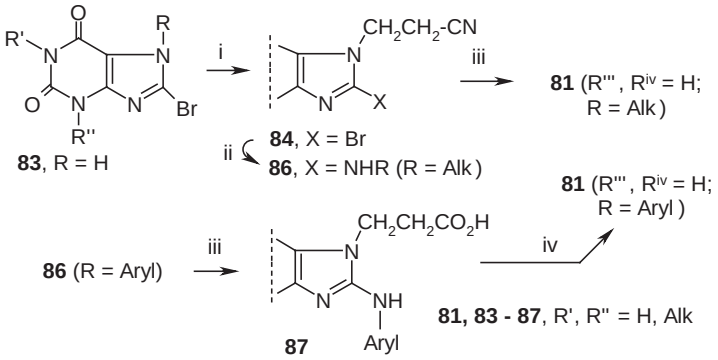


Scheme 19

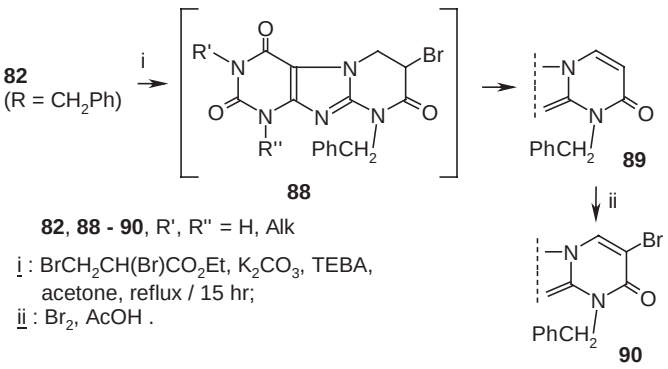
esters under catalysis of either Triton B or potassium alkoxide (87PHA371, 89LA1251, 89MI1) (Scheme 19).

A variation of this method started from 8-bromoxanthine **83**. Its cyanoethylation with acrylonitrile afforded 8-bromo-7-(*β*-cyanoethyl)xanthine **84** followed by aminolysis with alkylamines or arylamines to **86**. Action of hydrochloric acid on the 8-alkylamino derivative of **86** resulted in cyclization to the tricyclic **81**. Analogous treatment of hydrochloric acid on the 8-arylamino derivative of **86** caused only hydrolysis of the nitrile group and furnished the 7-(2-carboxyethyl) derivative **87**. The third ring of **81** had to be closed with diphenylphosphoryl azide (88UKZ1084, 98JHC135) (Scheme 20).

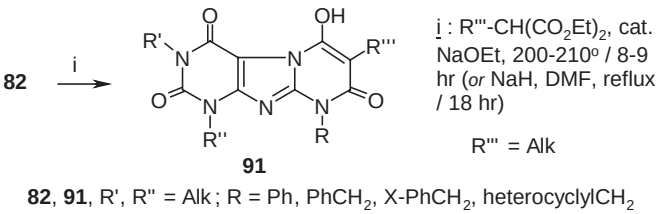
8-Benzylaminoxanthine **82** gave on reaction with ethyl 2,3-dibromo-propanoate in the presence of triethylbenzylammonium chloride (TEBA) and potassium carbonate the 1,3-dialkyl-9-benzylpyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-trione **89** through the 7-bromo-6,7-dihydro intermediate **88** following elimination of hydrogen bromide



Scheme 20



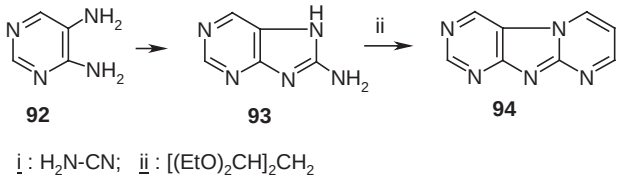
Scheme 21



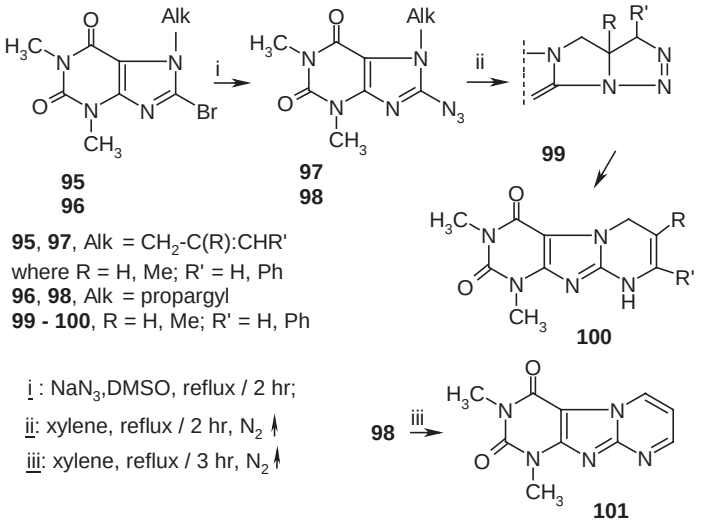
Scheme 22

(97PHA279). The bromination of the pyrimido[2,1-*f*]purine **89** took place at position 7 to give **90** (Scheme 21).

The third synthesis consisted of the reaction of 8-substituted amino-1,3-dialkylxanthine with an excess of diethyl malonate under catalysis by sodium ethoxide, or alternatively in dimethylformamide with sodium hydride as catalyst. Both routes afforded 1,3,7,9-substituted 6-hydroxypyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-triones **91** (86JMC1099, 84EUP(A)1) (Schemes 22).



Scheme 23



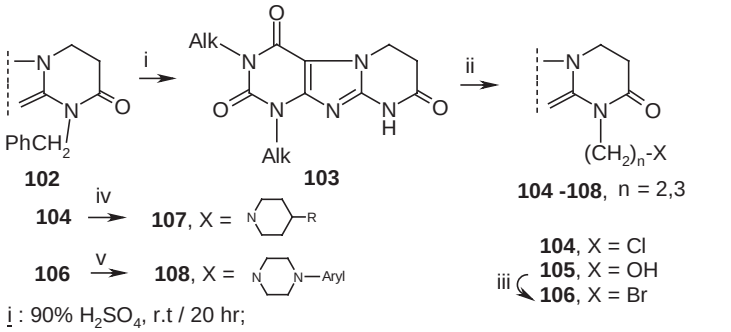
Scheme 24

The fourth method employed the reaction of 8-aminoxanthine (**93**) with malondialdehyde tetraacetal to close the pyrimidine ring to furnish pyrimido[2,1-*f*]purine (**94**) (94JHC81) (Scheme 23).

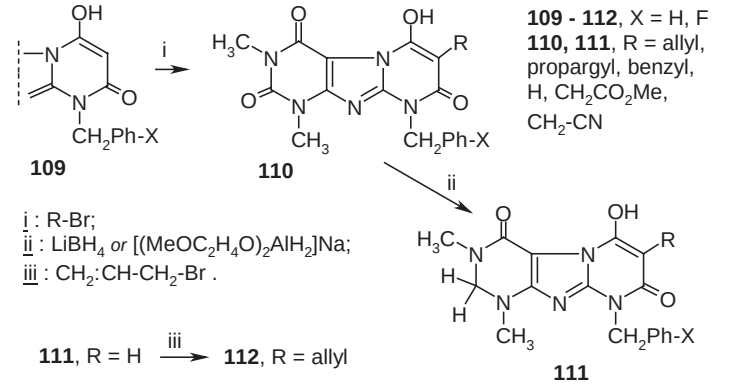
The fifth method is characterized by an *N*(7)-alkenylation or *N*(7)-alkynylation of potassium 8-bromoxanthine to **95** and **96**; replacement of bromine by an 8-azido group formed **97** and **98** that lost nitrogen to form 1,3-dimethylpyrimido[2,1-*f*]purine-2,4(1*H*,3*H*)-diones **100** or their 6,9-dehydro derivatives **101** (89S681) (Scheme 24).

The acid-catalyzed debenzylation occurred with **102** to give the 1,3-dialkyl-6,7-dihydropyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-trione **103** (87PHA371, 97PHA279) (Scheme 25). Alkylation of **103** with α-bromo-ω-chloroalkane and ω-chloroalkanol gave 9-(ω-chloroalkyl) **104** and 9-(ω-hydroxyalkyl) derivatives **105**, respectively. Subsequent reaction with phosphorous bromide produced the 9-(ω-bromoalkyl) **106**. Compounds **104** and **106** reacted with substituted piperidines (**R = Alk**, **OH**, **CO_2Et**, **CH_2Ph**) or arylpiperazines to yield 9-(ω-substituted amino alkyl) derivatives **107** or **108** (92MI1, 91MI1) (Scheme 25).

Sodium salt of 9-benzyl-1,3-dimethyl-6-hydroxypyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-trione **109** (**X = H**) underwent regioselective alkylation with reactive



Scheme 25



Scheme 26

alkyl bromides to furnish the 7-alkylated products **110** (**X = H**). Formation of the 6-*O*-alkylated products was not observed (86H2179) (Scheme 26). Regiospecific reduction of the carbonyl group in position 2 of **110** (**R = H**, **Alk**) to the CH_2 group, i.e., to 2,3-dihydro-6-hydroxypyrimidine[2,1-*f*]purine-4,8(1*H*, 9*H*)-diones **111**, was effected by an excess of lithium borohydride, or with sodium bis(-2-methoxyethoxy)-aluminum hydride. The silylation of the 6-hydroxyl in **109** with hexamethyldisilazane catalyzed by ammonium sulfate resulted in an enhanced solubility of the modified **110** in dioxane and made possible the complete reduction of C(2)═O to C(2)H_2 to give **111** within 1–3 days (88JOC3265) (Scheme 26). The reduction regiospecificity of **110** (**R = allyl**) to **111** (**R = allyl**) having 9-(2-thienyl-methyl)-4-propyl and 9-benzyl-7-[(E)-2-butenyl] groups was corroborated by ^{1}H-NMR and X-ray analyses (91AX(C)1902, 94AX(C)952, 96AX(C)2076), respectively. A regioselective alkylation with allyl-type alkyl bromides onto position 7 to the corresponding 7-allyl derivatives **112** occurred also with 2,3-dihydro-6-hydroxypyrimido[2,1-*f*]purin-4,8(3*H*,9*H*)-diones **111** (**R = H**) (86MIP1) (Scheme 26).

Pyrimido[2,1-*f*]purinediones are antagonists of A_1, A_2 adenosine receptors (01MI1). Of pharmacological interest were pyrimido[2,1-*f*]purinetriones **107** and **108**: 9-{3-[4-(phenyl)piperazin-1-yl]propyl}- and 9-{3-[4-(pyrimidin-2-yl)piperazin-1-yl]propyl derivatives they showed a strong sedative effect (91MI1), $5HT_{1A}$ agonistic activity (99EJM167, 95EJM587) and caused hypothermia and lower locomotor activity in mouse (95PHA453, 92MI1). The 7-alkyl-6-hydroxypyrimido[2,1-*f*]-purine-2,4,8(1*H*,3*H*,9*H*)-triones **112** exhibited antiinflammatory and antiarthritic (86JMC1099), antiallergic and antiinflammatory activities (86MIP1).

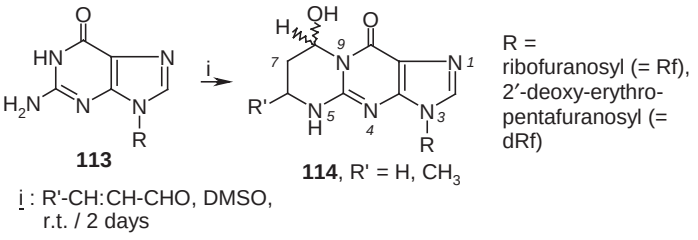
2. *Pyrimido[1,2-a]purines*

This group of compounds was reported as 1,N^2-propanoguanines in the former literature. Four methods to achieve them are available: the first was based on a reaction of guanine or its derivatives with α,β-unsaturated aldehydes or ketones. Guanosine **113** reacted with acrolein or crotonaldehyde to give 8-hydroxy-5,6,7,8-tetrahydro-3-(β-D-ribofuranosyl)-6-*R*′-pyrimido[1,2-*a*]purin-10(3*H*)-one **114** in low yield. Its structure was determined by ^{1}H-NMR. The reaction with 2′-deoxyguanosine proceeded similarly with methyl vinyl ketone or 2-cyclohexen-1-one in 5–14% yields (83TL4491, 88JOC14, 88JOC30, 90MI2) (Scheme 27).

To afford greater amounts of 3-(2-deoxy-β-D-*erythro*-pentafuranosyl)-5,6,7,8-tetrahydropyrimido[1,2-*a*]purin-10(3*H*)-one **119** for toxicologic studies, 2′-deoxyguanosine **113** was alkylated with 1-bromo-3-butene to give 1-(3-butenyl)-2′-deoxyguanosine **115** followed by oxidation with osmium tetroxide and *N*-methylmorpholine *N*-oxide to the 1-(3,4-dihydroxybutyl) derivative **116**. Cleavage with sodium periodate produced the 1-(3-oxopropyl) derivative **117**. The latter cyclized spontaneously to the isomeric **118**, and the final **119** was obtained by elimination of the 6-hydroxyl with sodium cyanoborohydride (02MI1) (Scheme 28).

The second method based on a reaction of guanine with alkyl- or aryl-malondialdehydes produced 7-substituted pyrimido[1,2-*a*]purine-10(1*H*)-ones **120** (76JOC294). These compounds showed fluorescent properties similar to those of ''wye bases''of the imidazo[1,2-*a*]purines group. This method also served for the preparation of volatile 7-(pentafluorophenyl) derivate **120** (**R** = $\mathbf{C_6F_5}$), the structure of which was established by GC-MS analysis (86JOC3244) (Scheme 29).

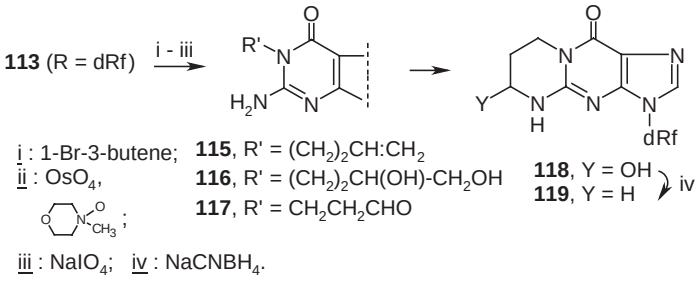
The third synthesis included fusion of 2-methylthio-1,4,5,6-tetrahydropyrimidine **121** with 4-amino-1*H*-imidazole-5-carbonitrile **122** to afford 4,6,7,8-tetrahydropyrimido[1,2-*a*]purin-10(1*H*)-imine (**123**) (01JHC743) (Scheme 30).



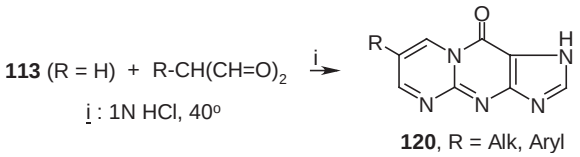
113 **114**, R' = H, CH_3

i : R'-CH:CH-CHO, DMSO, r.t. / 2 days

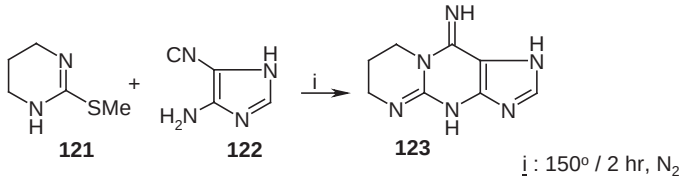
Scheme 27



Scheme 28



Scheme 29



Scheme 30

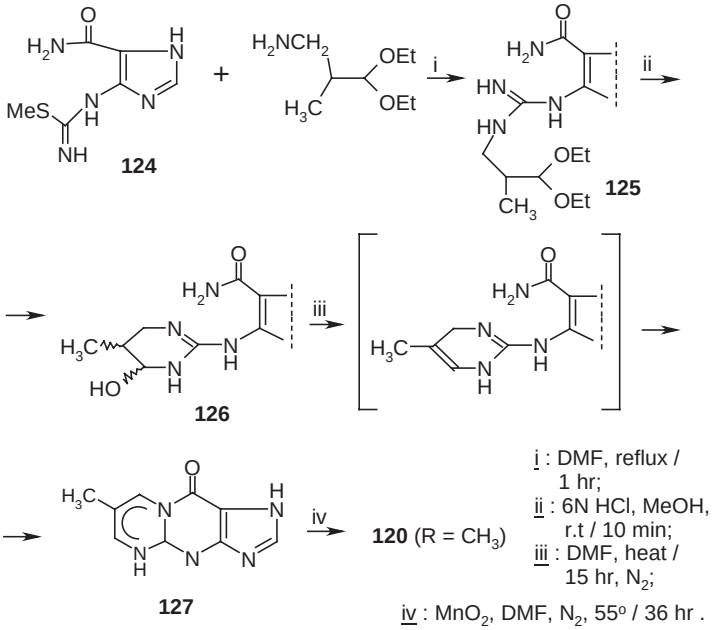
The fourth method afforded products similar to those of the second method, but is more complicated. Thus, 3-amino-2-methylpropionaldehyde diacetal was condensed with isothiourea **124** and the resulting guanidine **125** underwent an intramolecular cyclization to the tetrahydropyrimidine derivative **126** that easily closed the central pyrimidine ring on heating to give the tricyclic **127**. The product **120** (**R = CH_3**) was obtained by oxidation with manganese dioxide (81JOC815) (Scheme 31).

The ^{1}H- ^{13}C- and ^{15}N-NMR spectra of *N*(1)- or *N*(3)-substituted pyrimido[1,2-*a*]purinones were studied in (86T6541, 87T365).

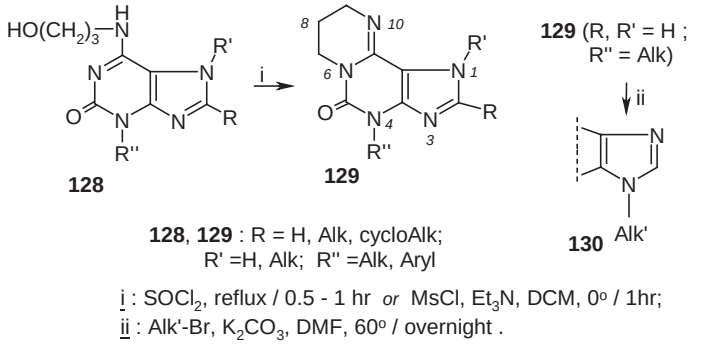
The mutagenicity of guanosine or deoxyguanosine adducts with acrolein and its analogs on bacteria and laboratory animals was reported in e.g. (99JMC947, 99MI1). However, little is known about the precise mutagenic behavior of these adducts at the level of DNA replication.

3. *Pyrimido[2,1-i]purines*

The title products are accessible by two methods. The first started from 6-[(3-hydroxypropyl)amino]purine **128** and thionyl chloride to furnish the 6-[(3-chloropropyl)amino]



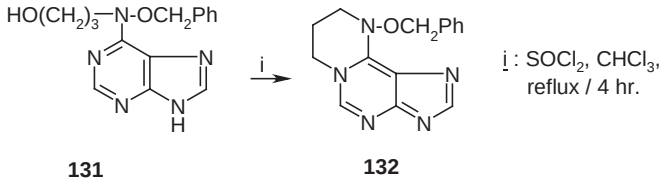
Scheme 31



Scheme 32

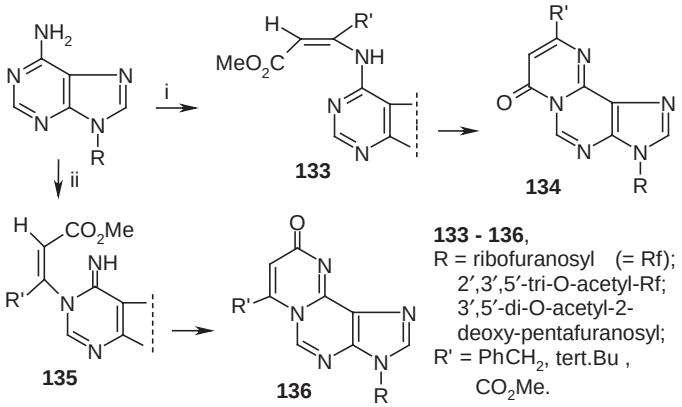
derivative as an intermediate, which in turn closed the pyrimidine ring to the 4-alkyl- or 1,4-dialkyl-1,4,5,6-tetrahydropyrimido[2,1-*i*]purin-5(1*H*)-one **129**. Mesyl chloride and triethylamine employed in place of thionyl chloride gave through the intermediate 6-[(3-mesyloxypropyl)amino] derivative the same **129**. Alkyl derivative **130** could be prepared by alkylation of **129** ($\mathbf{R'} = \mathbf{H}$) in an aprotic medium (93JHC241, 97JMC3248, 01CPB188) (Scheme 32).

Cyclization of 6-[(3-hydroxypropyl)-*O*-benzylhydroxyamino]purine **131** with thionyl chloride to 10-benzyloxy-7,8,9,10-tetrahydropyrimido[2,1-*i*]purine (**132**) (01TL5941) is a variation of this method. The intermediate **131** was obtained from 6-chloropurine and 3-(*O*-benzylhydroxyamino)-propanol (98H1673) (Scheme 33).



131 **132**

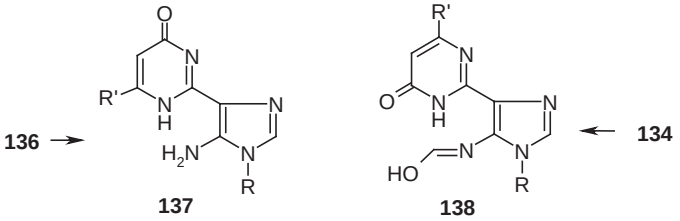
Scheme 33



Scheme 34

The second method was based on a reaction of adenosine or its derivatives (having the saccharide hydroxyl groups protected) with alkynates to afford two isomeric products **134** and **136** differing due to the primary attack of the alkynate triple bond at either their *N*(1) or the exocyclic amino group. The third ring was closed by a reaction between the ester and the exocyclic amino group to give either 7-R′-3-R-3, 9-dihydropyrimido[2,1-*i*]purin-9-one **136** or the *N*(1) to give 9-R′-3-R-3,7-dihydropyrimido[2,1-*i*]purin-7-one **134**. Reaction conditions were decisive for forming the particular isomer. Thus, isomer **134** separated in a kinetically controlled reaction from nonpolar media (e.g. dichloromethane), while in a polar medium (e.g. ethanol–water) the cyclizate remained in solution and due to a Dimroth rearrangement a thermodynamically more stable isomer **136** separated after 18 h. Cyclization to **136** (**R′ = benzyl**, **tert.butyl**) was not hindered even by a bulky substituent (84TL3471, 92JOC1579, 95H1197) (Scheme 34).

Pyrimido[2,1-*i*]purines possess fluorescence properties. Opening the central pyrimidine ring took place under mild conditions in the presence of ammonia or alkylamines to give 2-(1-R-5-aminoimidazol-4-yl)-6-R′-1,4-dihydropyrimidin-4-one (**137**). The second ring was also opened with triethylammonium hydrogen carbonate (TEAB) at room temperature, the formyl group at the 5-aminoimidazole moiety was



i : NH_3, DMF - H_2O, mild heat; ii : TEAB, EtOH - H_2O, r.t. / 4 hr, pH 8 .

Scheme 35

preserved in 2-(1-R-5-formamidoimidazol-4-yl)-6-R′-1,4-dihydropyrimidin-4-one (**138**). Opening the tricyclic structure of **136** and **134** resulted in the loss of the fluorescent properties (92JOC1579, 96RTC99) (Scheme 35).

4. *Pyrimido[1,2,3-cd]purines*

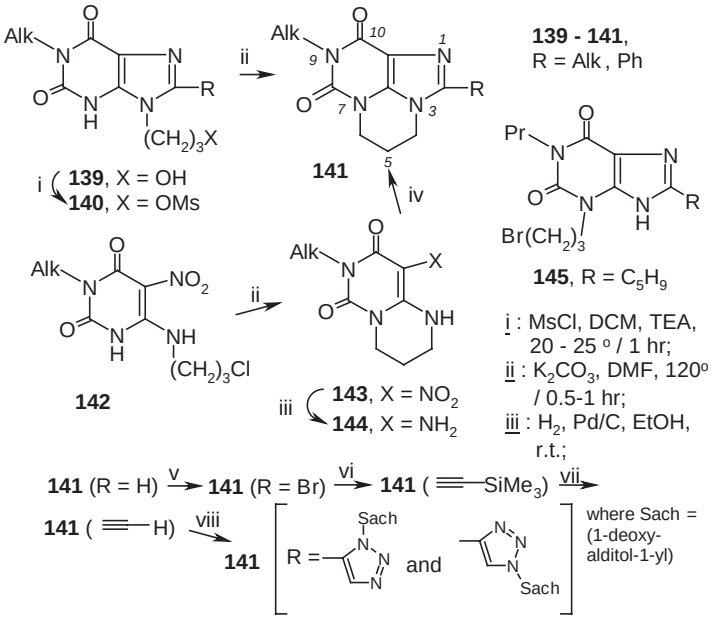
There are two different routes. In the first the starting material for this peri-annulated pyrimido-purine were either the purine or imidazo[*a*]pyrimidine derivatives to which the third pyrimidine ring was fused.

In the second pyrimido[1,2-*c*]pyrimidine derivatives subsequently add an imidazole ring. The first method utilized a 9-(3-hydroxypropyl)-8-alkyl- or an -8-arylxanthine derivative **139**; their mesylation led to an intermediate **140** and following intramolecular alkylation gave the **141**. An alternative route started with a 6-(3-chloropropyl)amino-5-nitrouracil derivative **142** which gave, on an intramolecular alkylation, **143** and the subsequent reduction of nitro group the 9-amino-pyrimido[1,2-*c*]pyrimidine derivative **144**. Its acid-catalyzed reaction with orthocarboxylates afforded the 2-alkyl- or 2-aryl-5,6-dihydro-4*H*,8*H*-pyrimido[1,2,3-*cd*]purin-8,10(9*H*)-dione **141** (95S837).

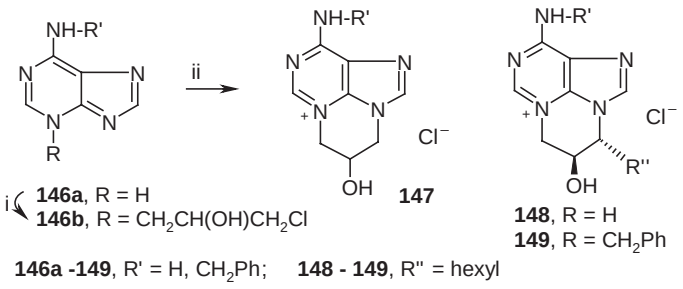
Bromination of **141** (**R = H**) gave 2-bromo **141** (**R = Br**) and this was converted by Sonogashira reaction into trimethylsilyl-ethyne **141** (**R = C≡C-Si[CH$_3$]$_3$**). The protective trimethylsilyl group was removed by hydrolysis to give 2-ethynyl-5,6-dihydro-4*H*, 8*H*-pyrimido[1,2,3-*cd*]purin-8,10(9*H*)-dione **141** (**R = C≡CH**). Cycloaddition of 1-azido-1-deoxy-alditols to the terminal triple bond of the latter produced two regioisomers **141** by ([1,2,3]triazol-4- or -5-yl) group as **R** (00JHC1033) (Scheme 36).

Preparation of 1-propyl-8-cyclopentyl-3-(3-bromopropyl)xanthine **145** from the 3-(3-hydroxypropyl) derivative and phosphorus tribromide was accompanied with an intramolecular alkylation in 10% yield to produce the tricyclic **141** (**Alk = propyl**, **R = cyclopentyl**). This reaction was not optimized and preparatively employed for the synthesis of compounds of type **141** (00JMC4973).

Formation of 10-amino-5,6-dihydro-5-hydroxy-4*H*-pyrimido[1,2,3-*cd*]-purinium chloride **147** presented a further example of the intramolecular alkylation of 3-(3-chloro-2-hydroxypropyl)adenine **146b** (75JHC1045). Similarly 9-[(3-tosyloxy- or 3-mesyloxy-2-hydroxy-1-alkyl)-propyl]adenine and its 6-benzylamino derivative



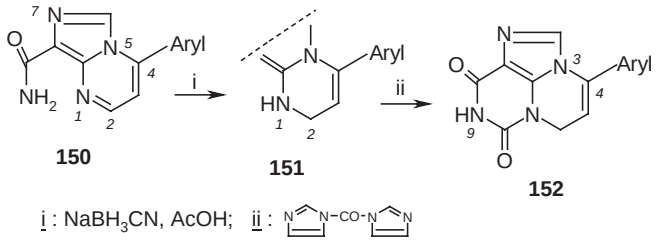
Scheme 36



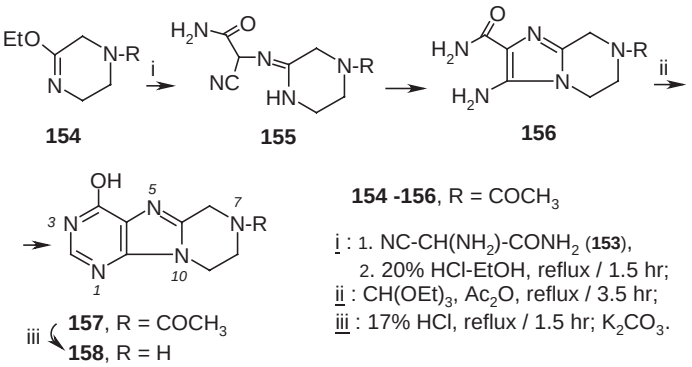
Scheme 37

furnished the 4-alkyl-10-amino-5,6-dihydro-5-hydroxy analogs **148** or **149** (92JMC4180) (Scheme 37).

The second method started from 4-arylimidazo[1,5-*a*]pyrimidine-8-carboxamide **150**; its selective reduction with sodium cyanoborohydride gave the 1,2-dihydro derivative **151** and subsequent cyclization with 1,1′-carbonyldiimidazole formed the 4-aryl-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*) **152** (90USP1) (Scheme 38).



Scheme 38



Scheme 39

In this subgroup of pyrimido-purines the 4-[(3-trifluoromethyl)phenyl]-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)dione **152** and its 4-heterocyclyl-9-alkyl- or 9-benzyl analogs were pharmacologically interesting as cognition enhancers, anxiolytics and antihypertensives (90USP1).

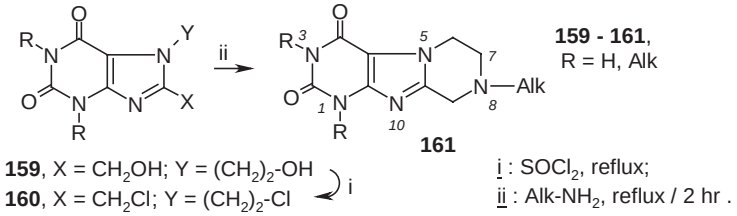
D. Pyrazino-Purines

1. *Pyrazino[1,2-e]purines*

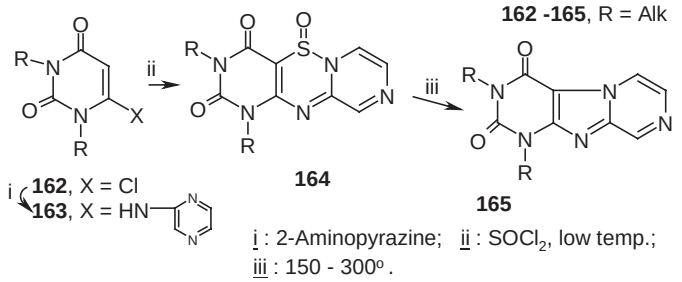
Reaction of amino-cyanacetamide (**153**) and 2-ethoxy-4-acetyl-5,6-dihydro-3*H*-pyrazine **154** afforded 3-amino-7-acetylimidazo[1,2-*a*]piperazine **156** through the intermediate **155**. The third ring was built by heating with triethyl orthoformate and acetic anhydride to give 4-hydroxy-7-acetylpiperazino[1,2-*e*]purine **157**. The acetyl group in position 7 was eliminated by heating with hydrochloric acid to compound **158** (67KFZ(4)16) (Scheme 39).

2. *Pyrazino[2,1-f]purines*

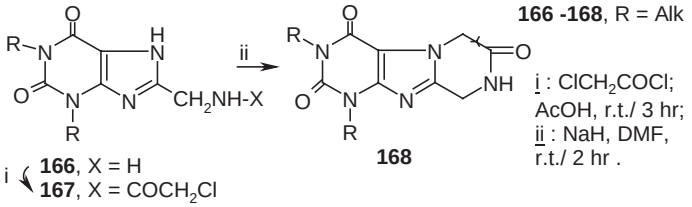
The first method used a reaction of 8-hydroxymethyl-7-(2-hydroxyethyl)-xanthine derivative **159** with thionyl chloride to produce dichloro derivative **160** which, on



Scheme 40



Scheme 41



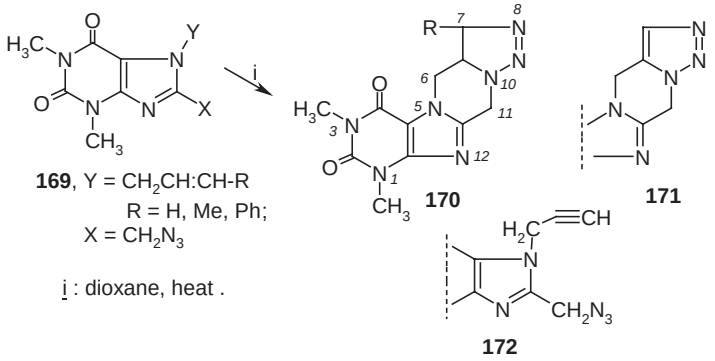
Scheme 42

reaction with primary alkylamines, gave 8-alkyl-1,3-dialkyl-6,7,8,9-tetrahydropyrazino[2,1-*f*]purine-2,4(1*H*,3*H*)-dione **161** (60MIP1, 60GEP1) (Scheme 40).

The second method was based on a thermal decomposition of pyrazino-pyrimidothiadiazine **164** to the pyrazino[2,1-*f*]purine-2,4-dione **165**. The intermediate **164** was synthesized from 6-chloro-1,3-dialkyluracil **162** and 2-aminopyrazine to furnish 1,3-dialkyl-6-(2-pyrazinylamino)uracil **163**. The intermediate **164** was obtained subsequently with thionyl chloride (69GEP(O)1) (Scheme 41).

Pyrazino[2,1-*f*]purine-2,4,7-triones were prepared by the third method: the 8-aminomethylxanthine derivative **166** was treated with chloroacetyl chloride to produce **167** followed by cyclization with sodium hydride in an aprotic medium converting it into 1,3-dialkyl-8,9-dihydropyrazino[2,1-*f*]purine-2,4,7-(1*H*,3*H*,6*H*)-trione **168** (94JHC81) (Scheme 42).

A special method employed the intramolecular 1,3-dipolar cycloaddition of 7-(2-alkenyl)-8-azidomethyl-1,3-dimethylpurine-2,4(1*H*,3*H*)-diones **169** on heating in



Scheme 43

dioxane to produce the tetracyclic 7-substituted 1,3-dimethyl-6,6a,7,11-tetrahydro[1,2,3]triazolo[1′,5′:1,2]pyrazino[5,4-*f*]purine-2,4-(1*H*,3*H*)-diones **170**. When the cyclization proceed with a propargyl derivative **172**, the 6,11-dihydro[1,2,3]triazolo[1′,5′:1,2]pyrazino[5,4-*f*]purin-2,4(1*H*,3*H*)-dione **171** was formed. The necessary 8-azidomethyl compounds **169** and **172** were prepared from the corresponding 8-hydroxymethylpurines through the 8-chloromethyl or 8-bromomethyl derivatives (88CCC319) (Scheme 43).

E. Oxazino-Purines

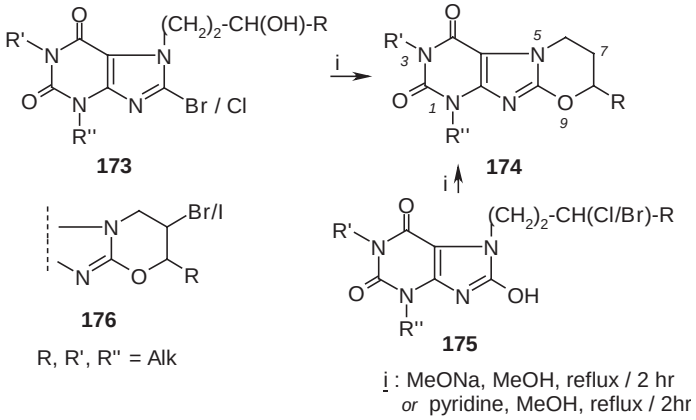
The most studied compounds in this series were purines annulated to an oxazine ring at bond f and less frequently at bond e.

1. *Oxazino[2,3- and 3,4-f]purines*

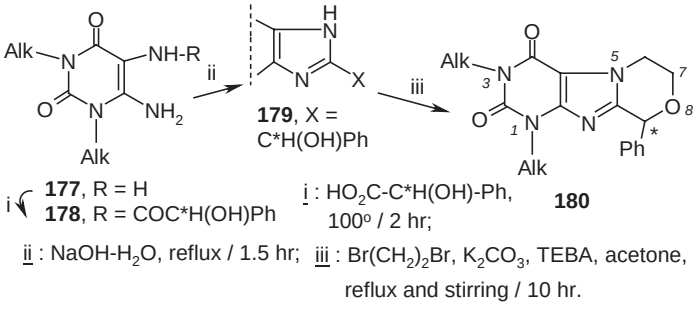
The first method made use of cyclization of 7-(3-hydroxyalkyl)-8-halo-xanthines **173** in alkali, sodium alkoxide or pyridine to the tricyclic 1,3-dialkyl- or 1,3,8-trialkyl-7,8-dihydro-6*H*-[1,3]oxazino[2,3-*f*]purine-2,4(1*H*,3*H*)-dione **174** (71MI1). This product is water-insoluble and therefore precipitated when using alkali. Alternative starting materials were the 7-(3-haloalkyl)-8-hydroxyxanthines **175** cyclized under the same conditions (71MI1) (Scheme 44).

Cyclization of 7-(2-bromo- or 2-iodo-3-hydroxypropyl)-8-bromoxanthines (prepared from 7-allyl-8-bromo derivatives by addition of hypobromous or hypoiodous acids) with alkali to give 7-bromo- or 7-iodo derivatives **176** offered another variation (71AP117) (Scheme 44).

The second method employed 8-(α-hydroxybenzyl)xanthines **179** and 1,2-dibromoethane reacting in the presence of potassium carbonate and benzyltriethylammonium chloride (TEBA) as a phase-transfer catalyst to give 6,7-dihydro-1,3-dimethyl-9*H*-[1,4]oxazino[3,4-*f*]purine-2,4(1*H*,3*H*)-dione (**180**). The intermediate **179** was obtained by acylation of diaminopyrimidine **177** with rac-mandelic acid and



Scheme 44

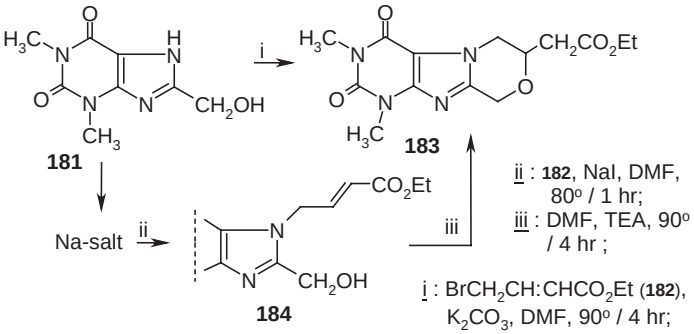


Scheme 45

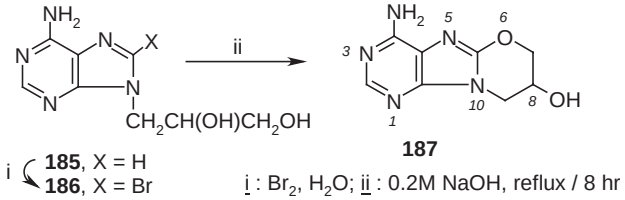
subsequent alkaline cyclization of the 5-acylamino derivate **178**. The composition of the racemic mixture of **180** was determined by ^{1}H-NMR in the presence of enantiomerically pure dirhodium tetrakis-[(*R*)-α-methoxy-α-(trifluoromethyl)-α-phenyl acetate] (00EOC3489) (Scheme 45).

The base-catalyzed intramolecular addition of the 8-hydroxymethyl group to the activated double bond in the 3-ethoxycarbonyl-2-propenyl group in position 7 of the xanthine ring presented the third method. This addition took place when the 8-hydroxymethyl derivative **181** was alkylated with ethyl (E)-4-bromo-2-butenoate (**182**) to give ethyl (1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-9*H*-[1,4]oxazino-[3,4-*f*]purin-7-yl)acetate **183** in the presence of potassium carbonate. Provided the alkylation conditions were milder and the alkylation was catalyzed by sodium iodide, the cyclization intermediate, ethyl (E)-4-[8-(hydroxymethyl)theophyllin-7-yl]-2-butenoate (**184**), was isolated. Cyclization to the tricyclic product occurred by heating **184** with triethylamine (91S625) (Scheme 46).

The oxazine ring of compounds **174** proved resistant against alkali, amines and hydrazines; mineral acids opened the ring to 7-(3-chloro- or 3-bromo-alkyl)-8-hydroxy-theophyllines **175** (71MI1).



Scheme 46



Scheme 47

Compound **180** showed an antiepileptic activity and affinity to adenosine receptors (00EOC3489).

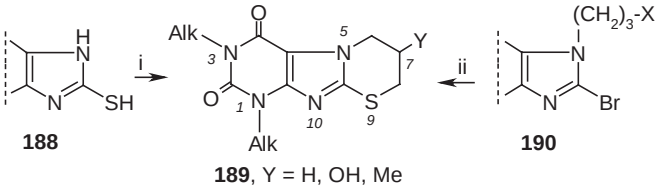
2. *Oxazino[3,2-e]purines*

The 9-(2,3-dihydroxypropyl)-8-bromoadenine (**186**) afforded 4-amino-8,9-dihydro-7*H*-[1,3]oxazino[3,2-*e*]purin-8-ol **187** on heating with alkali. The intermediate **186** was prepared from 9-(2,3-dihydroxypropyl)adenine **185** by bromination in water (83CCC1910). Compound **187** was also isolated on treatment with ammonia in a very low yield (86CCC459) (Scheme 47).

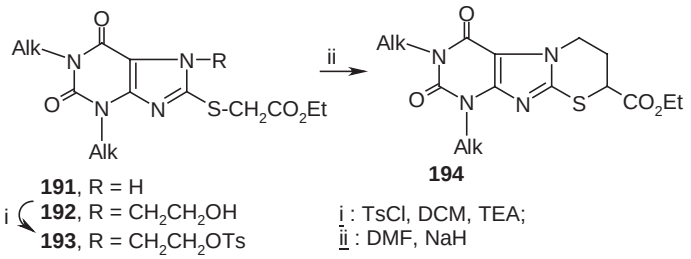
F. Thiazino-Purines

1. *Thiazino[2,3- and 3,4-f]purines*

The first access to this tricyclic skeleton was based on a double alkylation of 8-mercaptoxanthine **188** with a 2-substituted 1,3-dibromopropane to afford 1,3-dialkyl-7,8-dihydro-7-Y-6*H*-[1,3]thiazino[2,3-*f*]purine-2,4(1*H*,3*H*)-dione **189** (75MI1). A variation of this method employed the reaction of 8-bromo-7-(3-bromopropyl)xanthine **190** with sodium sulfide either in dimethylformamide or methoxyethanol (62MI2, 96KFZ(3)49) (Scheme 48).



Scheme 48



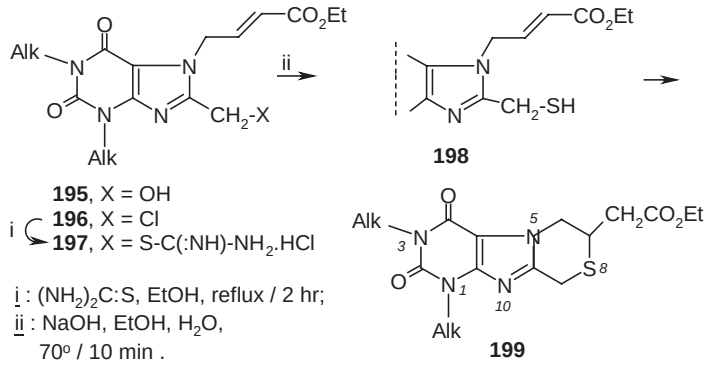
Scheme 49

The second method includes an intramolecular alkylation of the C-anion of the SHC^{-}-CO_2Et group to give the ethyl 1,3-dialkyl-1,2,3,4,7,8-hexahydro-2,4-dioxo-6*H*-[1,3]thiazino[2,3-*f*]purine-8-carboxylate **194**. The C-anion is generated by sodium hydride. The starting (7-R-theophyllin-8-yl)thioacetate **191** was prepared by alkylation of 8-mercaptotheophylline with ethyl chloroacetate in the presence of triethylamine followed by alkylation with chloroethanol to *N*-7-(2-hydroxyethyl) **192** and then its tosylation to **193** (88SC1299) (Scheme 49).

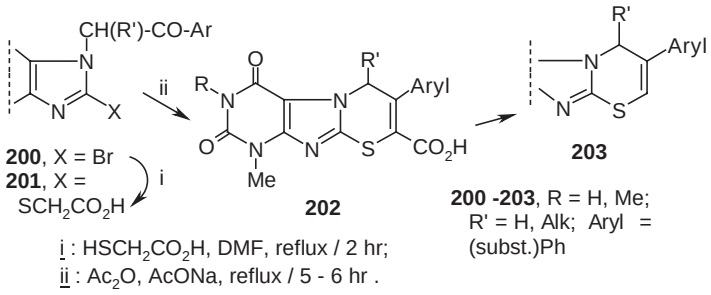
The third method was based on an intramolecular nucleophilic addition of a mercapto group to the activated double bond of the unsaturated alkyl group of ethyl 4-[8-(mercaptomethyl)theophyllin-7-yl]butenoate **198** to produce ethyl (1,3-dialkyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-9*H*-[1,4]thiazino[3,4-*f*]purin-7-yl)acetate **199** (91S625). The intermediate **198** could not be isolated, evidently due to a rapid nucleophilic addition of the SH group to the unsaturated 7-alkyl group (Scheme 50).

The fourth method used condensation of [7-(phenacyl)theophyllin-8-yl]thioacetic acid **201** to the 8-carboxylic acid **202** by the action of acetic anhydride and sodium acetate. The acid then underwent decarboxylation to 1-methyl-3-R-6-R′-7-aryl-6*H*-[1,3]thiazino[2,3-*f*]purine-2,4(1*H*,3*H*)-dione **203**. The intermediate **201** was prepared from 8-bromoxanthine and thioglycolic acid (90KGS967) (Scheme 51).

The fifth method employed an intramolecular condensation of the Claisen type. Condensed were the 7-cyanomethyl-8-cyanomethylthio-, 7-alkoxycarbonylmethyl-8-alkoxycarbonylmethylthio- and 7-cyanomethyl-8-alkoxycarbonylmethylthio-theophyllines. The C-anion at the carbon next to the sulfur atom, generated from **204** to **206** by sodium hydride, was the intermediate in all the reactions. The C-anion,



Scheme 50



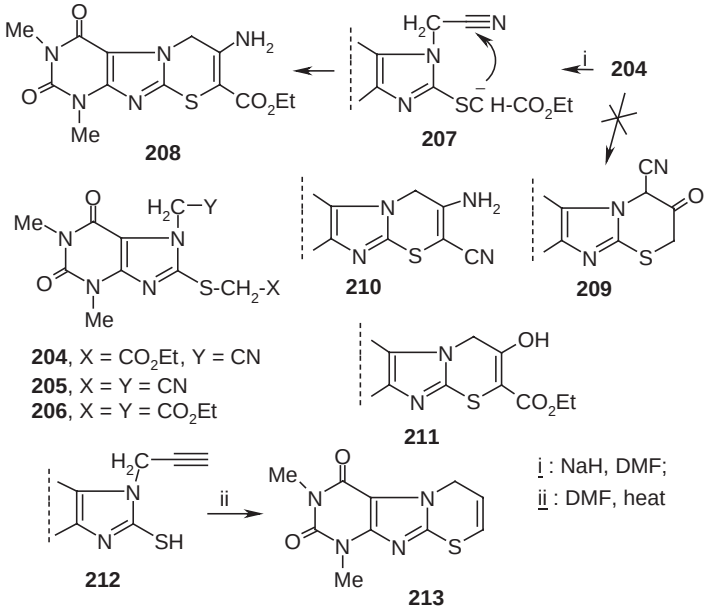
Scheme 51

stabilized by the effect of the 3*d* sulfur orbitals, reacted with the nitrile group or the esterified carboxyl group to furnish the ethyl 7-amino-1,2,3,4-tetrahydro-1, 3-dimethyl-2,4-dioxo-6*H*-[1,3]thiazino[2,3-*f*]purine-8-carboxylate **208**, 7-amino-8-carbonitrile **210** or ethyl 7-hydroxy-8-carboxylate **211**. Condensation directed toward the keto-nitrile **209** did not occur because the C-anion was not formed at the carbon neighboring the *N*-7 of the purine ring. The identification was deduced from the ^{1}H-NMR spectra of compounds **208**, **210** and **211** on comparison with that of 6*H*-[1,3]thiazino[2,3-*f*]purine-2,4(1*H*,3*H*)-dione **213**. Compounds **204**–**206** obtained from 8-mercaptotheophylline by alkylation of the mercapto group with Cl–CH_2–X and then of the *N*-7 at the purine skeleton with Cl–CH_2–X (91S625). Compound **212** was prepared from 8-bromo-7-propargyltheophylline on treatment with sodium hydrosulfide and then converted into **213** by heating (93M1143) (Scheme 52).

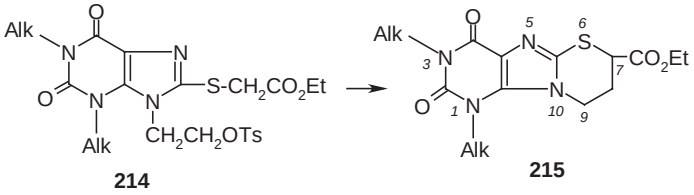
Mass spectral fragmentation of compounds **203** was reported in (90KGS967).

2. *Thiazino[3,2- and 4,3-e]purines*

The first approach to an [*e*]-annulated purine was based upon an intra-molecular alkylation of a C-anion neighboring the sulfur atom at position 8 of ethyl [9-(2-tosyloxyethyl)theophyllin-8-yl]thioglycolate **214** to give ethyl 1,2,3,4,7,8-hexahydro-1,



Scheme 52



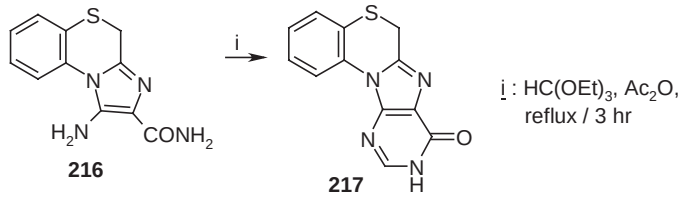
Scheme 53

3-dimethyl-2,4-dioxo-9*H*-[1,3]thiazino[3,2-*e*]purine-7-carboxylate **215** (88SC1299) (Scheme 53). This synthesis consisted of the same steps as given in the preparation of the [2,3-*f*]-analog (cf. Scheme 49).

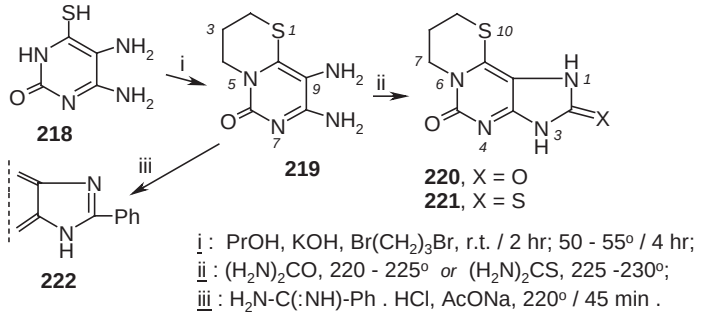
The second method was based on a reaction of triethyl orthoformate with 9-amino-6*H*-imidazo[2,1-*c*][1,4]benzothiazine-8-carboxamide **216** to give 6*H*-purino[8,9-*c*][1,4]benzothiazin-8(9*H*)-one **217**. The necessary **216** was obtained from 3-ethoxy-2*H*-[1,4]benzothiazine and aminocyanoacetamide (70KFZ(12)22) (Scheme 54).

3. *Thiazino[2,3-i]purines*

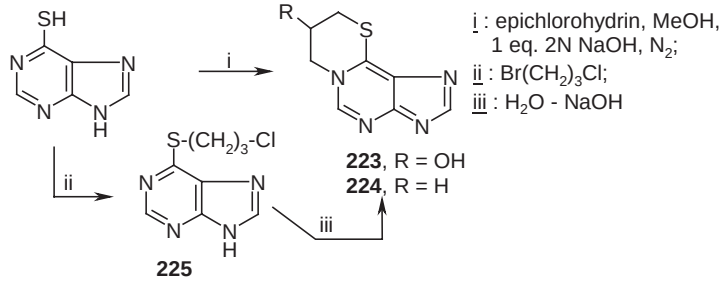
The first approach employed a reaction of 5,6-diamino-4-thiouracil (**218**) with 1,3-dibromopropane to give 8,9-diamino-3,4-dihydro-2*H*-pyrimido[6,1-*b*][1,3]-thiazin-6-one (**219**). The diamine **219** was melted with urea or thiourea to give 8,9-dihydro-7*H*-[1,3]thiazino[2,3-*i*]purine-2,5(1*H*,3*H*)-dione (**220**) or



Scheme 54



Scheme 55

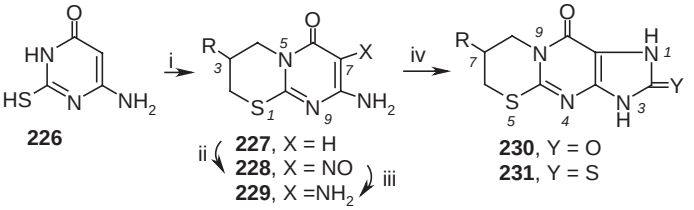


Scheme 56

2-thioxo-[1,3]thiazino[2,3-*i*]purin-5-one (**221**) (92FES1315). Benzamidine in place of urea afforded the corresponding 2-phenyl analog **222** (96JMC2529) (Scheme 55).

The second method started from 6-mercaptopurine and epichlorohydrin to afford 8-hydroxy-7,8-dihydro-9*H*-[1,3]thiazino[2,3-*i*]purine **223**.The by-product of this reaction was 8-hydroxymethyl-7,8-dihydrothiazolo[2,3-*i*]purine (92JOC6335). A two-step annulation of the thiazine ring was demonstrated by the reaction of the sodium salt of 6-mercaptopurine and 1-bromo-3-chloropropane to furnish 6-(3-chloro-propyl)thiopurine (**225**), followed by cyclization in alkali to give the tricyclic **224** (01KFZ172) (Scheme 56).

Compound **222** showed an inhibitory effect against xanthine oxidase (96JMC2529).



i : 2-PrOH, H_2O-NaOH, Cl- or $BrCH_2$-CH(R)-CH_2Br, r.t. / 1 hr; 60º/ 7 hr;
ii : $NaNO_2$, AcOH; iii : $Na_2S_2O_4$, NH_4OH; iv : $(NH_2)_2C$:Y, heat over m.p.

Scheme 57

4. *Thiazino[3,2-a]purines*

The title compounds were prepared by the same route as the [*i*]-annulated purines, the first method differing in that the 5,6-diamino-4-thiouracil was substituted by 6-amino-2-thiouracil (**226**). The latter reacted with a 1,3-dibromoalkane to give a pyrimido[2,1-*b*][1,3]thiazin-6-one **227**. Its nitrosation and reduction afforded a 7,8-diamino derivative **229** through the intermediate **228**. The third ring was closed by melting **229** with urea or thiourea to give 7,8-dihydro-6*H*-[1,3]thiazino[3,2-*a*]purine-2,10(1*H*,3*H*)-dione **230** or 2-thioxothiazino[3,2-*a*]purin-10(1*H*)-one **231** (Scheme 57).

Compounds **230** and **231** showed a modest activity against Gram-positive bacterial strains (91FES899).

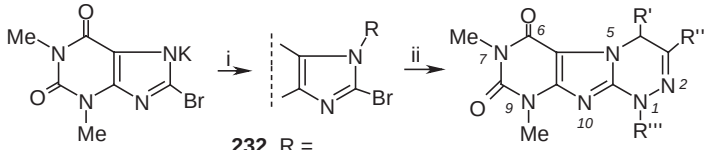
G. Triazino-Purines

The most investigated heterocycles of this group were the f- and a-annulated derivatives.

1. *Triazino[3,2- and 3,4-f]purines*

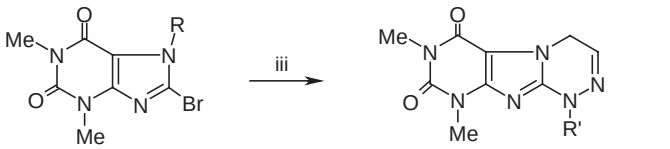
The first, and most elaborated method led to 1,4-dihydrotriazino[3,4-*f*]purines. It was based on the following synthetic steps: the sodium or potassium salt of 8-bromotheophylline was alkylated with phenacylchloride or -bromide to furnish the 8-bromo-7-phenacyl derivative **232** followed by reaction with an arylhydrazine to give the corresponding hydrazone **233** that without isolation gave the 1,4-dihydro-7,9-dimethyl-4-R′-3-R″-1-R‴-[1,2,4]triazino[3,4-*f*]purine-6,8(7*H*,9*H*)-dione **234** on heating. The key intermediate **232** could be substituted by 8-(methyl-sulfonyl)-7-phenacyl-xanthine derivatives (69MI1, 74UKZ215, 75MI3, 81MI1, 86KFZ427, 74KGS1696) (Scheme 58).

A variation of this method was the reaction of 8-bromo-7-acetaldehyde **236** with hydrazines to give 8-bromo-7-acetaldehydohydrazones **237** followed by cyclization to yield the [1,2,4]triazino[3,4-*f*]purinediones **238** without a substituent at position 3. The necessary acetaldehyde **236** was obtained by an oxidative cleavage of 8-bromo-7-(2,3-dihydroxypropyl) derivative **235** with periodic acid (85MI1) (Scheme 59).



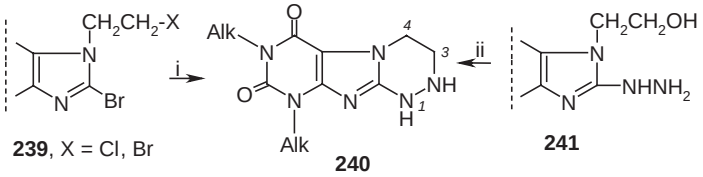
i : Cl- *or* BrCH(R')-CO-R''; ii : pyridine, R'''-$NHNH_2$, reflux / 4 hr *or* BuOH, cat.pyridine, R'''-$NHNH_2$, reflux / 6 - 7 hr .

Scheme 58



i : HIO_4 .$2H_2O$; ii : H_2N-NH-R';
iii : heat

Scheme 59



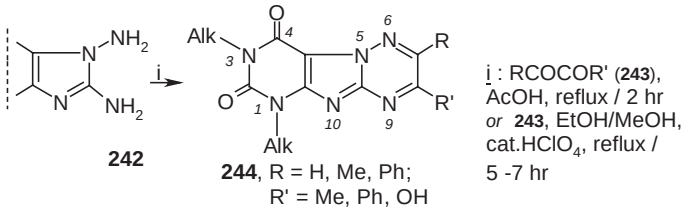
i : NH_2NH_2 . H_2O, 160 - 170°/ 3 - 4 hr; ii : $SOCl_2$, 25° / 1 hr; reflux / 3 hr .

Scheme 60

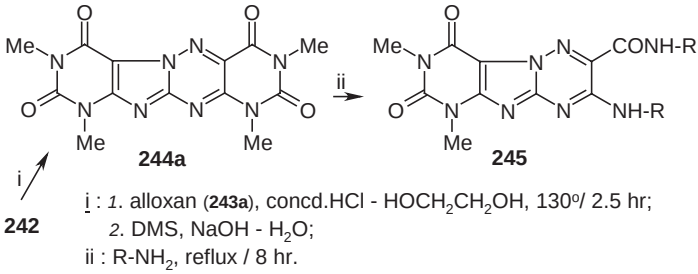
The second synthesis was based on a cyclization of 7-(2-chloro- or 2-bromoethyl)-8-bromoxanthine **239** with hydrazines to yield 7,9-dialkyl-1,2,3,4-tetrahydro-[1,2,4]triazino[3,4-*f*]purine-6,8(7*H*,9*H*)-diones **240**. An identical product was also obtained from 8-hydrazino-7-(2-hydroxyethyl)-xanthine **241** with thionyl chloride (75MI2) (Scheme 60).

The third method was based on a reaction of 7,8-diaminoxanthine **242** with α-dicarbonyl compounds **243** (butanedione, phenylglyoxal, benzil, pyruvic acid, phenanthrenequinone, etc.). The reaction time could be shortened substantially with boric or polyphosphoric acid as catalyst. The 1,3-dialkyl-7-R-8-R′-[1,2,4]triazino[3,2-*f*]purine-2,4(1*H*,3*H*)-diones **244** were then isolated (87KGS1398, 88UKZ531, 88JHC791). The position of substituents R, R′ were corroborated by ^{1}H-NMR and MS (Scheme 61).

A special case was the reaction of the 7,8-diamine **242** with alloxane (**243a**) catalyzed by hydrochloric acid to furnish 2,4,7,9-tetramethylpurino[7,8-*g*]



Scheme 61



Scheme 62

6-azapteridine-1,3,8,10(2*H*,4*H*,7*H*,9*H*)-tetrone **244a**. Its reaction with alkylamines gave 8-alkylamino-1,3-dimethyl-2,4-dioxo-[1,2,4]triazino-[3,2-*f*]purine-7-(*N*-alkyl)carboxamide **245** (87CPB4031) (Scheme 62).

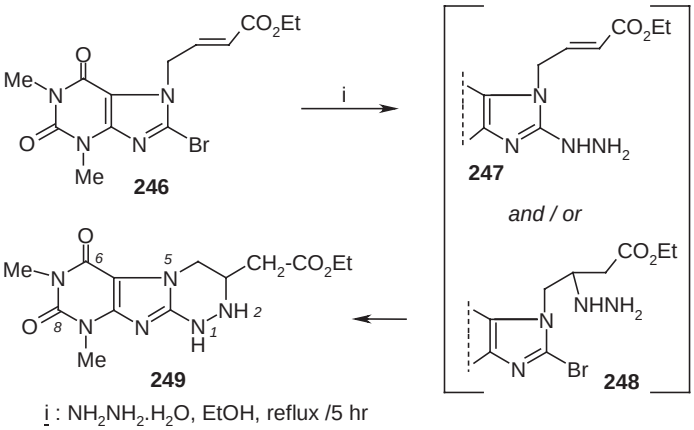
The fourth method started from ethyl (E)-4-(8-bromotheophyllin-7-yl)-2-butenoate (**246**). There are two possible routes to **249**: by either nucleophilic substitution with hydrazine hydrate to **247** and a subsequent nucleophilic addition of the 8-hydrazino group to the 7-unsaturated alkenyl group, or by addition of hydrazine to the above-mentioned alkenyl group to **248** and then a nucleophilic substitution of the 8-bromo group and cyclization to yield ethyl (7,9-dimethyl-6,8-dioxo-1,2,3,4,6,7,8,9-octahydro-[1,2,4]triazino[3,4-*f*]purin-3-yl)acetate (**249**). The intermediate **246** was obtained by alkylation of the potassium salt of bromotheophylline with ethyl (E)-4-bromo-2-butenoate in the presence of potassium carbonate (91S625) (Scheme 63).

The fifth method afforded 3-R-4*H*-[1,2,4]triazino[3,4-*f*]purine-4,6,8(1*H*, 7*H*, 9*H*)-triones **252** by treating 8-hydrazinotheophylline (**250**) with ethyl glyoxylates or diethyl ketomalonate via hydrazono derivative **251**. The substituent R-3 was keto acid dependent (01JHC607) (Scheme 64).

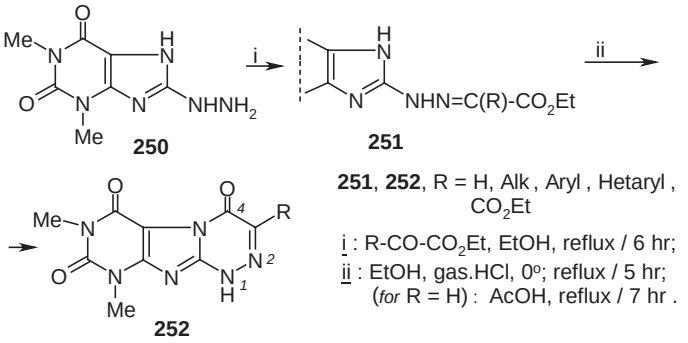
N-Bromosuccinimide and compound **253** furnished **255** with an unsaturated triazine ring and its reaction with phosphorus pentasulfide gave the 6-mercapto derivative **256** (81MI1) (Scheme 65).

The compound **254** with an *N*(7)-H can be alkylated with halogenoacetates in the presence of potassium carbonate to yield the 7-(ethoxycarbonyl-methyl) derivative **257**; its hydrazinolysis gave the hydrazide **257a** (86KFZ427) (Scheme 65).

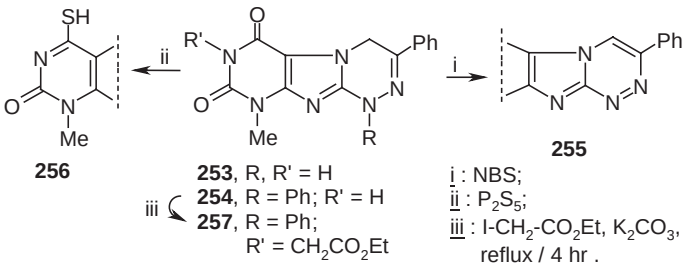
Compound **257a** showed strong neuroleptic and diuretic effects (86KFZ427). Compound **245** had antitumor efficacy (87CPB4031).



Scheme 63



Scheme 64



Scheme 65

2. *Triazino[1,2- and 2,3-a]purines*

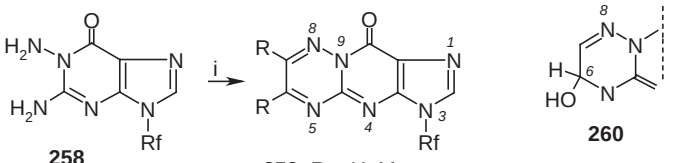
The first synthesis started from 1-aminoguanosine (**258**) and glyoxal or diacetyl to afford 3-(β-D-ribofuranosyl)-[1,2,4]triazino[2,3-*a*]purin-10(3*H*)-one **259** or its 6,7-dimethyl derivative. The intermediate **260** with a hydroxyl at position 6 can be isolated when

glyoxal at room temperatures is used; at elevated temperatures the product dehydrated to **259** (**R = H**) (74JOC937) (Scheme 66).

The second method employed guanines **261a**, methyl *N*-cyanomethane-imidate (**264**) and sodium methoxide to produce the fluorescent 8-amino-3-(β-ribofuranosyl)- or -3-benzyl[1,3,5]triazino[1,2-*a*]purin-10(3*H*)-ones **262**. The tricyclic ribonucleoside **262** (**R = Rf**) reverted to the starting **261a** in alkali and, therefore, it served as a "protected guanosine". This reagent with chloracetaldehyde and sodium methoxide is used as a spray for the fluorescent detection of guanosine and adenine as derivatives on TLC (84JA6847, 85JOC2468) (Scheme 67).

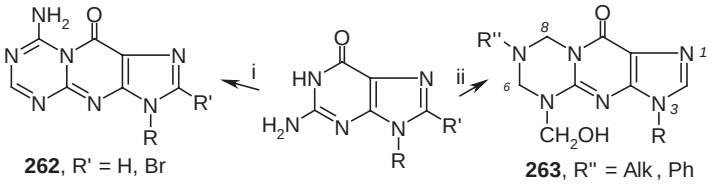
The Mannich reaction of guanine, formaldehyde and alkyl- or arylamine, in the third method produced 7-alkyl- or 7-aryl-5-hydroxymethyl-3-methyl- or 3-(2-deoxy-β-D-ribofuranosyl)-5,6,7,8-tetrahydro-[1,3,5]triazino[1,2-*a*]purin-10(3*H*)-one **263** (87BOK204, 01BMC729) (Scheme 67).

The triazine ring was built in the fourth method from a 2-aminopurine, e.g., from 2′,3′,5′-tri-*O*-benzoylguanosine **265** and *N*-chlorocarbonyl isocyanate (**266**) as a bifunctional reagent in the presence of triethylamine. The resultant 3-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-[1,3,5]triazino[1,2-*a*]purine-6,8,10(5*H*,7*H*,3*H*)-trione (**267**) gave, on deprotection of the saccharide hydroxyl groups with methanolic ammonia, compound **268**. The structures of both these compounds were demonstrated by ^{1}H- and ^{13}C-NMR and by an X-ray analysis (88JOC3959) (Scheme 68).



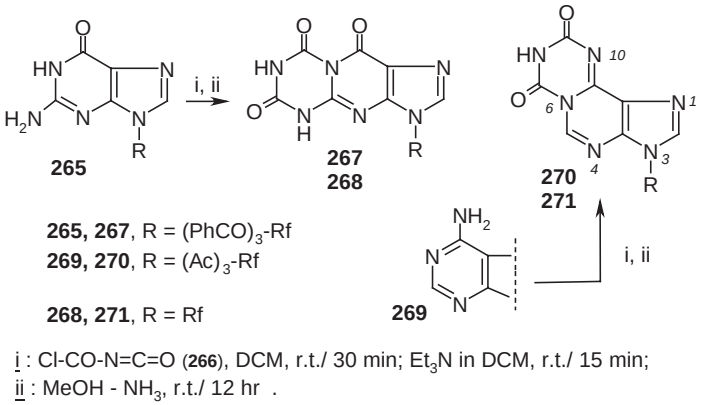
i : (*for* R = H) O=CH-CH=O, H_2O, 50° / 1 hr; (*for* R = Me) MeCOCOMe, EtOH, 0.1N HCl, r.t./ 10 days

Scheme 66



i : (*for* **261a**) 7 eq. MeO-CH=N-CN (**264**), 2 eq. NaOMe, MeOH, r.t. / 24 hr;
ii : (*for* **261b**) 40% HCHO, R''-NH_2, 20 --> 60°; r.t. / 24 hr .

Scheme 67



Scheme 68

Compounds **263** underwent easily a hydrolysis back to guanine, formaldehyde and alkyl- or arylamine. They are stable in anhydrous solvents only (87BOK204).

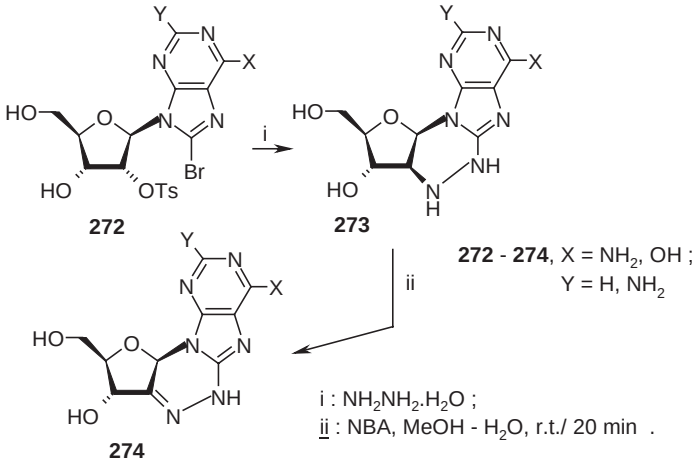
The structure determinations of compound **262** by X-ray analysis and ^{15}N-NMR were published in (84JA6847) and (91T6689).

3. *Triazino[2,1-i]purines*

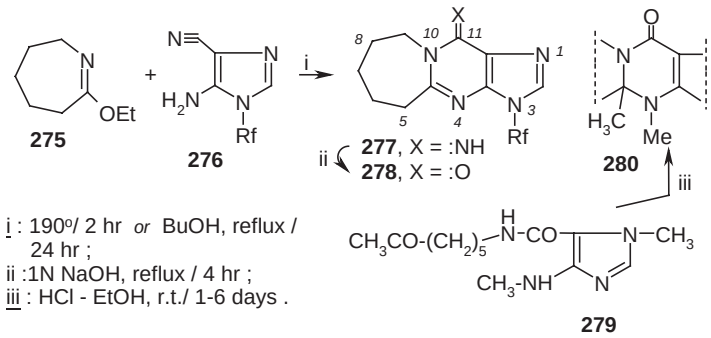
Compounds of this type were synthesized by analogy with the triazino [1,2-*a*]purine-triones as shown in the Scheme 68, but now *N*-chlorocarbonyl isocyanate (**266**) reacted with a nucleoside with an amino group at position 6, e.g. adenosine with the acetylated saccharide moiety **269**. The product of this reaction was 3-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-[1,3,5]triazino[2,1-*i*]purine-7,9(3*H*,8*H*)-dione (**270**). The protecting groups were hydrolyzed away with methanolic ammonia to produce **271**. Its structure was proven by NMR and X-ray (88JOC3959) (Scheme 68).

4. *Triazino[4,3-e]purines*

Tricyclic structures of this type have been little studied. Their synthesis was published with 8-bromoadenosine, guanosine and inosine. First, the 2′-hydroxy group of 8-bromo-3-(ribofuranosyl)purines had to be converted into the 2′-tosyloxy group (**272**) followed by treatment with hydrazine hydrate to give 8,2′-hydrazo-9-(2′-deoxy-*β*-D-arabinofuranosyl)purine **273**. The last step was the action of *N*-bromoacetamide (NBA) to yield 2′, N^{β}-didehydro-8,2′-hydrazo-9-(2′,3′-dideoxy-*β*-D-arabino-furanosyl)purine **274**. The intermediate **272** was accessible by tosylation of a 2′,3′-*O*-dibutylstannylene compound (85JCS(P1)2347) (Scheme 69).



Scheme 69



Scheme 70

III. Purines Fused to Seven- and Eight-Membered Heterocycles

A. Azepino-Purines

1. *Azepino[1,2-a]purines*

Two methods provided access to this skeleton from imidazole derivatives. In the first reaction of 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carbonitrile **276** with 2-ethoxy-1-azacycloheptene **275** gave 11-imino-3-(β-D-ribofuranosyl)-5,6,7,8,9,11-hexahydro-3*H*-azepino[1,2-*a*]purine **277**. The by-product was 2,N^6-pentamethylene-adenosine due to the Dimroth rearrangement of **277**. Hydrolysis of the 11-imino group in **277** afforded the corresponding 11-oxo derivative **278** (79LA1872) (Scheme 70).

The second method started from 1-methyl-4-methylamino-*N*-(6-oxo-heptyl)imidazo-5-carboxamide (**279**) and ethanolic hydrogen chloride. This

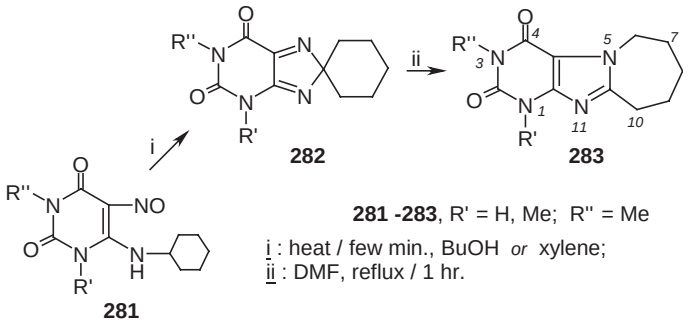
reagent closed both the azepine and pyrimidine rings to furnish the 4,4a,5,6,7,8,9,11-octahydro-1,4,4a-trimethyl-1*H*-azepino[1,2-*a*]purin-11-one **280** in low yield (86CPB36) (Scheme 70).

2. *Azepino[2,1-f]purines*

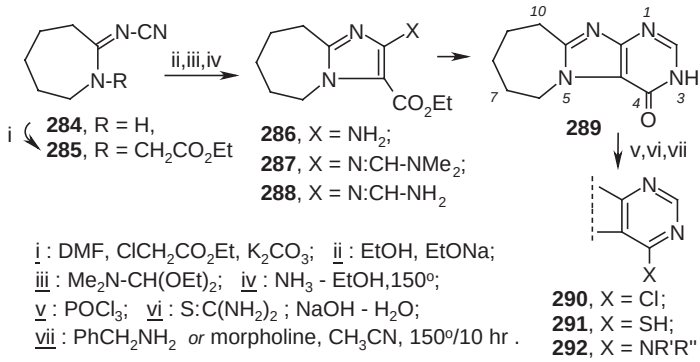
The first method employed the thermal rearrangement of 8,8-pentamethylene-xanthine **282** to 7,8,9,10-tetrahydro-1,3-dialkyl-1*H*-azepino[2,1-*f*]purine-2,4(3*H*,6*H*)-dione **283**. The intermediate **282** was obtained by cyclodehydration of 6-cyclohexylamino-5-nitrosouracil **281** (64ZC454, 65MIP1, 66LA(692)134) (Scheme 71).

In the second method alkylation of a *N*-cyanoamidine **284** in an aprotic medium with ethyl chloroacetate in the presence of potassium carbonate gave **285** followed by conversion of the latter by sodium ethoxide into imidazole derivative **286**. Subsequent reaction with dimethylformamide diacetal and ethanolic ammonia produced the formamidine derivatives **287** and **288**, which cyclized to the 7,8,9,10-tetrahydro-6*H*-azepino[2,1-*f*]purin-4(3*H*)-one (**289**) (92KFZ(9-10)63, 95KFZ(2)27) (Scheme 72).

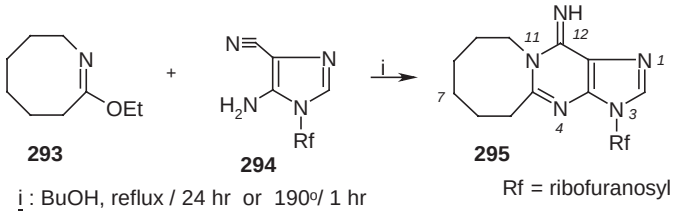
The enol form of **289** was converted into the 4-chloro **290** with phosphoryl chloride on heating. It then reacted either with thiourea to afford the 4-thione **291**



Scheme 71



Scheme 72



Scheme 73

through the thiouronium salt or with primary and secondary amines to give **292** (95KFZ(2)27) (Scheme 72).

B. Azocino-Purines

1. *Azocino[1,2-a]purines*

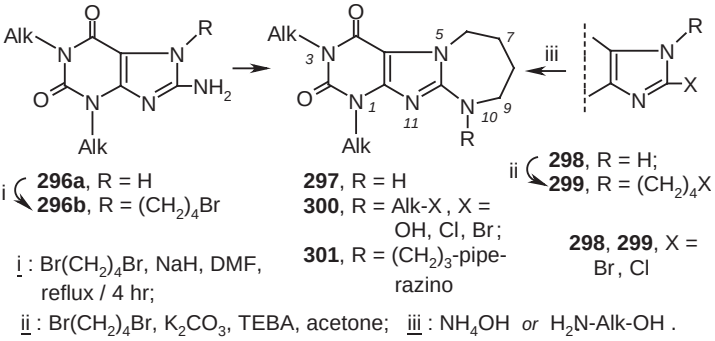
The 12-imino-3-(β-D-ribofuranosyl)-3,5,6,7,8,9,10,12-octahydro-azocino[1,2-*a*]purine (**295**) was obtained from 5-amino-1-(β-D-ribo-furanosyl)imidazole-4-carbonitrile (**294**) and 2-ethoxy-1-azacyclooctene (**293**) at elevated temperatures (79LA1872) (Scheme 73).

C. Diazepino-Purines

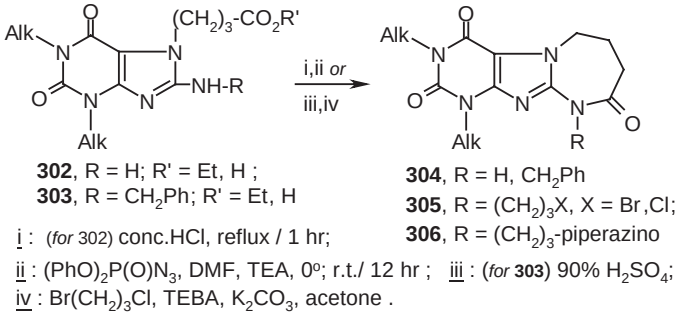
1. *Diazepino[2,1-f]purines*

Compounds of this structural type can best be prepared by alkylation of 8-aminotheophylline (**296a**) with a 1,4-dibromobutane and sodium hydride. The intermediate **296b** cyclized to 1,3-dialkyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[2,1-*f*]purine-2,4(1*H*,3*H*)-dione **297** under the alkylation conditions. A variation started from 8-bromotheophylline (**298**) and a 1,4-dibromobutane to afford the 8-halo-7-(4-halobutyl) **299** under the conditions of phase-transfer catalysis. The following nucleophilic substitution with ammonia or an aminoalcohol gave the tricyclic **297** or **300** (94MI1, 98JHC135, 76GEP(O)1) (Scheme 74).

Another variation employed 4-bromobutyrate to obtain ethyl (8-amino-theophyllin-7-yl)butyrate (**302**, $\mathbf{R'} = \mathbf{Et}$). Acid hydrolysis furnished the substituted butyric acid **302** ($\mathbf{R'} = \mathbf{H}$) and following treatment by diphenylphosphoryl azide gave the 7,8-dihydro-1,3-dialkyl-6*H*-[1,3]diazepino[2,1-*f*]purine-2,4,9(1*H*,3*H*,10*H*)-trione (**304**) (98JHC135). A modification started from the 8-benzylamino derivative **303**. A double hydrolysis converted it into 4-(8-aminotheophyllin-7-yl)butyric acid (**302**, $\mathbf{R'} = \mathbf{H}$) and an alkylation with 1-bromo-3-chloropropane yielded the 10-chloropropyl derivative under phase-transfer catalysis conditions. This was followed by cyclization to the amide tricyclic **305** (94MI1) (Scheme 75).



Scheme 74



Scheme 75

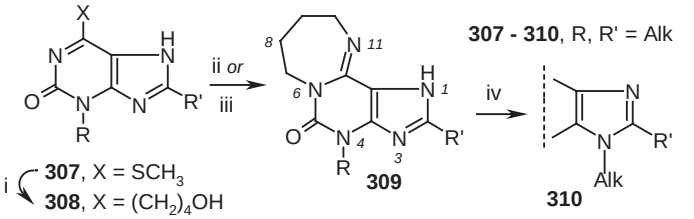
The halogen in a side-chain at *N*(10) of **305** can be displaced by *N*-substituted piperazine to give **306**. Derivatives **300** without a keto group in position 9 behaved similarly.

The structure of compound **304** (**R = CH_2Ph**) was determined by an X-ray diffraction analysis (90MI1).

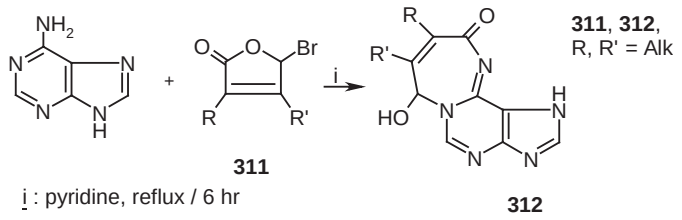
The hydrochloride of compound **301** showed a strong long-lasting analgesia and sedation (94MI1). Diazepino[2,1-*f*]purines generally disclosed a $5HT_{1A}$-agonistic activity (99EJM167).

2. *Diazepino[2,1-i]purines*

To date two preparations have been published. The first was based on a dehydrative cyclization of 6-(4-hydroxybutylamino)purine **308** by thionyl chloride to yield 2,4-dialkyl-7,8,9,10-tetrahydro-1*H*-[1,3]diazepino[2,1-*i*]purin-5(4*H*)-one **309**. The necessary intermediate **308** was prepared from 6-methylthiopurine **307** and 4-aminobutanol. Variation of this procedure was the mesylation of **308** to give the 6-(4-mesyloxybutylamino) derivative, followed by cyclization to the tricyclic **309** (93JHC241, 97JMC3248, 02JMC3440) (Scheme 76).



Scheme 76



Scheme 77

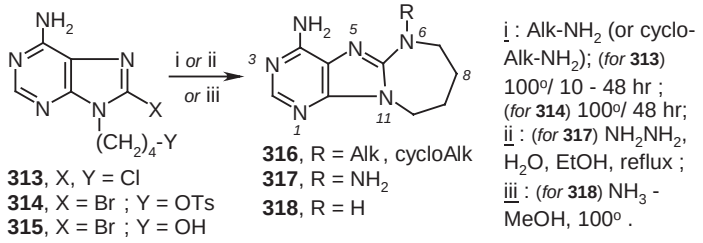
The second method was based on the reaction of aminopurines with α, β-unsaturated 5-membered lactones. Thus, adenine reacted with 5-bromo-3,4-dialkyl-2(5*H*)-furanone **311** to give 8-R′-9-R-7-hydroxy-1*H*-[1,3]diazepino[2,1-*i*]purin-10(7*H*)-one (**312**) (73JOC3878) (Scheme 77).

The imidazole moiety of **309** can be alkylated at position *N*(3) to the 2,3,4-trialkyl derivative **310** (97JMC3248). Compounds **312** are unstable and give adenine in alkali (73JOC3878).

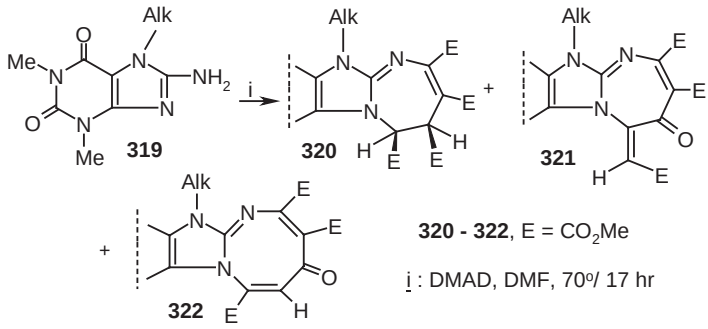
Compounds **310** are inhibitors of cAMP-specific phosphodiesterase (PDE IV) (97JMC3248).

3. *Diazepino[1,2-e]purines*

The first and preparatively most advantageous method for this heterocycle started from 8-chloro-9-(4-chlorobutyl)adenine **313** and primary or cycloalkylamines to furnish 6-alkyl- or 6-cycloalkyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine **316**. When amines were replaced by hydrazine hydrate, 6-amino derivative **317** was obtained. Methanolic ammonia led to the parent tricyclic compound **318**. The required dichloro derivative **313** was prepared from 8-bromo-9-(4-hydroxybutyl)-adenine (**315**) and thionyl chloride. The expected 8-bromo-9-(4-chlorobutyl) derivative was a by-product of this reaction due to an exchange of the 8-bromo for 8-chloro group. The intermediate **314** resulted from tosylation of the 9-(hydroxybutyl) derivative **315**, but in a low yield (00CCC1109) (Scheme 78).



Scheme 78



Scheme 79

The second method used 7-alkyl-8-aminotheophyllines **319** with dimethyl acetylenedicarboxylate (DMDA) in an aprotic medium with the formation of three main products: tetramethyl 5-alkyl-1,3,4,5,9,10-hexahydro-1,3-dimethyl-2,4-dioxo-2*H*-[1,3]diazepino[1,2-*e*]purine-7,8,9,10-tetracarboxylate (**320**) (24–44%), dimethyl 5-alkyl-1,3,4,5,9,10-hexahydro-10-(2-methoxy-2-oxoethylidene)-1,3-dimethyl-2,4,9-trioxo-2*H*-[1,3]diazepino[1,2-*e*]purine-7,8-dicarboxylate (**321**) (10–13%) and [1,3]diazocino[1,2-*e*]purine-trione derivative **322** (10–18%). Products **320**, **321** and **322** were separated by column chromatography. This method is of no preparative value. However, pyrimido[1,2-*e*]purinetriones were obtained when this reaction was carried out in boiling methanol (91CPB270) (Scheme 79).

4. *Diazepino[1,2,3-cd]purines*

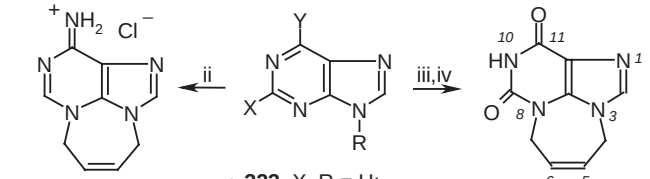
The diazepine ring was formed by alkylation of a purine with a 1,4-dichloro-2-butene. Thus, adenine (**323**) and a 4-fold excess of 1,4-dichloro-2-butene gave (Z)-9-(4-chloro-2-buten-1-yl)adenine (**324**) on phase-transfer catalysis with tetrabutylammonium fluoride (TBAF). The intermediate **324** afforded 4,7-dihydro-11*H*-[1,3]diazepino[1,2,3-*cd*]purin-11-imine hydrochloride (**325**) on an intramolecular alkylation. Similarly, 2-amino-6-chloropurine (**323**) (**X = NH$_2$, Y = Cl, R = H**) alkylated with dichlorobutene gave **326**. This was followed by cyclization and

subsequent hydrolysis of the 9-imino and 11-chloro groups to afford the diazepino[1,2,3-*cd*]purine dione **328** (91JMC421) (Scheme 80)

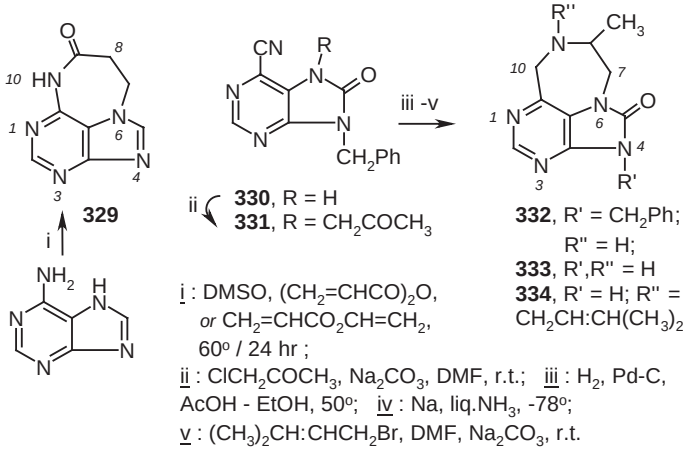
5. *Diazepino[1,2,3-gh]purines*

The first method leading to the peri-condensed ring system consisted of a reaction between adenine and acrylic anhydride or vinyl acrylate in an aprotic medium to give the 6-(acrylamido)purine followed by intra-molecular addition of N(7)H to the double bond of the acid group to afford 7,8-dihydro-[1,4]diazepino[1,2,3-*gh*]purin-9(10*H*)-one **329** (19–26%). The same reaction in alkali produced 3-(carboxyethyl)adenine (85JHC109) (Scheme 81).

The second method made use of the following steps. Alkylation of 6-cyano-9-benzylpurin-8-one (**330**) with chloroacetone gave the 6-cyano- 7-(2-oxopropyl)



Scheme 80



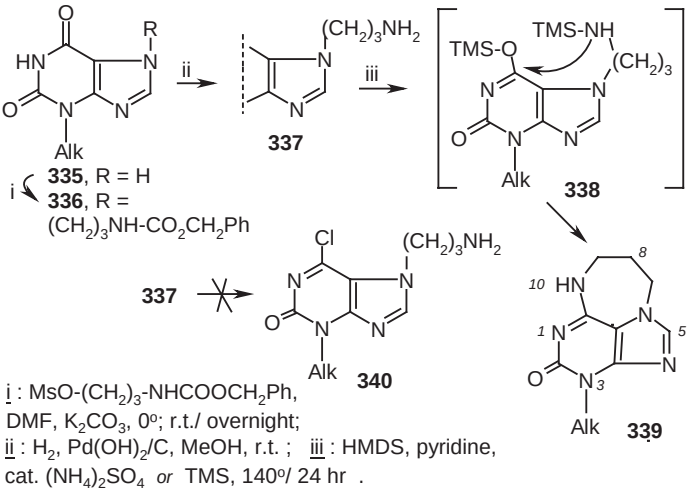
Scheme 81

purinone **331**; hydrogenation of the nitrile group of **331** followed by a reductive amination of the 7-(2-oxopropyl) group produced 4-benzyl-7,8,9,10-tetrahydro-8-methyl-[1,4]diazepino[1,7,6-*gh*]purin-5(4*H*)-one (**332**). Removal of the 4-benzyl group by sodium in liquid ammonia resulted in compound **333**. The starting purinone **330** was obtained by hydrolysis of 9-benzyl-8-bromo-6-cyanopurine with alkali (91BMC531) (Scheme 81).

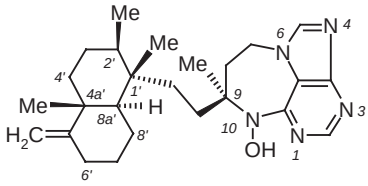
The third method was based on a silylation-amination reaction. The necessary 3-alkyl-7-(3-aminopropyl)xanthine was prepared from a 3-alkyl-xanthine **335** by alkylation with (*N*-benzyloxycarbonyl)aminopropyl methanesulfonate in the presence of potassium carbonate. The benzyl group from the resulting [7-(*N*-benzyloxycarbonyl)aminopropyl]-3-alkylpurine-2,4-dione **336** was removed by a catalytic hydrogenation over palladium hydroxide to give the 7-(3-aminopropyl)-3-alkylpurine-2,4-dione **337**. An attempt to close the diazepino ring from **337** through **340** by means of phosphoryl chloride failed due to degradation of the latter in the presence of a chlorination agent (77KFZ30, 99CPB1322). More successful proved the application of the silylation–amination reaction of **337** with hexamethyl-disilazane (HMDS) through the intermediate **338**, which yielded the 3-alkyl-3,7,8,9-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purin-2(10H)-one **339** as shown in the Scheme 82 (99CPB1322).

The metabolites Asmarine A–C isolated from the sponge Rapailia from the Red Sea were shown to have a diazepino[1,2,3-*gh*]purine structure. Asmarin A = 9-{2-[(1R,2S,4aS, 8aR)-decahydro-1,2,4a-trimethyl-5-methylene-1-naphthyl]ethyl}-7,8,9,10-tetrahydro-10-hydroxy-9-methyl-[1,4]diazepino[1,2,3-*gh*]purine **341**. Asmarines B and C differ in the decalin moiety—they have a *cis*-ring junction of the decalin **342**, while Asmarin A has a *trans*-ring junction of the decalin. Asmarin C has one more methyl group at C(5).

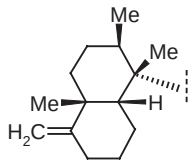
The structure of Asmarines were established by ^{1}H- ^{13}C-NMR and X-ray diffraction analyses (98TL3323) (Scheme 83).



Scheme 82

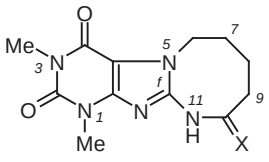


341

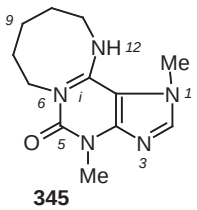


342

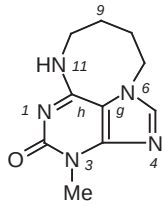
Scheme 83



343, X = H_2
344, X = O



345



346

Scheme 84

The action of dilute alkali on compounds **329** resulted in cleavage of the amide group to 3-(adenin-7-yl)propionic acid (85JHC109). The *N*(9) of compound **333** can be alkylated with alkyl bromide to the corresponding 9-alkyl derivative **334** (91BMC531).

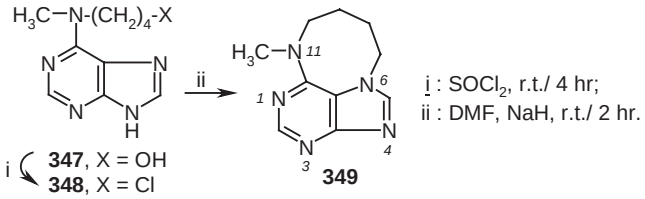
Compound **339** showed little PDE IV inhibition activity (99CPB1322). Asmarines A–C were effective against human lung and human colon carcinoma (98TL3323).

D. Diazocino-Purines

The *diazocino[1,2-f]purine* ring can be obtained from 8-amino-theophylline by a similar procedure as given for the diazepino[1,2-*f*]purines (cf. Scheme 74) and a 1,5-dibromopentane in place of a 1,4-dibromobutane.

The reaction proceeded through the 8-amino-7-(5-bromopentyl) derivative to give the 1,3-dimethyl-6,7,8,9,10,11-hexahydro-[1,3]diazocino[2,1-*f*]purine-2,4(1*H*,3*H*)-dione **343**. The 1,3-dimethyl-6,7,8,9-tetrahydro-[1,3]diazocino[2,1-*f*]purine-2,4,10(1*H*,3*H*,11*H*)-trione **344** was synthesized from 8-amino-theophylline and ethyl 5-bromovalerate through the corresponding ethyl 8-amino-7-valerate; its cyclization was effected by diphenylphosphoryl azide (98JHC135) (Scheme 84).

The *diazocino[2,1-i]purine* was prepared from 6-methylthio-3-methyl-purinone in an analogous approach as that for the diazepino[2,1-*i*]purinone (cf. Scheme 76) with the difference that 5-aminopentanol was used in place of 4-aminobutanol. The intermediate 6-(5-hydroxypentylamino)-3-methylpurin-2-one was cyclized with thionyl chloride to give 1,7,8,9,10,11-hexahydro-1,4-dimethyl-[1,3]diazocino[2,1-*i*]purin-5(4*H*)-one hydrochloride **345** (02JMC3440) (Scheme 84).



Scheme 85

The formation of triethyl 5-alkyl-1,2,3,4,5,9-hexahydro-1,3-dimethyl-2,4,9-trioxo-[1,3]diazocino[1,2-*e*]purine-7,8,11-tricarboxylic acid **322** and two diazepino[1,2-*e*]purine derivatives was described in the subchapter on diazepino-purines (cf. Scheme 79) (91CPB270).

1. *Diazocino[1,2,3-gh]purines*

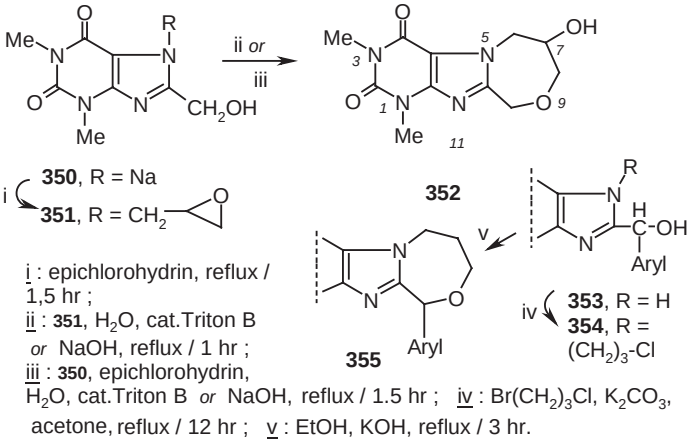
The first method included a nucleophilic substitution of 6-chloropurine with 4-(methylamino)butanol to produce the 6-[(*N*-4-hydroxybutyl-*N*-methyl)amino]purine **347**. Subsequent chlorination with thionyl chloride gave the chloro derivative **348**; its intramolecular alkylation in the presence of sodium hydride closed the diazocine ring under formation of 7,8,9,10-tetrahydro-11-methyl-11*H*-[1,4]diazocino[1,2,3-*gh*]purine (**349**) (84JHC333) (Scheme 85).

The second approach was identical to the preparation of diazepino[1,2,3-*gh*]purine derivatives by the silylation–amination route (cf. Scheme 82), the difference was the key intermediate 7-(4-aminobutyl)-3-methylpurine-2,4-dione. The product was then 3-methyl-7,8,9,10-tetrahydro-11*H*-[1,4]-diazocino[1,2,3-*gh*]purin-2(3*H*)-one (**346**) (99CPB1322) (Scheme 84).

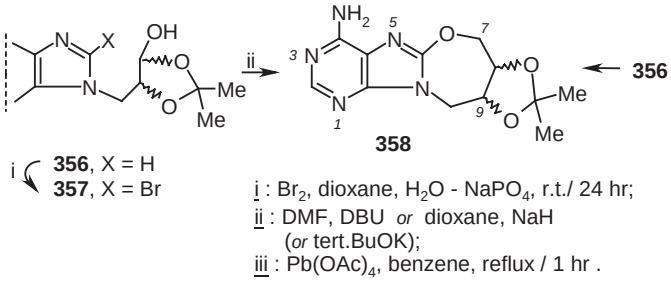
E. Oxazepino-Purines

1. *Oxazepino[3,4-f]purines*

The reaction of sodium 8-hydroxymethyltheophylline (**350**) with epichlorohydrin produced 8-hydroxymethyl-7-(2,3-epoxypropyl)-theophylline (**351**); then cyclization in alkali gave 7,8-dihydro-7-hydroxy-1,3-dimethyl-1*H*,6*H*-[1,4]oxazepino[3,4-*f*]purine-2,4(3*H*,10*H*)-dione (**352**). An alternative route to **352** uses the one-pot reaction of **350** (**R** = **H**) with epichlorohydrin and water catalyzed by either Triton B or alkali. The structure was demonstrated by mass-spectral fragmentation (78CCC3414). Similarly, alkylation of 8-(α-hydroxybenzyl)theophylline (**353**) with 1-bromo-3-chloropropane under phase-transfer catalysis gave the 7-(3-chloropropyl)-8-(α-hydroxybenzyl) derivative **354** and then intramolecular alkylation afforded 7,8-dihydro-10-phenyl-1,3-dimethyl-1*H*,6*H*-[1,4]oxazepino[3,4-*f*]purine-2,4(3*H*,10*H*)-dione (**355**). Chiral discrimination of **355** was made by ^{1}H-NMR using a dirhodium complex (00EOC3489) (Scheme 86).



Scheme 86



Scheme 87

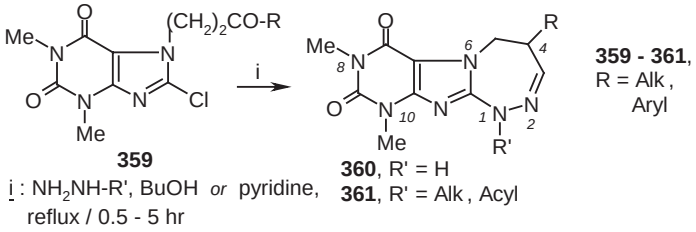
2. *Oxazepino[3,2-e]purines*

A base-catalyzed cyclization of 8-bromo-9-(2,3-*O*-isopropylidene-2,3,4-trihydroxybutyl)adenine (**357**) produced the 7,8,9,10-tetrahydro-8,9-(isopropylidene)dioxy-[1,3]oxazepino[3,2-*e*]purin-4-amine (**358**). The bromo derivative **357** was prepared by bromination in aqueous dioxane. The tricyclic **358** was also obtained from the starting 9-(2,3-*O*-isopropylidene-2,3,4-trihydroxybutyl)adenine **356** by oxidative cyclization with lead tetraacetate (96CCC442) (Scheme 87).

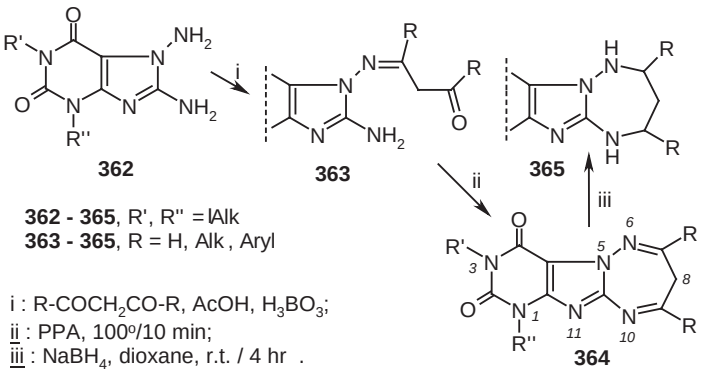
F. Triazepino-Purines

1. *Triazepino[f]purines*

The first and most common method was based on a reaction of 8-chloro-7-(3-oxoalkyl- or 4-aryl-3-oxopropyl)theophylline (**359**) and hydrazine hydrate or alkylhydrazine. The hydrazone thus formed was not isolated, but treated with the



Scheme 88



Scheme 89

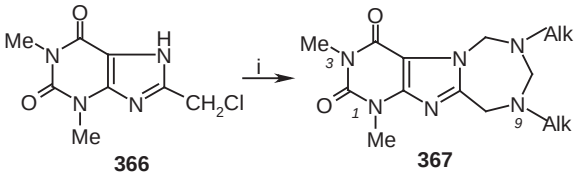
8-chloro group of purine to give 4,5-dihydro-4-alkyl- or 4-aryl-8,10-dimethyl-1*H*-[1,2,4]triazepino[3,4-*f*]purine-7,9(8*H*,10*H*)-dione (**360**). The intermediate **359** was prepared from the alkali salt of 8-chlorotheophylline (69MI1, 75FES122, 82MI1) (Scheme 88).

The second method employs the reaction of 7,8-diaminotheophylline (**362**) with *β*-diketones in the presence of boric acid to afford the Schiff base **363**, then heating with polyphosphoric acid to close the triazepine ring to the 1,3,7,9-tetraalkyl-8*H*-[1,2,4]triazepino[3,2-*f*]purine-2,4(1*H*, 3*H*)-dione (**364**). Reduction of the latter with sodium borohydride furnished the tricyclic **365** with a saturated triazepine ring (88JHC791) (Scheme 89).

The third method used 8-chloromethyltheophylline (**366**) and a saturated solution of methyl- or ethylamine in dichloromethane, which served also as a reagent, to furnish the 7,8,9,10-tetrahydro-7,9-dialkyl-1,3-dimethyl-6*H*-[1,3,5]triazepino[7,1-*f*]purine-2,4(1*H*,3*H*)-dione **367** (90AG917) (Scheme 90).

The N(1)H in compound **360** could be acylated with anhydrides of lower aliphatic acids or added to acrylonitrile (cat. Triton B) (75FES122).

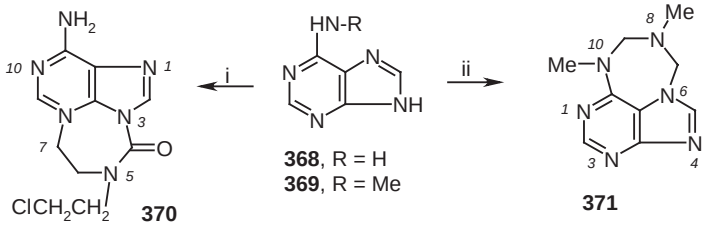
2. Triazepino[1,2,3-cd and -gh]purines. Adenine (**368**) and bis-(*β*-chloroethyl)carbamoyl chloride afforded the 11-amino-5-(2-chloroethyl)-6,7-dihydro-[1,3,5]triazepino[1,2,3-*cd*]purin-4(5*H*)-one (**370**) (75PHA498) (Scheme 91).



366 **367**

i : CH_2Cl_2, anhydr. Me-NH_2 *or* $EtNH_2$, -30° --> r.t./ 10 hr, reflux / 0.5 hr

Scheme 90



370 **368**, R = H **369**, R = Me **371**

i : $(ClCH_2CH_2)_2N$-CO-Cl, pyridine, r.t. / 3 days ; ii : 2 HCHO, CH_3NH_2, H_2O - EtOH, pH 8 .

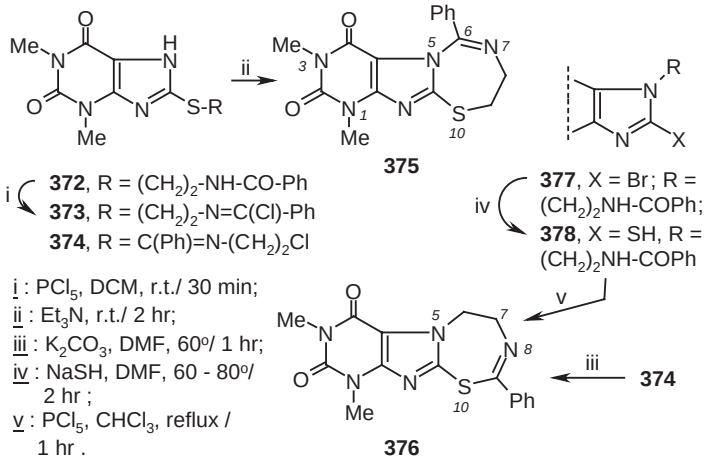
Scheme 91

$N^{(6)}$-Methyladenine (**369**) reacted with formaldehyde and methylamine in a Mannich reaction to furnish the 7,8,9,10-tetrahydro-8,10-dimethyl-[1,3,5]triazepino[1,7,6-*gh*]purine (**371**). Its structure was demonstrated by ^{1}H-NMR (87BOK1230) (Scheme 91).

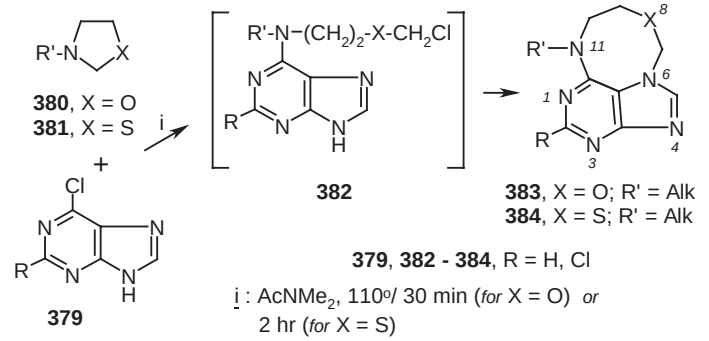
G. Thiadiazepino-Purines

The 6-phenyl-8,9-dihydro-1,3-dimethyl-[1,3,5]thiadiazepino[2,3-*f*]purine-2,4(1*H*,3*H*)-dione **375** was obtained by a three-step synthesis from 8-mercaptotheophylline and 2-(benzoylamino)ethyl chloride through 8-(benzoylaminoethyl)mercaptotheophylline **372** and its chlorimido derivative **373**, which cyclized with triethylamine to the required **375**.

Similarly, 9-phenyl-6,7-dihydro-1,3-dimethyl-[1,3,5]thiadiazepino[2,3-*f*]-purine-2,4(1*H*,3*H*)-dione (**376**) was prepared from either 8-mercaptotheophylline and *N*-(2-chloroethyl)benzimido chloride through the [*N*-(chloroethyl)-*S*-theophyllin-8-yl]benzothioimide **374** followed by cyclization, or from 8-bromo-7-(2-benzoylaminoethyl)theophylline **377** through the corresponding 8-mercapto derivative **378** and through the *in situ* formed chlorimido compound by reaction with phosphorus pentachloride. The structures of both **375** and **376** were demonstrated by ^{1}H, ^{13}C-NMR and mass spectral fragmentation (94M1273) (Scheme 92).



Scheme 92



Scheme 93

H. Oxdiazocino- and Thiadiazocino-Purines

The reaction of 6-chloropurines **379** with 3-alkyloxazolidine (**380**), or 3-alkylthiazolidine (**381**) afforded the tricyclic 11-alkyl-10,11-dihydro-7*H*,9*H*-[1,3,6]oxadiazocino[3,4,5-*gh*]purines **383**, or analogous [1,3,6]thiadiazocino[3,4,5-*gh*]purines **384** [84JHC333] (Scheme 93).

References

60GEP1 E. Carstens, J. Donat, and F. Hausschild, Chem. Werke Radebeul, Ger. Pat. 1086707 (1960) [*CA* **55** 27380 (1961)].

60MIP1 E. Carstens, J. Donat, and F. Hausschild, Ger. (East) Pat. 19587 (1960) [*CA* **55** 19969 (1960)].

62MI1 M. Eckstein, *Diss. Pharm. (Poland)*, **14**, 435 (1962) [*CA* **60** 8030 (1964)].

62MI2 M. Eckstein, *Diss. Pharm. (Poland)*, **14**, 401 (1962) [*CA* **60** 8030 (1964)].
64ZC454 H. Goldner, G. Dietz, and E. Carstens, *Z. Chem.*, **4**, 454 (1964).
65MI1 R. G. Glushkov and O. Yu. Magidson, *Biol. Aktiv. Soedin., Akad. Nauk SSSR*, 12 (1965) [*CA* **63** 16351 (1965)].
65MIP1 H. Goldner, G. Dietz, and E. Carstens, Ger. (East) Pat. 39143 (1965) [*CA* **63** 13342 (1965)].
66LA(692)134 H. Goldner, G. Dietz, and E. Carstens, *Liebigs Ann.*, **692**, 134 (1966).
67KFZ(4)16 V. G. Granik and R. G. Glushkov, *Khim.- Farm. Zh.*, **1** (4), 16 (1967) [*CA* **68** 68955 (1968)].
68MI1 M. Eckstein and W. Loson, *Diss. Pharm. Pharmacol. (Poland)*, **20**, 35 (1968) [*CA* **69** 43891 (1968)].
69GEP(O)1 Pfizer, Chas and Co. (I. M. Goldman), Ger. Offen. 1809013 (1969) [*CA* **72** 12771 (1970)].
69MI1 H. Pazdro and M. Eckstein, *Diss. Pharm. Pharmacol. (Poland)*, **21**, 39 (1969) [*CA* **71** 81309 (1969)].
70KFZ(12)22 B. M. Pyatin, V. G. Granik, and R. G. Glushkov, *Khim.- Farm. Zh.*, **4** (12), 22 (1970) [*CA* **74** 12019 (1971)].
71AP117 K. H. Kleine and R. Haller, *Arch. Pharm. (Weinheim)*, **304**, 117 (1971).
71MI1 J. Zajaczkowska and M. Eckstein, *Diss. Pharm. Pharmacol. (Poland)*, **23**, 209 (1971) [*CA* **75** 151760 (1971)].
73JOC3878 I. L. Doerr and R. E. Willette, *J. Org. Chem.*, **38**, 3878 (1973).
73MI1 M. Eckstein and A. Drabczynska, *Pol. J. Pharmacol. Pharm.*, **25**, 171 (1973) [*CA* **79** 92162 (1973)].
74JOC937 G. L. Anderson, B. H. Rizkalla, and A. D. Broom, *J. Org. Chem.*, **39**, 937 (1974).
74KGS1696 M. V. Povstyanoi, P. M. Kochergin, E. V. Logachev, E. A. Jakubovskii, A. V. Akimov, and V. V. Androsov, *Khim. Geterotsikl. Soedin.*, 1696 (1974) [*CA* **82** 97995 (1975)].
74UKZ215 M. V. Povstyanoi, A. V. Akimov, and P. M. Kochergin, *Ukr. Khim. Zh.*, **40**, 215 (1974) [*CA* **80** 146112 (1974)].
75FES122 M. Eckstein and J. Zajaczkowska, *Farmaco, Ed. Sci.*, **30**, 122 (1975).
75JHC1045 T. P. Seden and R. W. Turner, *J. Heterocycl. Chem.*, **12**, 1045 (1975).
75MI1 A. K. Bagrii, G. F. Galenko, and P. M. Kochergin, *Dopov. Akad. Nauk Ukr. RSR, Ser. B*, 801 (1975) [*CA* **84** 43959 (1976)].
75MI2 M. V. Povstyanoi, P. M. Kochergin, and A. V. Akimov, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **18**, 1812 (1975) [*CA* **84** 90124 (1976)].
75MI3 M. V. Povstyanoi, P. M. Kochergin, A. V. Akimov, and V. V. Androsov, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **18**, 1316 (1975) [*CA* **84** 4911 (1976)].
75PHA498 W. Schulze, G. Letsch, and D. Tresselt, *Pharmazie*, **30**, 498 (1975).
76GEP(O)1 Laboratoire le Brun SA, (J. R. Quelet), Ger. Offen. 2609397 (1976) [*CA* **85** 192771 (1976)].
76JOC294 R. C. Moschel and N. J. Leonard, *J. Org. Chem.*, **41**, 294 (1976).
77KFZ30 R. G. Glushkov, I. M. Ovcharova, M. A. Muratov, M. E. Kaminka, and M. D. Mashkovskii, *Khim.- Farm. Zh.*, **11** (1), 30 (1977) [*CA* **86** 189860 (1978)].
78CCC3414 A. Rybár, L. Štibranyi, and J. Leško, *Collect. Czech. Chem. Commun.*, **43**, 3414 (1978).
79LA1872 K. Ienaga and W. Pfleiderer, *Liebigs Ann. Chem.*, 1872 (1979).
80FRP1 R. Szebeni, D. Korbonits, K. Harsanyi, L. Molnar, L. Szekeres, Gy. Papp, and Gy. Sebestyen, Chinoin, Hungary, Fr. Pat. 2438658 (1980) [*CA* **94** 47366 (1981)].

80FZK(4)65 O. A. Kremzer, Yu. V. Strokin, and B. A. Priimenko, *Farm. Zh. (Kiev)*, (4), 65 1980 [*CA* **94** 65625 (1981)].

80GEP(O)1 R. Szebeni, D. Korbonits, K. Harsanyi, L. Molnar, L. Szekeres, Gy. Papp, and Gy. Sebestyen, Chinoin, Hungary, Ger. Offen. 2843195 (1980) [*CA* **93** 114576 (1980)].

80KPS626 B. A. Priimenko, N. L. Romanenko, S. N. Garmesh, A. Yu. Chervinskii, and A. K. Sheinkman, *Khim. Prir. Soedin.*, 626 (1980) [*CA* **94** 175057 (1981)].

80RTC20 M. J. Wanner, J. J. M. Hageman, G. J. Koomen, and U. K. Pandit, *Recl. Trav. Chim. Pays-Bas*, **99**, 20 (1980).

81JOC815 A. W. Czarnik and N. J. Leonard, *J. Org. Chem.*, **46**, 815 (1981).

81KGS1102 A. A. Kremzer, Yu. V. Strokin, N. A. Klyuev, and V. P. Buryak, *Khim. Geterotsikl. Soedin.*, 1102 (1981) [*CA* **96** 19864 (1982)].

81MI1 B. A. Priimenko, N. I. Romanenko, S. N. Garmash, and M. V. Povstyanoi, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **24**, 1495 (1981) [*CA* **96** 122762 (1982)].

82MI1 N. I. Romanenko, B. A. Priimenko, S. N. Garmash, and A. K. Sheinkman, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **25**, 121 (1982) [*CA* **96** 199650 (1982)].

83CCC1910 A. Holý, *Collect. Czech. Chem. Commun.*, **48**, 1910 (1983).

83TL4491 G. Galliani and C. Pantarotto, *Tetrahedron Lett.*, **24**, 4491 (1983).

84EUP(A)1 Schering Corp. (D. J. Blythin), Eur. Pat. Appl. 107165 (1984) [*CA* **101**, 72526 (1984)].

84JA6847 N. J. Leonard, R. S. Hosmane, Y. S. Agasimundin, L. J. Kostuba, and F. T. Oakes, *J. Am. Chem. Soc.*, **106**, 6847 (1984).

84JHC333 H. Griengel, W. Hayden, and A. Plessing, *J. Heterocycl. Chem.*, **21**, 333 (1984).

84TL3471 M. Olomucki, J. Y. Le Gall, S. Colinard, F. Durant, B. Norberg, and G. Evrad, *Tetrahedron Lett.*, **25**, 3471 (1984).

85JCS(P1)2347 K. Minamoto, H. Nakade, T. Tanaka, Y. Fijiki, and T. Sasaki, *J. Chem. Soc., Perkin Trans. 1*, 2347 (1985).

85JHC109 N. M. Brahme and W. T. Smith Jr., *J. Heterocycl. Chem.*, **22**, 109 (1985).

85JOC2468 Y. S. Agasimundin, F. T. Oakes, L. J. Kostuba, and N. J. Leonard, *J. Org. Chem.*, **50**, 2468 (1985).

85MI1 N. I. Romanenko, B. A. Priimenko, I. V. Fedulova, and A. Yu. Chervinskii, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **28**, 32 (1985) [*CA* **104** 129866 (1985)].

86AP566 A. Rudolph and R. Haller, *Arch. Pharm. (Weinheim)*, **319**, 566 (1986).

86CCC459 A. Holý, J. Kohoutová, A. Merta, and I. Votruba, *Collect. Czech. Chem. Commun.*, **51**, 459 (1986).

86CPB36 T. Ohsaki, T. Kuruki, and T. Ueda, *Chem. Pharm. Bull.*, **34**, 36 (1986).

86H2179 D. M. Solomon, D. J. Conn, Sh. Ch. Wong, and J. J. Kaminski, *Heterocycles*, **24**, 2179 (1986).

86JMC1099 D. J. Blythin, J. J. Kaminski, M. S. Domatski, J. Spitler, D. M. Solomon, D. J. Conn, Sh. Ch. Wong, L. L. Verbiar, and L. A. Bober, *J. Med. Chem.*, **29**, 1099 (1986).

86JOC3244 G. Sabbioni, S. R. Tannenbaum, and D. E. G. Shuker, *J. Org. Chem.*, **51**, 3244 (1986).

86KFZ427 N. I. Romanenko, I. V. Fedulova, B. A. Priimenko, B. A. Samura, L. M. Kapkan, A. Yu. Chervinskii, T. M. Pekhterova, and S. N. Garmash, *Khim.-Farm. Zh.*, **20**, 427 (1986) [*CA* **106** 18498 (1987)].

86MI1 N. I. Romanenko, B. A. Priimenko, N. A. Klyuev, and I. V. Fedulova, *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.*, **29** (6), 20 (1986) [*CA* **106** 176320 (1987)].

86MIP1 Schering Corp. (D. H. Solomon and J. J. Kaminski), PCT Int. Appl. 86 06724 (1986) [*CA* **110** 114850 (1989)].

86T6541 J. Kjellberg and N. G. Johansson, *Tetrahedron*, **42**, 6541 (1986).

87BOK204 V. S. Volkov, A. M. Poverennyi, and E. D. Sverdlov, *Bioorg. Khim.*, **13**, 204 (1987) [*CA* **107** 39761 (1987)].

87BOK1230 V. S. Volkov, A. M. Poverennyi, and E. D. Sverdlov, *Bioorg. Khim.*, **13**, 1230 (1987) [*CA* **108** 70770 (1988)].

87CPB4031 T. Ueda, T. Adachi, J. Sakakibara, M. Asano, and J. Nakagami, *Chem. Pharm. Bull.*, **35**, 4031 (1987).

87JCS(P2)733 W. M. Odijk and G. J. Koomen, *J. Chem. Soc., Perkin Trans. 2*, 733 (1987).

87KGS1398 I. V. Navayan, V. V. Kuzmenko, A. F. Pozharskii, and N. A. Klyuev, *Khim. Geterotsikl. Soedin.*, 1398 (1987) [*CA* **109** 6475 (1988)].

87KGS1551 V. V. Kuzmenko, A. F. Pozharskii, A. I. Chernyshev, and I. M. Navayan, *Khim. Geterotsikl. Soedin.*, 1551 (1987) [*CA* **109** 37675 (1988)].

87PHA371 M. Pawlowski, *Pharmazie*, **42**, 371 (1987).

87T365 G. Remaud, J. Kjellberg, N. G. Johansson, and J. Chattopadhyaya, *Tetrahedron*, **43**, 365 (1987).

88CCC319 D. Hesek, A. Rybár, F. Považanec, A. Martvoň, and J. Kováč, *Collect. Czech. Chem. Commun.*, **53**, 319 (1988).

88JHC791 T. Ueda, T. Adachi, Sh. Nagai, J. Sakakibara, and M. Murata, *J. Heterocycl. Chem.*, **25**, 791 (1988).

88JOC14 F. L. Chung, K. R. Roy, and S. S. Hecht, *J. Org. Chem.*, **53**, 14 (1988).

88JOC30 J. H. N. Meerman, P. G. Pearson, G. P. Meier, and S. D. Nelson, *J. Org. Chem.*, **53**, 30 (1988).

88JOC3265 D. J. Conn, J. J. Kaminski, D. M. Solomon, and A. T. Mc Phail, *J. Org. Chem.*, **53**, 3265 (1988).

88JOC3959 Sh. Kumar and N. J. Leonard, *J. Org. Chem.*, **53**, 3959 (1988).

88SC1299 D. Hesek and J. Svetlik, *Synth. Commun.*, **18**, 1299 (1988).

88UKZ531 V. P. Gnidets, V. P. Kruglenko, M. V. Povstyanoi, P. B. Kurapov, and I. I. Grundberg, *Ukr. Khim. Zh.*, **54**, 531 (1988) [*CA* **110** 75450 (1989)].

88UKZ1084 N. I. Romanenko, I. V. Fedulova, N. A. Klyuev, A. Yu. Chevinski, B. A. Priimenko, A. N. Stepanov, and A. A. Kremzer, *Ukr. Khim. Zh.*, **54**, 1084 (1988) [*CA* **111** 39298 (1989)].

89LA1251 V. Kalcheva, D. Stoyanova, and V. Simonova, *Liebigs Ann. Chem.*, 1251 (1989).

89MI1 A. Drabczynska, M. Pawlowski, M. Gorczyca, D. Malec, and J. Modzelewski, *Pol. J. Pharmacol. Pharm.*, **41**, 385 (1989) [*CA* **113** 204407 (1990)].

89S681 D. Hesek, M. Tegza, A. Rybár, and F. Považanec, *Synthesis*, 681 (1989).

90AG917 G. Kaup and K. Sailer, *Angew. Chem.*, **102**, 917 (1990).

90JMC2073 R. C. Young, M. Jones, K. J. Miliner, K. K. Rana, and J. G. Ward, *J. Med. Chem.*, **33**, 2073 (1990).

90KGS967 S. N. Garmash, E. A. Skul'skaya, B. A. Priimenko, and N. A. Klyuev, *Khim. Geterotsikl. Soedin.*, 967 (1990) [*CA* **114** 101884 (1991)].

90MI1 J. Karolak-Wojciechowski and M. Pawlowski, *Crystallogr. Spectrosc. Res.*, **20**, 477 (1990) [*CA* **114**, 42750 (1991)].

90MI2 P. G. Foiles, Sh. A. Akerkar, L. M. Miglietta, and F. L. Chung, *Carcinogenesis (London)*, **11**, 2059 (1990) [*CA* **114** 76760 (1991)].

90USP1 American Cyanamid Co. (J.I. Levin) US Pat. 4904658 (1990) [*CA* **113** 115336 (1990)].

91AX(C)1902 Z. Karczmarczyk, J. Karolak-Wojciechowska, and M. Pawlowski, *Acta Crystallogr., Sect. C*, **C47**, 1902 (1991).

91BMC531 Ch. Y. Ho and M. J. Kukla, *Bioorg. Med. Chem. Lett.*, **1**, 531 (1991).

91CPB270 T. Ueda, Y. Kawabata, N. Murakami, Sh. Nagai, J. Sakakibara, and M. Goto, *Chem. Pharm. Bull.*, **39**, 270 (1991).

91FES899 P. Pecorari, M. Rinaldi, L. Costantino, A. Provvisionato, and C. Cermeli, *Farmaco, Ed. Sci.*, **46**, 899 (1991).

91JMC421 Sh. Phadtare, D. Kessel, T. H. Corbett, H. E. Renis, E. Court, and J. Zemlicka, *J. Med. Chem.*, **34**, 421 (1991).

91MI1 M. Pawlowski, A. Drabczynska, M. Gorczyca, D. Malec, and J. Modzelewski, *Pol. J. Pharmacol. Pharm.*, **43**, 61 (1991) [*CA* **116** 34326 (1992)].

91S625 D. Hesek, A. Rybár, and J. Bella, *Synthesis*, 625 (1991).

91T6689 C. Glemarec, Ye. Besidski, J. Chattopadhyaya, J. Kusmierek, M. Lahti, M. Oivanen, and H. Lonnberg, *Tetrahedron*, **47**, 6689 (1991).

91TL5693 S. H. Krawczyk and L. B. Townsend, *Tetrahedron Lett.*, **32**, 5693 (1991).

92FES1315 M. Rinaldi, P. Pecorari, L. Costantino, A. Provvisionato, M. Malagoli, and C. Cermeli, *Farmaco, Ed. Sci.*, **47**, 1315 (1992).

92JMC4180 G. C. B. Harriman, A. F. Poirot, and E. Abushanab, *J. Med. Chem.*, **35**, 4180 (1992).

92JOC1579 P. Roques, J. Y. Le Gall, L. Lacombe, and M. Olomucki, *J. Org. Chem.*, **57**, 1579 (1992).

92JOC6335 J. B. Press, J. J. Mc Nally, Z. G. Hajos, and R. A. Sawyers, *J. Org. Chem.*, **57**, 6335 (1992).

92KFZ(9-10)63 D. B. Nilov, A. V. Kadushkin, S. G. Kalistratov, A. S. Sokolova, I. S. Nikolayeva, V. V. Peters, and L. Yu. Krylova, *Khim.-Farm. Zh.*, **26** (9–10), 63 (1992) [*CA* **119** 160226 (1993)].

92MI1 A. Drabczynska, M. Pawlowski, M. Gorczyca, D. Malec, and J. Modzelewski, *Pol. J. Pharmacol. Pharm.*, **44**, 487 (1992) [*CA* **119** 195099 (1993)].

93JHC241 J. Shimada, T. Kuroda, and F. Suzuki, *J. Heterocycl. Chem.*, **30**, 241 (1993).

93JHC593 T. Kuroda and F. Suzuki, *J. Heterocycl. Chem.*, **30**, 593 (1993).

93M1143 D. Hesek and A. Rybár, *Monatsh. Chem.*, **124**, 1143 (1993).

94AX(C)952 A. K. Das, M. Datta, S. K. Mazundar, G. Bhaumik, B. Mazundar, and S. K. Talapatra, *Acta Crystallogr., Sect. C*, **C50**, 952 (1994).

94JHC81 F. Gatta, M. R. Del Guindice, A. Borioni, and C. Mustazza, *J. Heterocycl. Chem.*, **31**, 81 (1994).

94M1273 D. Hesek and A. Rybár, *Monatsh. Chem.*, **125**, 1273 (1994).

94MI1 M. Pawlowski, A. Drabczynska, M. Gorczyca, D. Malec, and J. Modzelewski, *Acta Pol. Pharm.*, **51**, 385 (1994) [*CA* **123** 143853 (1995)].

94UKZ300 N. I. Romanenko, I. V. Fedulova, B. A. Priimenko, N. I. Serikov, and N. A. Klyuev, *Ukr. Khim. Zh.*, **60**, 300 (1994) [*CA* **123** 55798 (1995)].

95EJM587 E. Chojnacka-Wojcik, A. Klodzinska, A. Drabczynska, M. Pawlowski, S. Charakchieva-Minol, G. Chlon, and M. Gorczyca, *Eur. J. Med. Chem.*, **30**, 587 (1995).

95H1197 R. F. de Boer, D. G. I. Petra, M. J. Wanner, A. Boesaart, and G. J. Koomen, *Heterocycles*, **41**, 1197 (1995).

95JHC1725 M. R. Del Giudice, A. Borioni, C. Mustazza, and F. Gatta, *J. Heterocycl. Chem.*, **32**, 1725 (1995).

95KFZ(2)27 D. B. Nilov, A. V. Kadushkin, I. F. Kerbnikova, I. S. Nikolaeva, V. V. Peters, T. A. Gus'kova, R. A. Dubinskii, and V. G. Granik, *Khim.-Farm. Zh.*, **29** (2), 27 (1995) [*CA* **124** 29706 (1996)].

95PHA453 M. Pawlowski, A. Drabczynska, M. Gorczyca, D. Malec, and J. Modzelewski, *Pharmazie*, **50**, 453 (1995).

95S837 O. Šimo, A. Rybár, and J. Alföldi, *Synthesis*, 837 (1995).

96AX(C)2076 A. K. Das, M. Datta, S. K. Mazundar, G. Bhaumik, B. Mazundar, and S. K. Talapatra, *Acta Crystallogr., Sect. C*, **C52**, 2076 (1996).

96CCC442 Z. Janeba, A. Holý, H. Votavová, and M. Masojídková, *Collect. Czech. Chem. Commun.*, **61**, 442 (1996).

96JMC2529 G. Biagi, A. Costantini, L. Costantini, I. Giorgi, O. Livi, P. Pecorari, M. Rinaldi, and V. Seartoni, *J. Med. Chem.*, **39**, 2529 (1996).

96KFZ(3)49 N. I. Romanenko, I. V. Fedulova, B. A. Priimenko, N. A. Klyuev, T. A. Pereverzeva, B. A. Samura, and E. V. Aleksandrova, *Khim.-Farm. Zh.*, **30** (3), 49 (1996) [*CA* **125** 75931 (1996)].

96MI1 A. Gueiffier, O. Chavignon, S. Mavel, J. -M. Chezal, J. -C. Teulade, Y. Blache, and J. -P. Chapat, *Heterocycl. Commun.*, **2**, 241 (1996) [*CA* **125** 275811 (1996)].

96RTC99 D. G. I. Petra, R. F. de Boer, G. J. Koomen, N. J. Meeuwenoord, E. Kuyl-Yeheskiely, G. A. van der Marel, and J. H. Van Boom, *Recl. Trav. Chim. Pays-Bas*, **115**, 99 (1996).

97JMC3248 H. Sawanishi, H. Suzuki, Sh. Yamamoto, Y. Waki, Sh. Kasugai, K. Ohya, N. Suzuki, K. -I. Miyamoto, and K. Takagi, *J. Med. Chem.*, **40**, 3248 (1997).

97PHA279 M. Pawlowski, J. Katlabi, and E. Szneler, *Pharmazie*, **52**, 279 (1997).

98BMC2197 T. Kaiya, T. Saga, Y. Yamagata, and K. Kohda, *Bioorg. Med. Chem. Lett.*, **8**, 2197 (1998).

98H1673 T. Fujii and T. Itaya, *Heterocycles*, **48**, 1673 (1998).

98JHC135 T. Ueda, R. Oh, Sh. -I. Nagai, and J. Sakakibara, *J. Heterocycl. Chem.*, **35**, 135 (1998).

98TL3323 T. Yosief, A. Rudi, Z. Stein, I. Goldberg, G. M. D. Gravalos, M. Sleyer, and V. Kashman, *Tetrahedron Lett.*, **39**, 3323 (1998).

99CPB1322 H. Suzuki, H. Sawanishi, R. Yamamoto, and K. -I. Miyamoto, *Chem. Pharm. Bull.*, **47**, 1322 (1999).

99EJM167 M. Pawlowski, J. Katlabi, A. Drabczynska, B. Duszinska, S. Charakchieva-Minol, A. Deren-Wesolek, E. Tatarczynska, E. Chojnacka-Wojcik, M. J. Mokrosz, and A. J. Bojarski, *Eur. J. Med. Chem.*, **34**, 167 (1999).

99JMC947 S. Khullar, Ch. V. Varaprasad, and F. Johnson, *J. Med. Chem.*, **42**, 947 (1999).

99MI1 F. -L. Chung, R. G. Nath, M. Nagao, A. Nishikawa, G. -D. Zhou, and K. Randerath, *Mutat. Res.*, **424**, 71 (1999) [*CA* **130** 348231 (1999)].

99PHA876 F. Pinguet, S. Mavel, C. Galtier, and A. Gueiffier, *Pharmazie*, **54**, 876 (1999).

00CCC1109 K. Meszarosová, A. Holý, and M. Masojídková, *Collect. Czech. Chem. Commun.*, **65**, 1109 (2000).

00EOC3489 S. Rockitt, H. Duddeck, A. Drabczynska, K. Kiec-Kononowicz, *Eur. J. Org. Chem.*, 2000, 3489.

00JHC1033 O. Šimo, A. Rybár, and J. Alföldi, *J. Heterocycl. Chem.*, **37**, 1033 (2000).

00JMC4973 A. R. Beauglehole, S. P. Baker, and P. J. Scammells, *J. Med. Chem.*, **43**, 4973 (2000).

00MI1 K. M. H. Nizamuddin, M. K. Srivastava, and Sh. Tiwari, *Indian J. Chem. Sect. B*, **39B**, 853 (2000) [*CA* **134**, 280799 (2001)].

01BMC729 T. Takahashi and Y. Hashimoto, *Bioorg. Med. Chem. Lett.*, **11**, 729 (2001).

01CPB188 M. Suzuki, H. Sawanishi, K. Yamamoto, K. Yokogawa, and K. -I. Miyamoto, *Chem. Pharm. Bull.*, **49**, 188 (2001).

01JHC607 F. De Settimo, A. H. Marini, G. Pardi, G. Primofiore, S. Salerno, and F. Simorini, *J. Heterocycl. Chem.*, **38**, 607 (2001).

01JHC743 A. Z. Chowdhury and Y. Shibata, *J. Heterocycl. Chem.*, **38**, 743 (2001).

01KFZ172 E. V. Aleksandrova, P. M. Kochergin, and I. E. Valashek, *Khim.-Farm. Zh. (Engl. Ed.)*, **35** (3), 172 (2001) [*CA* **136** 216585 (2002)].

01MI1 K. Kiec-Kononowicz, A. Drabczynska, E. Pekala, B. Michalak, Ch. E. Miller, B. Schumacher, J. Karolak-Wojciechowska, H. Duddeck, H. S. Rokkit, and R. Wartchow, *Pure Appl. Chem.*, **73**, 1411 (2001).

01TL5941 D. Pappo, A. Rudi, and Y. Kashman, *Tetrahedron Lett.*, **42**, 5941 (2001).

02JMC3337 E. -M. Priego, J. von Kuenzel, A. P. Ijzerman, M. -J. Camarasa, and M. -J. Peres-Peres, *J. Med. Chem.*, **45**, 3337 (2002).

02JMC3440 Ch. E. Müller, M. Thorand, R. Qurishi, M. Diekman, K. A. Jacobson, W. L. Padgett, and J. W. Daly, *J. Med. Chem.*, **45**, 3440 (2002).

02MI1 L. V. Nechev, I. D. Kozekov, A. K. Brock, C. J. Rizzo, and T. M. Harris, *Chem. Res. Toxicol.*, **15**, 607 (2002) [*CA* **137** 63416 (2002)].

02SL155 M. -J. Peres-Peres, E. -M. Priego, M. -L. Jimeno, and M. -J. Camarasa, *Synlett*, 155 (2002).

Fluorine-Containing Heterocycles. Part III: Synthesis of Perfluoroalkyl Heterocycles Using Perfluoroolefins Containing a Reactive Group at the Double Bond

Georgii G. Furin

Novosibirsk Institute of Organic Chemistry, Siberian Division of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation

This chapter "Fluorine-containing heterocycles. Part III" is a continuation of the recently published Part I (03AHC(86)129) and Part II (04AHC(87)273) that are reviews on fluorine-containing heterocycles. Part III deals with the synthesis of fluorine-containing heterocycles using perfluoroolefins with unsaturated fragments at the multiple bond and mononucleophilic reagents. Major attention is paid to the use of intramolecular nucleophilic cyclization of the products of addition at the multiple bonds of the substituent.

I. Introduction

Recently, our understanding of the unique properties of fluorine compounds has increased and many new uses (92M1, 84M2, 79TSC(4)373, 95OPPI33, 81AHC1) have appeared. Regioselective replacement of a hydrogen atom in aromatic or heterocyclic systems by a perfluoroalkyl group can deeply influence the physical and biological properties of such molecules and this has encouraged the use of fluoroorganic compounds such as pharmaceuticals, chelating agents, agrochemicals, and also in space technology (93M3, 91FBC, 82BAFC). Fluorine-substituted pharmaceuticals, agrochemicals, dyes and polymers have already been commercialized. Many heterocyclic

ADVANCES IN HETEROCYCLIC CHEMISTRY
VOLUME 88 ISSN: 0065-2725 DOI: 10.1016/S0065-2725(04)88004-8

compounds have unique biological activities. Therefore, the introduction of fluorine atoms into heterocyclic compounds is expected to markedly enhance or dramatically change their biological activities (96CR1, 94ZOR1704, 98THS(2)355, 94AHC1, 95CEN39, 90YGK16, 93JPP05 04979, 78JOC950, 82JMC956, 90JOC4448).

The synthesis of compounds containing fluorine is one of the most important parts of fluoroorganic chemistry (96CR1, 94ZOR1704, 98THS(2)355, 94AHC1). Its development is related to the high biological activity, which has been found in some derivatives of fluorinated heterocycles, and also with the possibility of using them for the synthesis of other useful compounds.

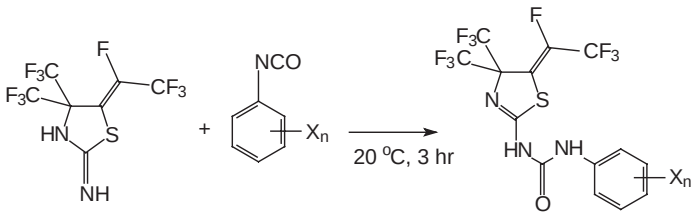
Key methods of the synthesis of heterocyclic compounds with perfluoroalkyl groups are based on two types of chemical transformations. The first type proceeds with an available heterocyclic system onto which the perfluoroalkyl group is entered. The second type includes construction of heterocyclic systems from blocks containing perfluoroalkyl groups or their fragments.

At the same time, the presence of fluorine atoms in starting materials allows a basis for the development of new methodologies for the formation of a new double bond in a molecule and construction of the heterocyclic system directly, and also provides new routes for the introduction of fluorine-containing functional groups. Double-bond generation is the key step of intramolecular cyclizations, especially if the process is conducted in the presence of a strong base. These processes have considerably expanded the possibilities for the preparation of heterocyclic compounds with perfluoroalkyl groups.

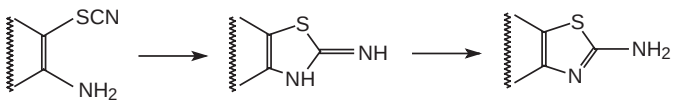
One such method uses the reaction of mononucleophilic reagents with perfluoroolefins containing functional groups at the multiple bond. The electrophilic multiple bonds of these groups serve as centers for nucleophilic addition, potentially generating new nucleophilic centers. The heterocyclic framework is then formed by intramolecular nucleophilic cyclization involving the multiple bond of the olefin and the new nucleophilic center. The functional groups can be SCN, N=C=S, C=O, etc. at the fluorinated multiple bond. The presence of the latter bond in the substrate is not indispensable. Rather, it is important that a multiple bond be generated in the α-position with respect to the functional group in the course of the reaction of the polyfluorinated compound with the nucleophilic reagent (98THS(2)355). Then the intramolecular nucleophilic cyclization will be governed by the nucleophilic center and the multiple bond in the fragment. This approach is applicable to the thiocyanate (SCN group) and isothiocyanate (N=C=S group) derivatives of perfluoroolefins (90YGK16). Due to the presence of these groups at the double bond of the heterocumulene residue, one can construct heterocyclic systems using mononucleophilic reagents.

II. Reactions of Thiocyanate and Isothiocyanate Derivatives of Fluoroolefins with N-Nucleophilic Reagents

Substrates of this type are derivatives of dithiocarbonic acid and heterocyclic compounds. Among the latter are the known effective pesticides based on



Scheme 1



Scheme 2

N-(thiozalin-2-yl)-N-2-phenylurea **1**. These are prepared by treatment of 2-imino-4,4-bis(trifluoromethyl)-5(tetrafluoroethylidene)-[1,3]-thiazoline **2** with aryl isocyanates (96CR1, 94ZOR1704, 98THS(2)355, 94AHC1) (Scheme 1).

Note that aromatic (α-aminothiocyanates) and aliphatic (enaminothiocyanates) compounds are widely employed in syntheses of thiazoles (87M73) (Scheme 2).

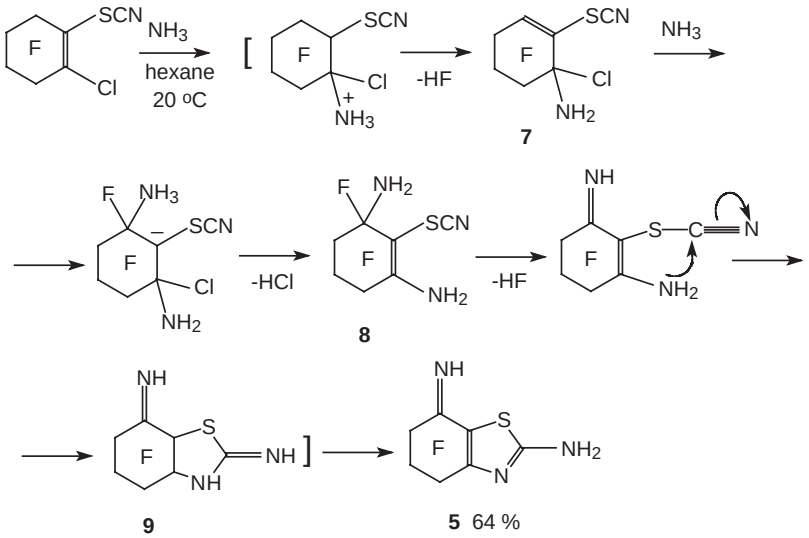
These transformations also proved to be characteristic of fluoroorganic derivatives (87M73, 92IZV343, 92AHC101, 91IZV2366). Aromatic aminothiothionate and aliphatic enaminothiocyanates are widely used for the synthesis of thiazoles and benzothiazoles (90YGK16). Among the latter are the known efficient pesticides (93JPP05 04979).

Syntheses of heterocyclic systems by cycloadditions and cyclocondensations of α,β-unsaturated isothiocyanates are well known. Additions of C- and N-nucleophiles to these compounds are regiospecific and form thioamides and thioureas. In the case of fluorinated α,β-unsaturated isothiocyanates, there are additional groups, namely, the highly electrophilic C═C double bond capable of a nucleophilic attack and mobile fluorine atoms in the allyl position.

Ammonolysis of 2-chloroperfluoro-1-cyclohexene-thio-cyanate **3** and perfluoro-2-methylpent-2-ene-3-thiocyanate **4** proceeds with intramolecular cyclization following the Thorn reaction, leading to fluorine-containing thiazoles. Indeed, the reaction of 2-chloroperfluoro-1-cyclohexene-thiocyanate and perfluoro-2-methylpent-2-ene-3-thiocyanate with gaseous ammonia gave 2-amino-7-iminoperfluoro-4,5,6-trihydro-ben-zo-1,3-thiazole **5**, 2-aminoperfluoro-4,4-dimethyl-4,5-dihydro-5-ethylidene-1,3-thiazole, and 2,4-diaminoperfluoro-4-methylpent-2-enethiocyanate-3 **6** in high yields (92HAC101) (Scheme 3).

The structure of compound **5** is confirmed by X-ray crystallography (92HAC101).

Successive addition of ammonia to the double bond at first gives compound **7** and then intermediate **8** and is followed in each case by the elimination of hydrogen halide (HF), finally giving diimine **9**. The combination of the amino group and the

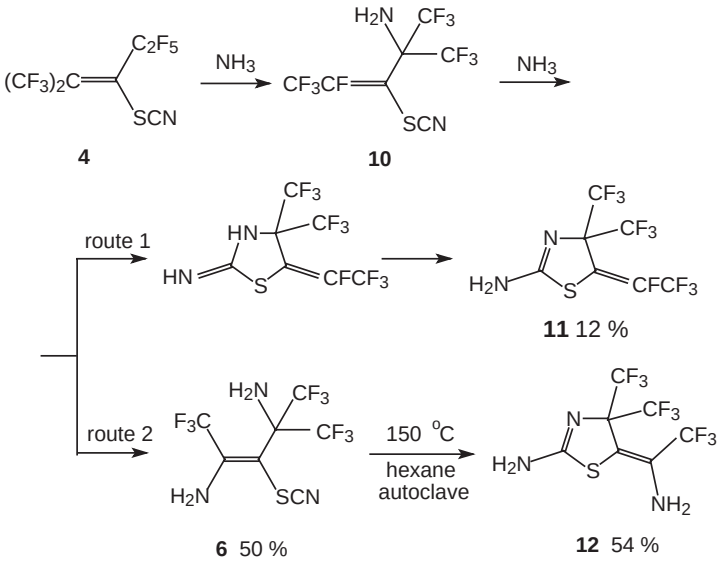


Scheme 3

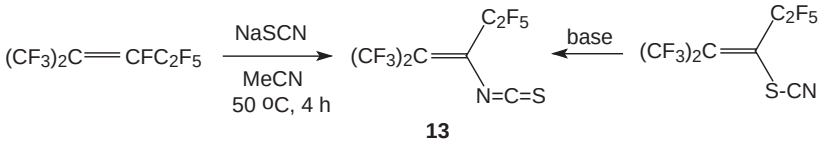
thiocyanate group in the β-position relative to the amino group in intermediate **8** leads to [1 + 5] intramolecular cyclization generating heterocyclic diimine **9**, stabilized in the form of amine **5**. The process is spontaneous and gives no intermediates, as reported in (92HAC101).

The nucleophilic attack of ammonia at the carbon atom of the double bond of compound **4** bearing two CF_3 groups forms β-aminothiocyanate **10**. Further transformations of this compound can follow one of two routes. Route 1 is intramolecular cyclization, which occurs as N-nucleophilic attack at the carbon of the thiocyanate group and forms (*E*)-2-amino-perfluoro-4,4-dimethyl-4,5-dihydro-5-ethylidene-1,3-thiazole **11** (83JCS(P1)1235) (Scheme 4). The reaction is stereospecific, and forms the *E*-isomer as the sole product **11** (XRD data) (92HAC101, 92IZV343). Route 2 is addition of ammonia at the C=C double bond with subsequent elimination of the fluoride ion, leading to the formation of 2,4-diamino-perfluoro-4-methylpent-2-ene-3-thiocyanate **6**, confirmed by X-ray analysis. Heating compound **6** in hexane at 150 °C (autoclave) for 7 h gave (*E*)-2-amino-4,4-bis-(trifluoromethyl)-4,5-dihydro-5-(1-amino-perfluoroethylidene)-1,3-thiazoline **12**, whose structure is also confirmed by X-ray data (92HAC101) (Scheme 4).

Consider the use of isothiocyanate perfluoroolefins in syntheses of heterocyclic compounds (77M3). Fluoroderivatives of α,β-unsaturated isothiocyanates have a highly electrophilic multiple C=C bond, capable of nucleophilic attack and mobile fluorine atoms in an allylic position. Such a structure substantially expands the synthetic opportunities for compounds of this class (92HAC101, 92IZV343). In the present review, the data on formation of a 1,3-thiazole skeleton with perfluoroalkyl groups are considered and generalized on the basis of the interaction of nucleophilic reagents with isothiocyanate derivatives of perfluoroolefins (94ZOR1704, 91IZV2366). α,β-Unsaturated isothiocyanates containing fluoro-substitutents



Scheme 4



Scheme 5

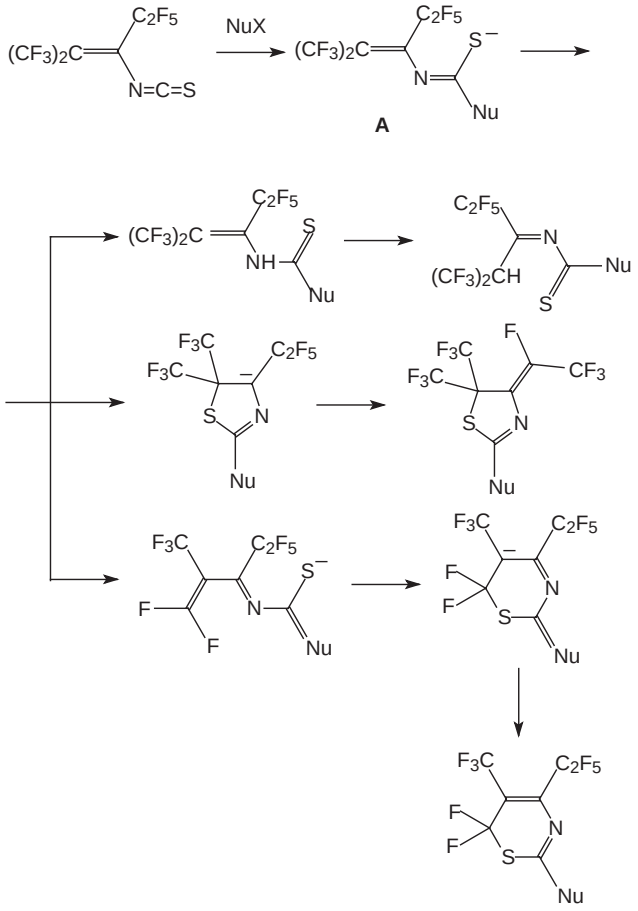
represent a preparatively useful building block for heterocyclic synthesis. It is known (69IZV1176) that the isothiocyanate group is rather reactive and enters into reaction with nucleophiles yielding additional products with a N═C connection.

Perfluoro-2-methyl-3-isothiocyanatopent-2-ene **13** was prepared by the reaction of perfluoro-2-methylpent-2-ene and sodium thiocyanate in acetonitrile (acetone, tetrahydrofuran, sulfolane, monoglyme) at 50 °C (yield 80%) or at 0 °C in benzonitrile (yield 93%) (95ZOR508), and isomerized to perfluoro-2-methyl-3-thiocyanatopent-2-ene in base (90IZV2599) (Scheme 5).

Another method for **13** is the isomerization of perfluoro-2-methyl-3-thiocyanatopent-2-ene under the action of bases involving the isomerization of the thermodynamically less stable isomer **4** to stable isomer **13**.

A. The Influence of the N-Nucleophile on the Construction of Five- and Six-Membered Heterocycles

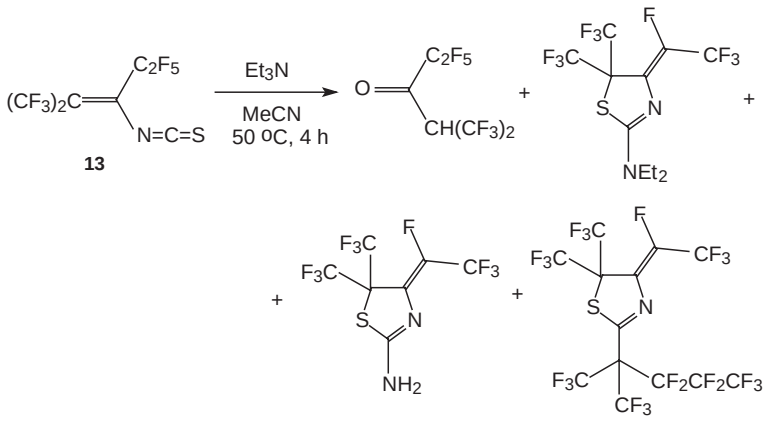
Due to the presence of a highly reactive N═C═S group directly bonded to the multiple bond in perfluoroolefin, the primary site of attack of the nucleophile occurs



Scheme 6

at the carbon atom of the N═C bond and generates thiolate nucleophile **A**. When amine-type nucleophiles are added to compound **13**, a perfluoroalkyl substituted 1-thia-3-azapentadienyl anion that has several options for stabilization, providing open-chain and heterocyclic compounds (pathways 1–3) (Scheme 6) is formed. The formation of the charged S-nucleophile from the thiocarbonyl group leads to the C═C–N═C–S conjugate system. Here, the intramolecular cyclization involves either the internal double bond, forming the five-membered ring or the terminal double bond, leading to the six-membered heterocycle (Scheme 6). If the generated S-nucleophile is not reactive enough, dithiocarbonic acid derivatives are formed (98UP1, 99JFC(95)141, 95JFC(75)131).

The nature of the nucleophilic reagent dictates the route of heterocyclic ring formation. This process demands the presence of a base, which plays a role in fluoride ion elimination. Usual bases include triethylamine (acetonitrile as solvent) and KOH (dimethylformamide as solvent).



Scheme 7

Triethylamine is also an active nucleophile capable of reacting at the carbon atom of the N═C═S group leading to a mixture of products. The reaction of perfluoro-2-methyl-3-isothiocyanato-pent-2-ene **13** with nucleophilic reagents gives a mixture among which 4,5-dihydrothiazoles are the major products (Scheme 7). The reaction, however, is sluggish and demands high temperatures.

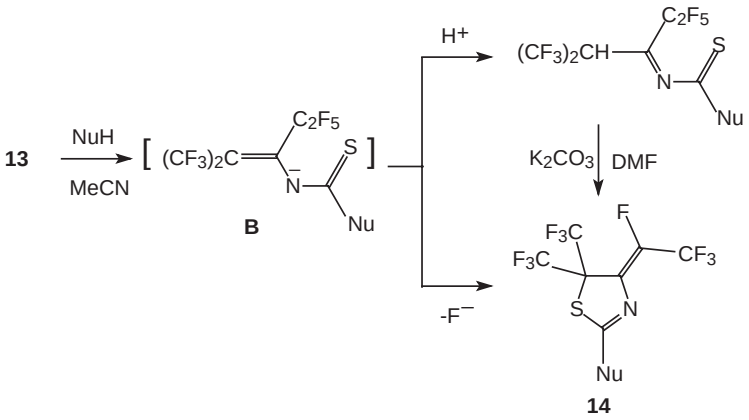
The isothiocyanate group is rather active; it reacts vigorously with nucleophilic reagents, giving additional products at the N═C bond. Even weak nucleophiles (water, alcohols) react with alkylisothiocyanates.

Due to the effect of the electron-accepting perfluoroalkenyl group, the reaction of **13** with water in tetrahydrofuran at 50 °C forms isomeric perfluoro-(2*H*-isopropyl)imines (1:1), liberating gaseous products (H_2S, CO_2, and COS) (95ZOR508). For reactions of **13** with nucleophilic reagents, therefore, it is recommended to use dry solvents.

The presence of a highly reactive N═C═S group directly bonded to the double bond in a perfluoroolefin leads to the primary attack of the nucleophile at the N═C bond, generating a S-nucleophile. Participation of the latter in further intramolecular nucleophilic cyclization involving the multiple bond forms a five-membered heterocyclic system. If the S-nucleophile is not active enough, the sole product is the derivative of dithicarbonic acid. For example, the reaction of perfluoro-2-methyl-pent-2-en-3-yl isothiocyanate with morpholine gave *N*-[1-pentafluoroethyl-2,2-bis(trifluoromethyl)-propylidene]-1-morpholine carbothioamide, whose crystal structure is confirmed by X-ray analysis (Scheme 8). Under alkaline conditions in bipolar aprotic solvents, these compounds generate an S-nucleophile, which adds at the multiple bond, giving the dihydrothiazole derivative **14** (78JFC193).

The interaction of **13** with the C-nucleophile generated from 1-methyl-indole, 1-morpholinocyclohexene-1, 1-morpholinocyclo-pent-1-ene, or 2-methyl-1-morpholino-prop-1-ene forms isomeric derivatives of 4,5-dihydrothiazole (92JFC(58)343) (Scheme 9).

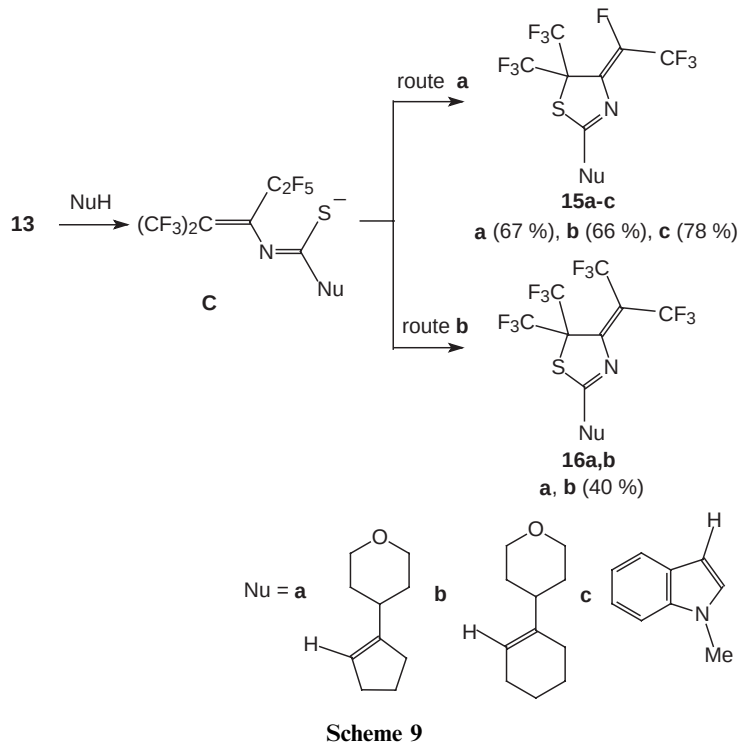
The reaction of **13** with *N*-methylbenzindole via 1-thia-3-azapentadienyl anion **D**, formed as an intermediate by intramolecular cyclization yields an isomer with an



NuH = C_2H_5OH, $HC(O)N(CH_3)_2$, H_2O

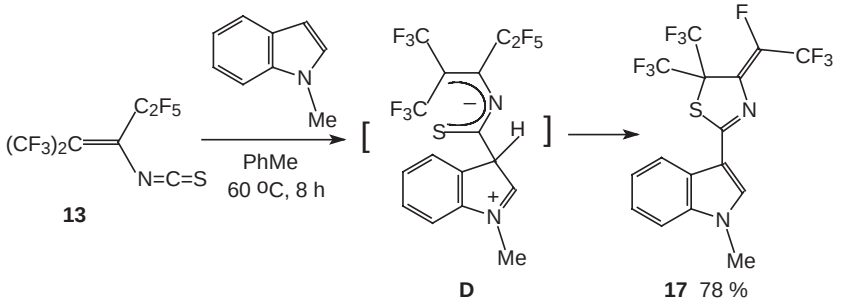
Nu = $^-OC_2H_5$, NMe_2

Scheme 8

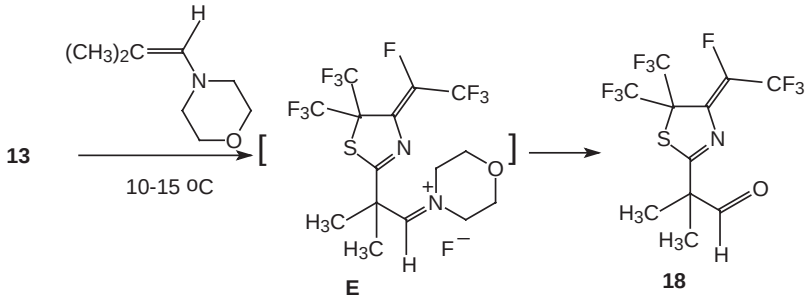


Scheme 9

E-configuration, which is less sterically hindered because of the interaction of the $(CF_3)_2C$ and CF_3 groups, (*E*)-3-[5,5-bis(trifluoro-methyl)-4-(2,2,2-trifluoro-1-trifluoromethyl-ethylidene)-4,5-dihydrothia-zol-2-yl]-1-methyl-1*H*-indole **17** (94H1015, 92JFC(58)343) (Scheme 10).



Scheme 10



Scheme 11

The intramolecular nucleophilic cyclization can occur by one of the two routes. In the first route, the S-nucleophile attacks the carbon atom of the multiple bond to give dihydrothiazole **17**. In the second route, nucleophilic substitution of the fluorine atom of the CF_2 group at the multiple bond takes place, forming another derivative of a dihydrothiazole. The latter route is interesting and unusual, because nucleophilic substitution of a fluorine in the aliphatic chain is not typical. An important role is probably played by the double bond in the α-position, affecting the mobility of fluorine (94H1015).

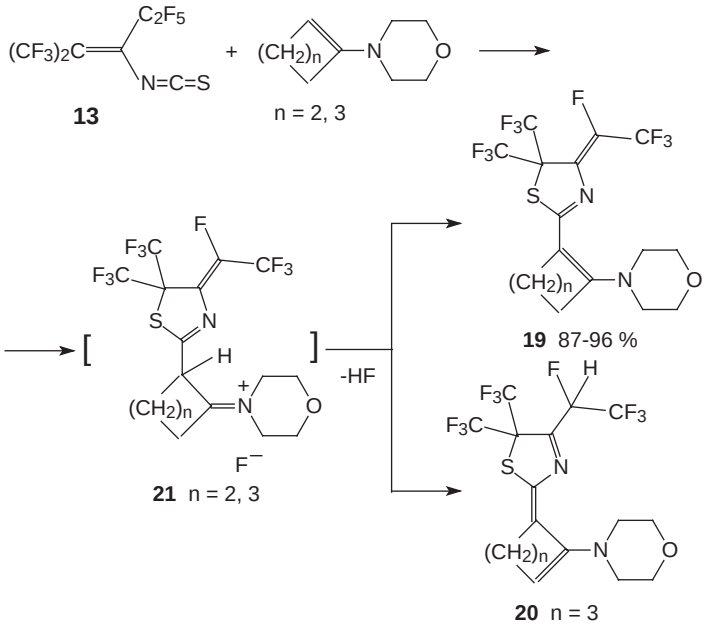
An analogous reaction between perfluoro-2-methylpent-2-en-3-yl-isothiocyanate **13** and 2-methyl-1-morpholinoprop-1-ene forms iminium salt **E** as a [1 + 5] cycloaddition product (94H1015). Hydrolysis of salt **E** yields the stable 2-[5,5-bis(trifluoromethyl)-4(2,2,2-trifluoro-1 trifluoro-methylethylidene)-4,5-dihydrothiazol-2-yl]-2-methylpropion-aldehyde **18**, which is of interest as a building unit for the syntheses of heterocyclic compounds by reactions of the aldehyde group (Scheme 11).

1-Morpholino-1-cyclohexene and 1-morpholino-1-cyclopentene react with perfluoro-2-methylpent-2-en-3-yl isothiocyanate to afford either the individual [1,3]-thiazolidines **19** or isomer mixture **20**, depending on the reaction conditions (Table 1) (94H1015).

When the reaction is performed in acidic media with equimolar amounts of reagents, only thiazolines **19** forms with high yields. In contrast, in basic media, the 1:2 ratio of reagents (at –5–0 °C) leads to a mixture of isomers **20** (13 and 87%,

Table 1. Ratio of isomers **19** and **20** depending on the reaction conditions, (94H1015).

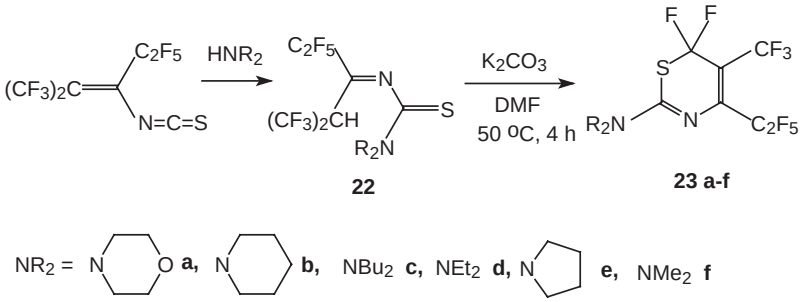
Substrate/enamine	Solvent	Temperature (°C)	Content (%)	
			19	**20**
1	—	2–20	92	8
1:2	Hexane	30–35	69	31
1:2	Acetonitrile	0–2	84	16
1:2	Et_2O	−5–0	13	87
1:1	Et_2O	−5–0	100	—



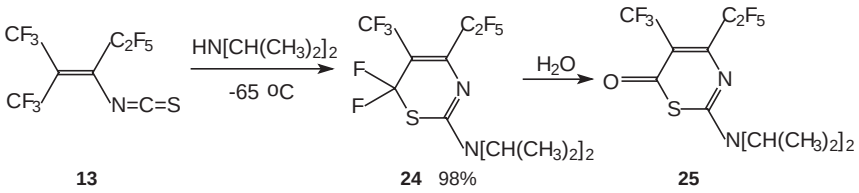
Scheme 12

respectively). The isomers presumably form immonium salt **21** via the common intermediate. This salt may be stabilized by deprotonation giving **19** and **20** (Scheme 12). The structures of **19** and **20** were confirmed by X-ray analysis (96JFC131); compound **20** has the *Z*-configuration.

The reaction with secondary amines unexpectedly led to a six-membered heterocycle instead of the five-membered one. The reactions of **13** with morpholine, pyrrolidine, piperidine, butylamine, and dimethylamine in acetonitrile initially give adducts, among which propylidenethioureas **22** proved to be more stable than propenylthioureas under these conditions. Heating **22** in dimethylformamide with KOH at 50 °C yielded six-membered 1,3-thiazines **23** (99ZOB1499, 99ZOR1481, and 97ZOR787) (Scheme 13). A similar effect on cyclization is produced by triethylamine.



Scheme 13

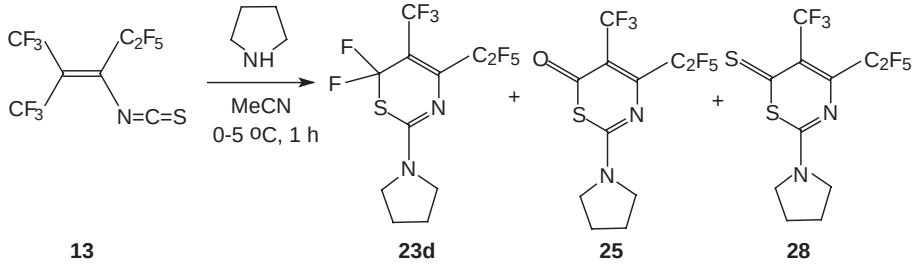


Scheme 14

For example, the reactions of perfluoro-2-methylpent-2-en-3-yl isothio-cyanate **13** with morpholine (97ZOB782) and dimethylamine (99ZOR1481) in the presence of triethylamine give 6,6-difluoro-2-morpholino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]-thiazine **23a** and 6,6-difluoro-2-dimethylamino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]-thiazine **23f** (99ZOB1499, 99ZOR1481, 97ZOR787), respectively. The formation of a derivative of 2-isopropylamino-6H[1,3]-thiazine **24** was also reported (92HAC101, 95JFC(75)131) for the reaction of compound **13** with isopropylamine (yield 98%) (Scheme 14). In this compound, the CF_2 group very easily undergoes hydrolysis to give 2-diisopropylamino-4-pentafluoro-ethyl-5-trifluoromethyl-1,3-thiazin-6-one (compound **25**) on prolonged standing in air or during column chromatography on silica gel. The structure of **25** has been proven by X-ray analysis (95JFC(75)131).

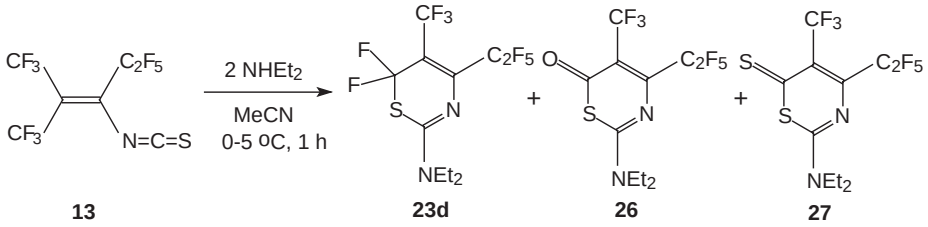
The reaction of **13** with diethylamine and pyrrolidine also forms other derivatives of 6H-[1,3]-thiazine; thus, hydrolysis led to 2-diethylamino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]-thiazin-6-one **25** and 2-pyrrolidino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]-thiazin-6-one **26** (Schemes 15 and 16). Unexpectedly, the reaction also gave 2-diethylamino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]-thiazine-6-thione **27** and 2-pyrrolidino-4-pentafluoroethyl-5-trifluoro-methyl-6H-[1,3]-thiazine-6-thione **28**. The structure of **25** and **28** is confirmed by X-ray analysis (Figure 1) (97IZV1355, 97ZOR787).

Based on these data, one can postulate that the character of the substituent at the thiocarbonyl group is the critical factor governing the direction of the intramolecular nucleophilic cyclization. Thus, in reactions of **29** with bases, the CH_2 groups of substituents R stabilize the positive charge on the nitrogen of the $C{=}NR_2^+$ bond,



13 **23d** **25** **28**

Scheme 15



13 **23d** **26** **27**

Scheme 16

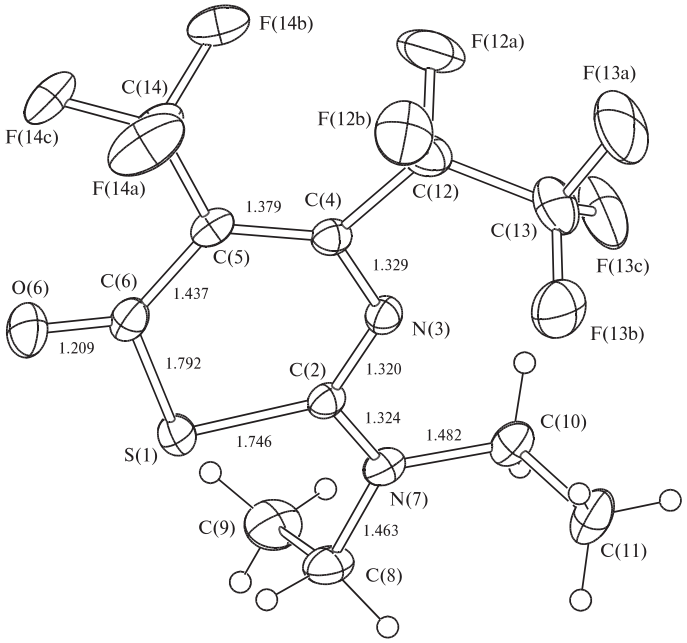
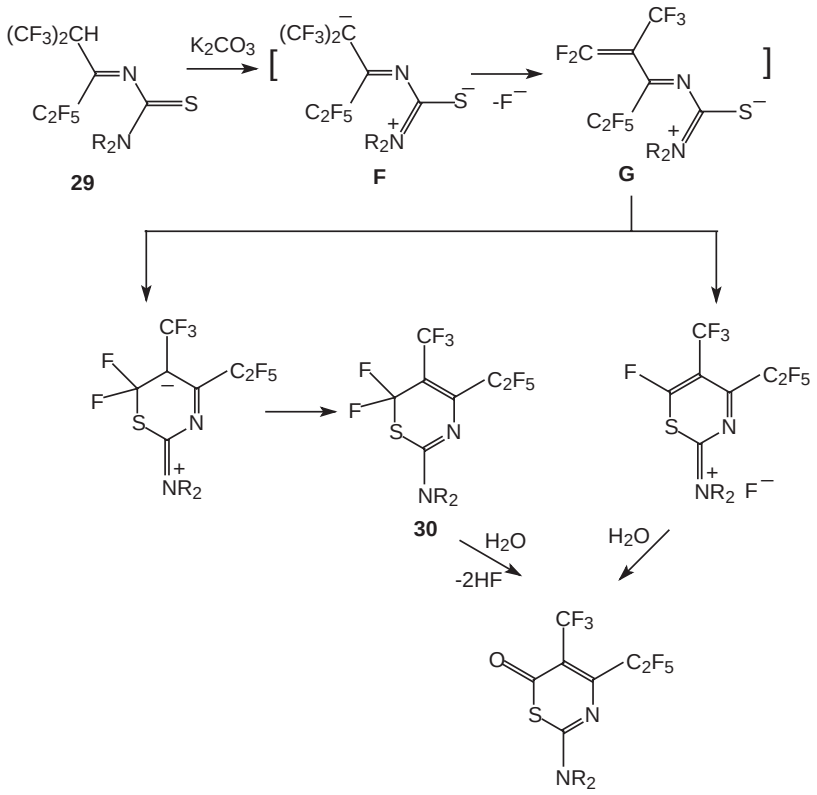


Figure 1. Structure of 2-diethylamino-4-pentafluoroethyl-5-trifluoromethyl-6*H*-[1,3]-thiazin-6-one **26**.

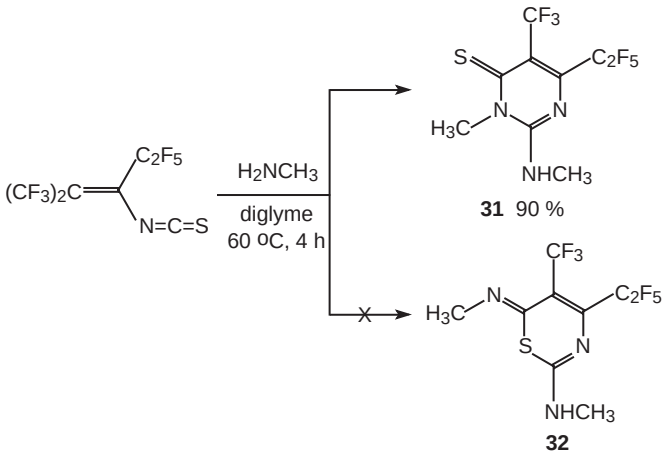


Scheme 17

generating a system of C═C–C═N multiple bonds and a charged S-nucleophile (intermediates **F** and **G**). In intermediate **G**, a terminal multiple bond is formed. Intramolecular nucleophilic cyclization under the action of an S-nucleophilic center at the terminal multiple bond leads to the six-membered heterocycle **30** (Scheme 17).

The reaction of perfluoro-2-methylpent-2-en-3-yl isothiocyanate **13** with excess methylamine in diglyme leads to 3-methyl-2-methylamino-6-penta-fluoroethyl-5-trifluoromethyl-3H-pyrimidine-4-thione **31**, but not to 2-methylamino-6-methylimino-4-pentafluoroethyl-5-trifluoromethyl-6H-[1,3]-thiazine **32** (97IZV1355) (Scheme 18). The structure of **31** is confirmed by X-ray analysis (Figure 2) (97IZV1355).

One can suggest the following route for the formation of compound **31** (Scheme 19). Methylamine initially attacks the carbon atom of the N═C═S group to form anion H, stabilized by fluoride ion elimination and transformed into compound **33**. Under conditions of basic catalysis with triethylamine, compound **33** generates anion I that undergoes intramolecular nucleophilic cyclization into **34** (Scheme 19). This compound has a very mobile fluorine atom at the double bond; in its reaction with methylamine, it is transformed into compound **35**. Recyclization of this compound via intermediate **J** leads to compound **31**.



Scheme 18

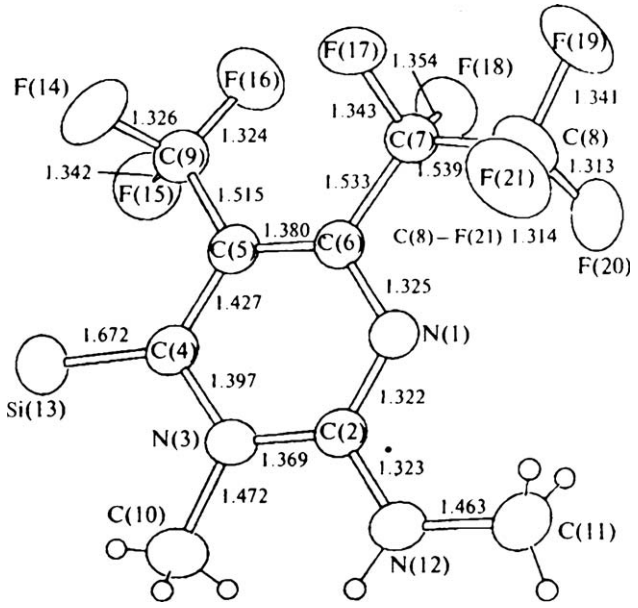
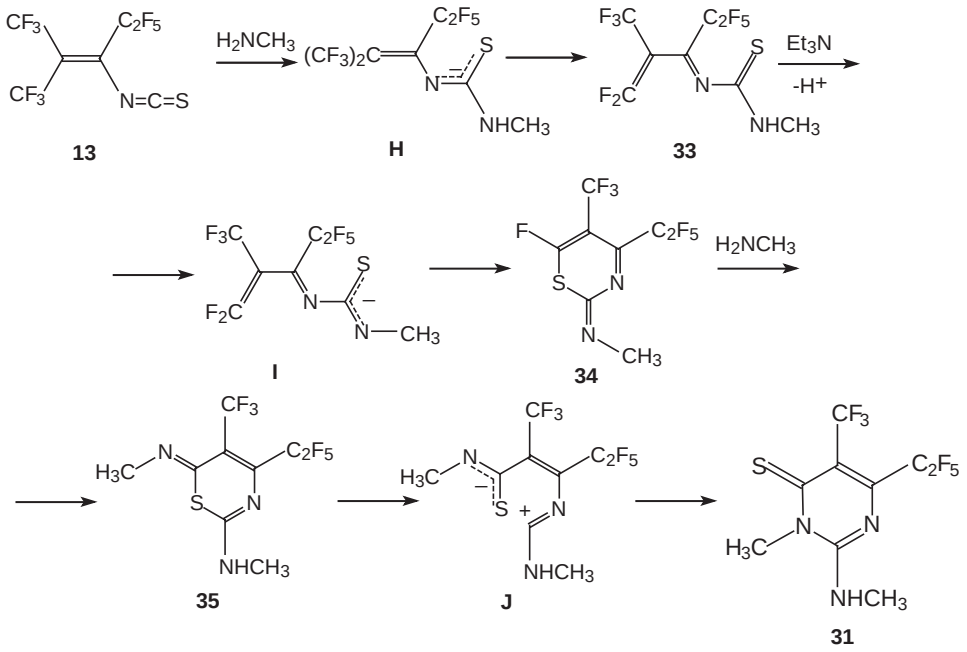


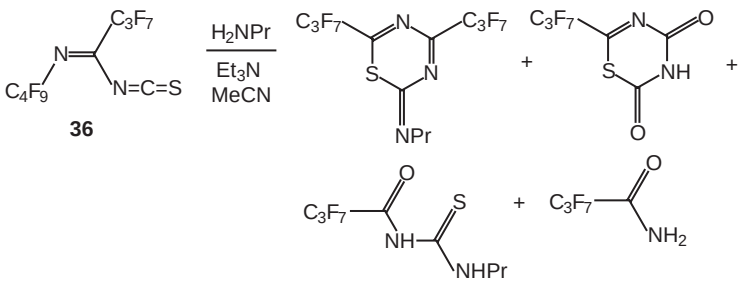
Figure 2. Structure of 3-methyl-2-methylamino-6-pentafluoroethyl-5-trifluoromethyl-3H-pyrimidine-4-thione **31** (97IZV1355).

On interaction of compound **36** and propylamine in the presence of triethylamine in acetonitrile, the mixture of products results (Scheme 20).

The reactions of perfluoro-2-methylpent-2-en-3-yl isothiocyanate with azoles in acetonitrile in the presence of an equimolar amount of triethylamine give five-membered heterocycles **37a–d** (derivatives of 4,5-dihydrothiazole[1,3]), whereas



Scheme 19

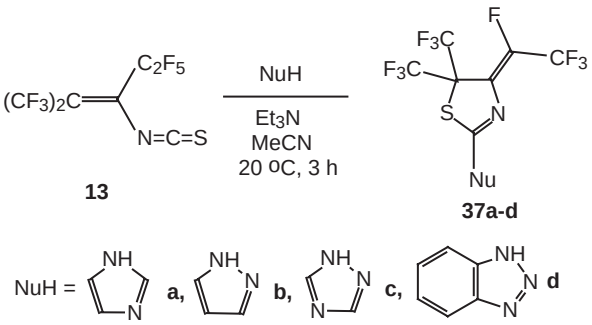


Scheme 20

similar reactions with secondary amines produce six-membered [1,3]-thiazines (derivatives of Δ^2-1,3-thiazole) (97ZOR777) (Scheme 21). The structure of 1[4-(1,2,2,2-tetrafluoro-ethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydrothiazol-2-yl-1*H*[1.2.4]-thiazole **37c** is confirmed by X-ray analysis (Figure 3) (97ZOR777).

The reaction of perfluoro-2-methylpent-2-en-3-yl isothiocyanate with pyrrole leads to the formation of 1,2-bis[4-tetrafluoroethylidene-5,5-bis(trifluoro-methyl)-4,5-dihydrothiazol-2-yl]pyrrole (97ZOR777), whose structure is confirmed by X-ray analysis (Figure 4) (97ZOR787).

The reaction of perfluoro-2-methylpent-2-en-3-yl isothiocyanate with carbazole, phenothiazine, 2-pyrrolidone, ammonia, or methylamine affords various 2-substituted derivatives of perfluoro(4-ethylidene-5,5-dimethyl-4,5-dihydrothiazole), opening up



Scheme 21

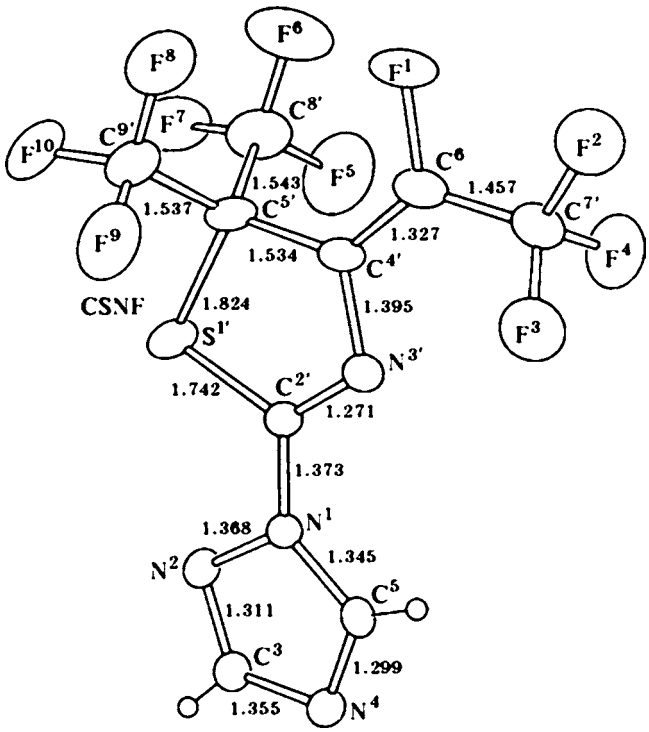


Figure 3. Structure of 2-(1,2,4-thiazol-1-yl)-4-tetrafluoroethylidene-5,5-bis(trifluoromethyl)-4,5-dihydrothiazole **37c** according to X-ray analysis (97ZOR777).

possibilities for extensive studies of the biological activity of this class of compounds (97ZOR787, 97IZV831) (Scheme 22).

The reactions of some 2-substituted 4,5-dihydrothiazoles with nitrogen-containing nucleophilic reagents led to new derivatives (97IZV831, 01IZV1027). Thus, compounds **39a**–**g** were synthesized from **37a** under the action of nucleophiles (Scheme 23). The structure of 2-amino-4(1,2,2,2-tetrafluoro-ethylidene)-5,5-bis

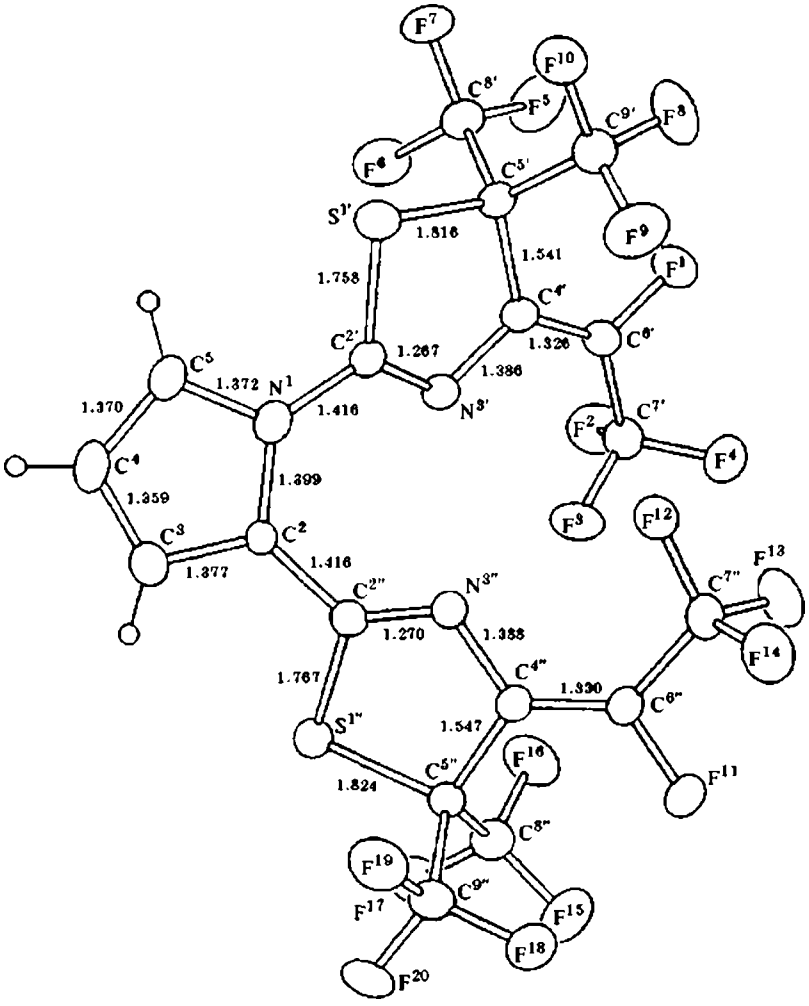
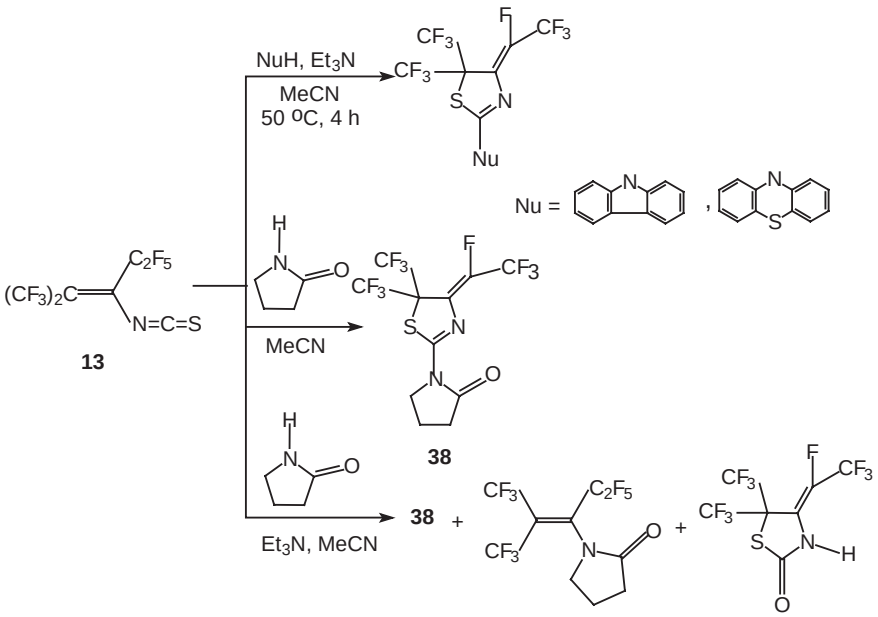


Figure 4. Structure of 1,2-bis[4-tetrafluoiroethylidene-5,5-bis(trifluoro-methyl)-4,5-dihydro-thiazol-2-yl]pyrrole according to X-ray analysis (97ZOR787).

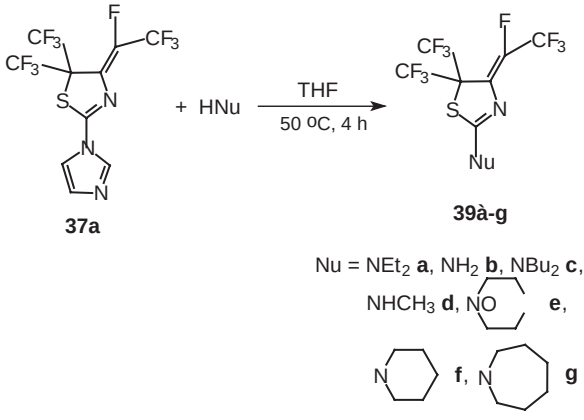
(trifluoromethyl)-4,5-dihydrothiazole **39b** is confirmed by X-ray analysis (Figure 5) (97ZOR787). Compound **39b** is obtained also by the interaction of perfluoro-2-methyl-2-pentene-3-yl-thiocyanate with ammonia (92HAC101).

Isomeric compound **39b** (2-amino-5-tetrafluoroethylidene-4,4-bis(trifluoro-methyl)-4,5-dihedrothiazole) is obtained by the interaction of perfluoro-2-methyl-2-pentene with thiourea (93KGK253, 97IZV831). The structure of both compounds is confirmed by X-ray analysis (93KGK253, 92HAC101).

At the initial stage, the N-nucleophile presumably adds at the C═N bond of **37a**, forming zwitterion **K** (Scheme 24). Transformation of the latter into zwitterion **L** by proton transfer leads to reaction products **39a–g** due to the elimination of imidazole.



Scheme 22



Scheme 23

The reaction of perfluoro-2-methylpent-2-en-3-yl isothiocyanate with 2-pyrrolidine in the presence of triethylamine forms a small amount of 4-tetrafluoroethylidene-5, 5-bis(trifluoromethyl)-tetrahydrothiazolone, whose structure is confirmed by X-ray analysis. Other products are 2-([1,2,4]-thiazol-1-yl)-4-tetrafluoro-ethyledene-5, 5-bis(trifluoromethyl)-4, 5-dihydro-thiazole and 1,2-bis[4-tetrafluoroethyledene-5,5-bis(trifluoromethyl)-4,5-dihydrothiazol-2-yl]pyrrole (01IZV1027). Triethylamine possibly acts as a nucleophile (since 2-pyrrolidone is a weak nucleophile) reacting

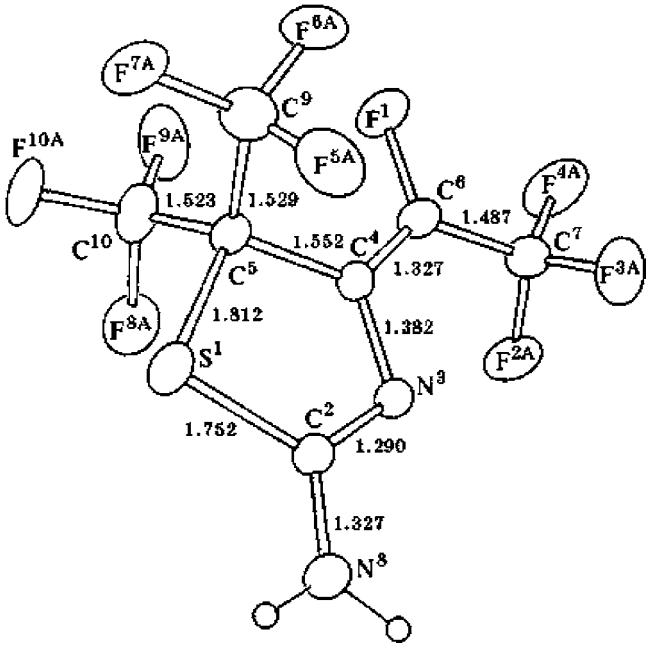
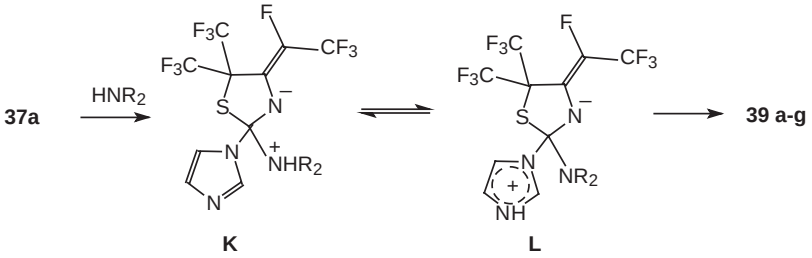


Figure 5. Structure of 2-amino-4-tetrafluoroethylidene-5,5-bis(trifluoro-methyl)-4,5-dihydro-thiazole **39b** according to X-ray analysis (97ZOR787).

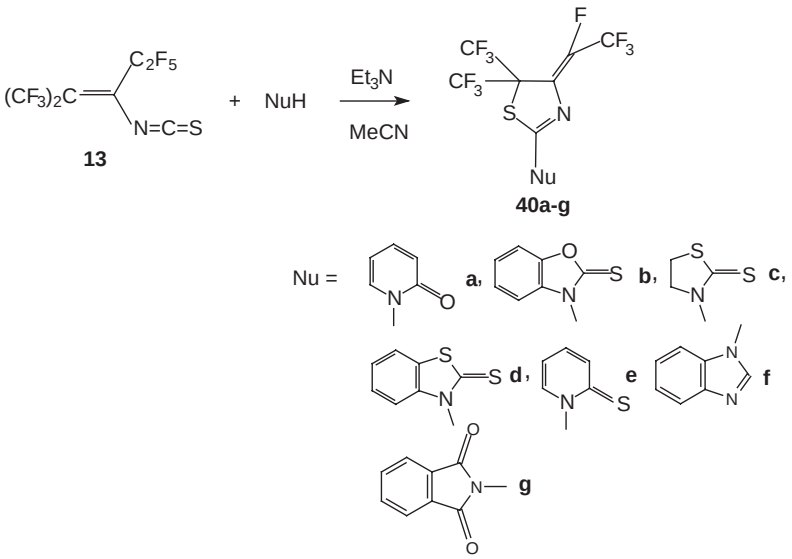


Scheme 24

at the carbon atom of the isothiocyanate group. The direction of cyclization depends on the type of the carbon skeleton and the nature of substituents in the nucleophile.

In the case of binucleophilc reagents, it is important to correctly determine the nucleophilic center that is responsible for the primary formation of the product, preceding the intramolecular nucleophilic cyclization. For N,S- and N,O-binucleophiles reacting with perfluoro-2-methylpent-2-en-3-yl isothiocyanate, the primary attack always occurs through the N-nucleophilic center (97IZV831).

In the reactions of perfluoro-2-methylpent-2-en-3-yl isothiocyanate with heterocyclic binucleophiles, the primary step is the attack of the N-nucleophilic center at



Scheme 25

the carbon atom of the N═C═S group, forming the corresponding anion (01IZV1027). The next step is intramolecular nucleophilic cyclization by the S-nucleophilic center, leading to 2-N-substituted derivatives of 4,5-dihydrothiazole **40a**–**g** (Scheme 25).

The reaction of perfluoro-2-methylpent-2-en-3-yl isothiocyanate with 2-mercaptothiazole and 2-mercaptopyridine in the presence of triethylamine in acetonitrile at –10 °C leads to 3-[4(*E*)-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-[2,3′]]-dithiazole-2′-thione and 1-[4(*E*)-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydro-thiazolyl-2-yl]-1*H*-pyridine-2-thione, respectively (97IZV831).

It was established (97IZV831) that the interaction of perfluoro-2-methyl-pent-2-en-3-yl isothiocyanate with 2-pyridinone in the presence of triethylamine in acetonitrile yields the N-substituted derivative of thiazoline (*E*)-1-[4-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoro-methyl)-4,5-dihydro-thiazol-2-yl]-pyridin-2-one **40a**, whose structure is confirmed by X-ray data (Figure 6) (02IZV1027) (Scheme 25).

When perfluoro-2-methylpent-2-en-3-yl isothiocyanate reacts with 2-mercaptobenzothiazole and 2-mercaptobenzoxazole in the presence of triethylamine in acetonitrile, the products are 3-[4(*E*)-(1,2,2,2-tetrafluoro-ethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydrothiazol-2-yl]-3*H*-benzo-thiazole-2-thione and 1-[4(*E*)-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(tri-fluoromethyl)-4,5-dihydrothiazol-2-yl]-3*H*-benzothiazole-2-thione, respectively, whose structure is confirmed by X-ray analysis (Figures 7 and 8).

It is conceivable that compound **40a** is formed according to Scheme 26 below. At the initial step, the N-nucleophilic center of 2-hydroxypyridine attacks the carbon atom of the N═C═S group, forming anion **M**.

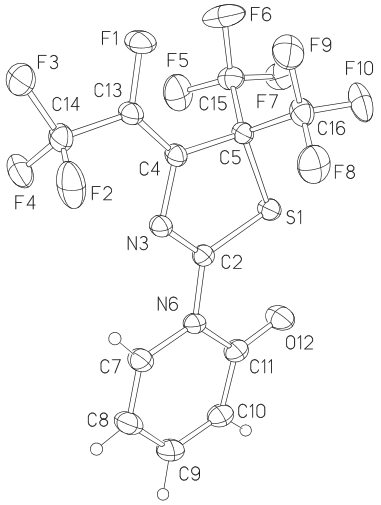


Figure 6. Structure of 1-[4(*E*)-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoro-methyl)-4,5-dihydrothiazol-2-yl]-1*H*-pyridine-2-one **40a** according to X-ray analysis (01IZV1027).

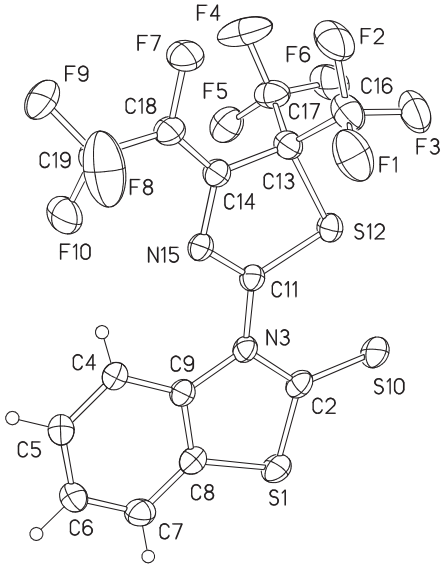


Figure 7. Structure of 1-[4(*E*)-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoro-methyl)-4,5-dihydrothiazol-2-yl]-3*H*-benzooxsazol-2-thion **40d** according to X-ray analysis (01IZV1027).

The next step is intramolecular nucleophilic cyclization, leading to heterocyclic compound **40a** via carbanion **N**. Thus the reactions of N,O-and N,S-ambident nucleophiles with perfluoro-2-methylpent-2-en-3-yl isothiocyanate give 2-substituted derivatives of 4,5-dihydrothiazole as the sole products.

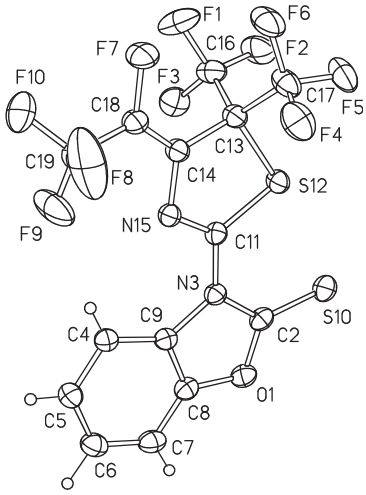
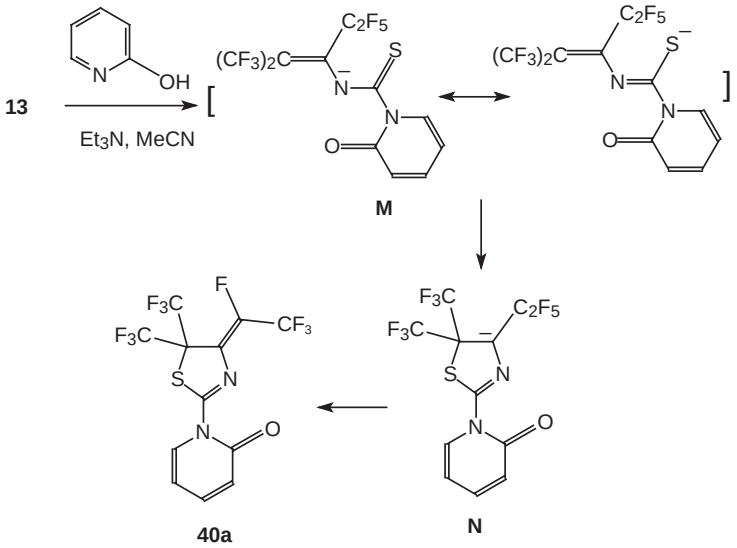
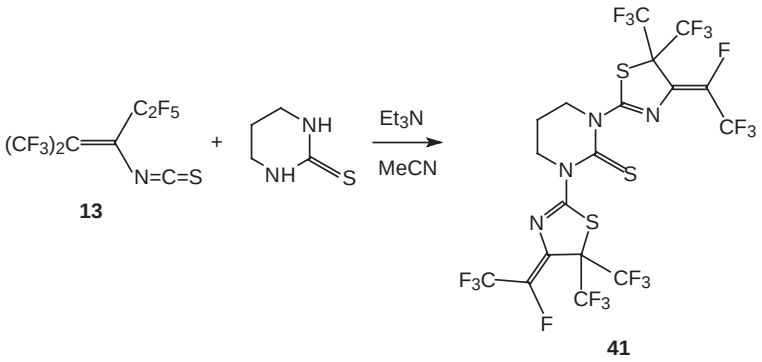


Figure 8. Structure of 3-[4(*E*)-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoro-methyl)-4,5-dihydrothiazol-2-yl]-3*H*-benzothiazol-2-thione **40b** according to X-ray analysis (01IZV1027).

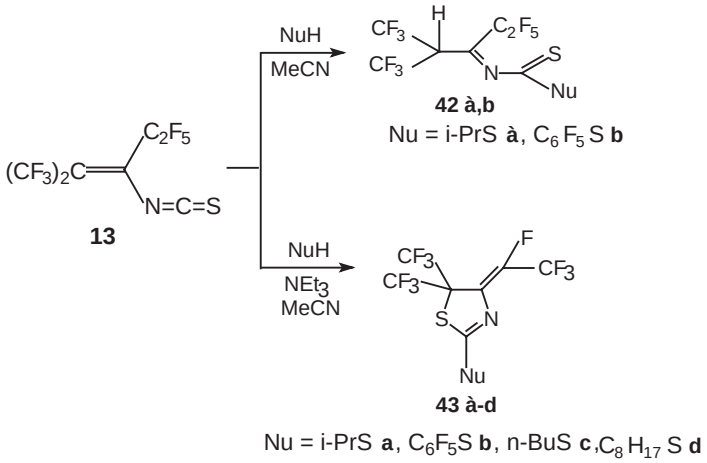


Scheme 26

At the same time, when perfluoro-2-methylpent-2-en-3-yl isothiocyanate **13** reacts with 3,4,5,6-tetrahydro-2-mercaptopyrimidine in the presence of triethylamine in acetonitrile at –20 °C, the product is 1,3-bis-[4(*E*)-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydrothiazol-2-yl]-tetrahydropyrimidine-2-thione **41**, indicating that perfluoro-2-methylpent-2-en-3-yl isothiocyanate is attacked by both N-nucleophilic centers (Scheme 27).



Scheme 27



Scheme 28

B. Synthesis of Derivatives of 4,5-Dihydro-[1,3]Thiazoles or Interaction of S-, O- and P-Nucleophilic Reagents and Perfluoro-2-Methyl-2-Pentene-3-Ylisothiocyanate

In the case of S-nucleophiles, generation of the charged S-nucleophilic center from the thiocarbonyl group leads to the formation of a C=C–N=C–S system. Here intramolecular cyclization can involve either the internal double bond, leading to a five-membered ring, or the terminal double bond, producing a six-membered ring (97ZOB782).

The action of S-nucleophilic reagents on perfluoro-2-methylpent-2-en-3-yl isothiocyanate **13** smoothly gives 2-substituted derivatives of 4,5-dihydro-[1,3]-thiazole, irrespective of the nature of the nucelophilic reagent. This reaction was performed with both neutral (alkylmercaptans, pentafluorothiophenol, and

2-mercaptobenzimidazole) and charged (sodium *N*,*N*-diethyldithiocarbamate, potassium ethyl, and methylxanthates) S-nucleophiles, and also with alkylmercaptans and pentafluorothiophenol in the presence of triethylamine and K_2CO_3 as bases (99ZOB1491).

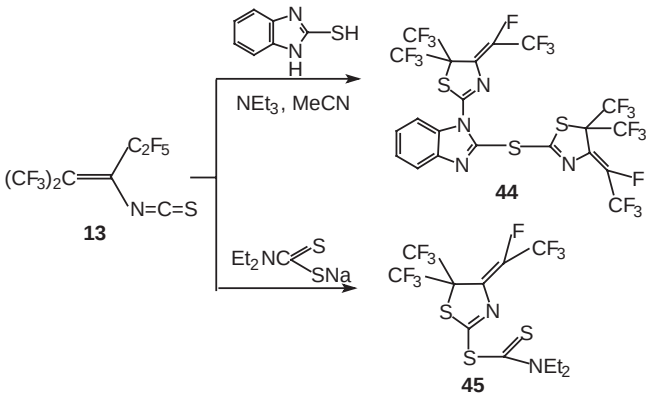
Perfluoro-2-methylpent-2-en-3-yl isothiocyanate **13** reacts smoothly with isopropylmercaptan and pentafluorothiophenol in acetonitrile at 40–50 °C, forming isopropyl and pentafluorothiophenyl *N*-(perfluoro-2-methyl-2*H*-pent-3-ylidene) dithiocarbamic ethers **42a,b** (Scheme 28). In the case of the reaction of **13** with isopropyl- (octyl-, butyl-)mercaptan in acetonitrile in the presence of triethylamine, the products are 2-isopropyl-(octyl-,butyl-)thio-(perfluoro-5,5-dimethyl-4-ethylidene)-4,5-dihydro-1,3-thiazoles **43b–d** (99ZOB1491).

With 2-mercaptobenzimidazole in the presence of triethylamine in aceto-nitrile, **13** forms 1(perfluoro-5,5-dimethyl-4-ethylidene-4,5-dihydrithiazol-2-yl)-2(perfluoro-5,5-dimethyl-4-ethylidene-4,5-dihydrothiazol-2-ylthio)-benzimidazole **44** (Scheme 28). 2-Mercaptobenzimidazole is an ambident nucleophile, leading to two dihydrothiazole rings (99ZOB1491) (Scheme 29).

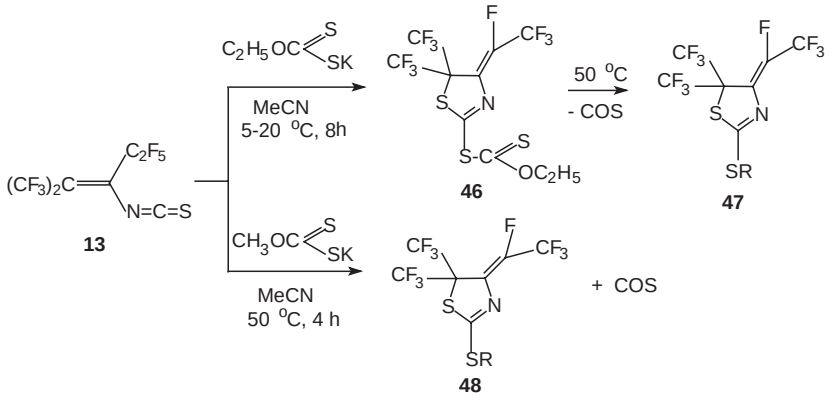
S-Nucleophiles, in particular, sodium *N*,*N*-diethyldithiocarbamate and potassium ethyl xanthate react with compound **13** to form 2-substituted derivatives of 4,5-dihydro-[1,3]-thiazole **45** and **46**, **47**, respectively (Scheme 30). Compound **46** is thermally unstable. At elevated temperatures, for example, when the reaction mixture is heated to 50 °C or distilled, the compound is transformed into **47**. The thermal stability of dihydro-[1,3]-thiazole with an S-C(S)Oalk group in the 2 position is sensitive to the structure of the alkoxy group. For example, in the case of the reaction of **13** with potassium methyl xanthate (Alk = OCH_3), the corresponding derivative of 2-(*O*-methylxanthato)-4,5-dihydro-[1,3]-thiazole cannot be isolated; compound 48 is the sole reaction product (Scheme 30).

For the reactions of compound **13** with S-nucleophilic reagents, one can suggest Scheme 31.

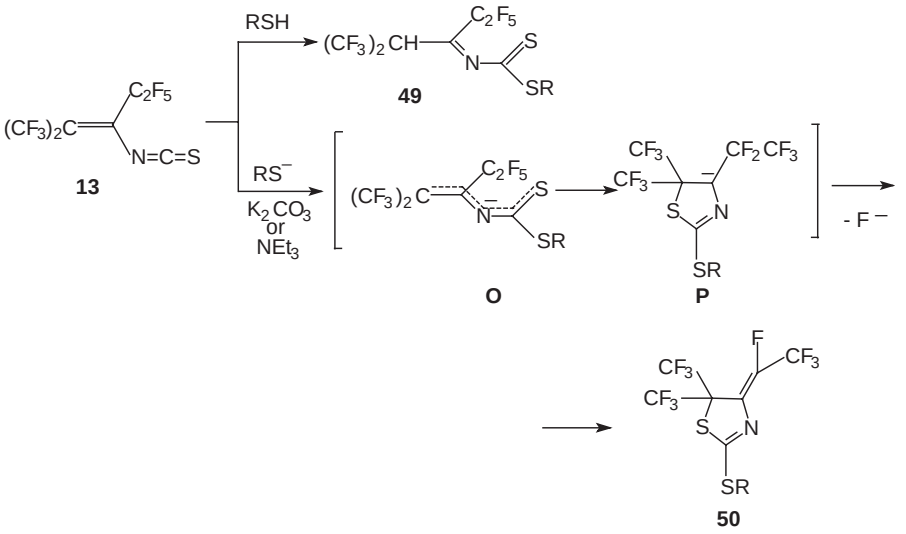
In the absence of bases, alkylmercaptan interacts with **13**, forming adduct **49**. In the presence of bases (triethylamine or K_2CO_3), the charged nucleophile attacks the carbon atom of the N═C bond of **13**, forming anion (**O**). Intramolecular cyclization



Scheme 29



Scheme 30

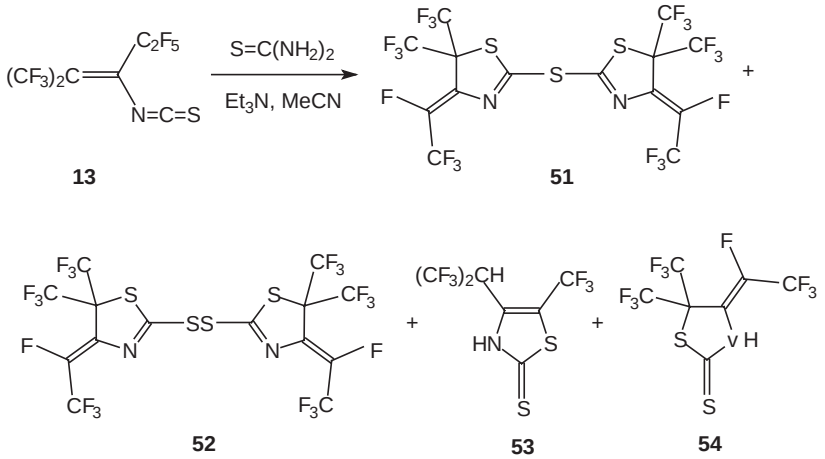


Scheme 31

of this anion leads to carbanion (**P**), transformed into 4,5-dihydro-1,3-thiazole derivative **50** by fluoride ion elimination from the $CF(CF_3)$ fragment.

Thus, the following consistencies have been found in the studies of the reactions of **13** with S-nucleophiles:

1. Interaction with mercaptans yields adducts without heterocycle formation.
2. Interaction of charged nucleophiles (sodium *N*,*N*-diethyldithiocarbamate, potassium ethyl- and methylxanthates) forms 2-substituted 4,5-dihydro-1,3-thiazoles.
3. Reactions with mercaptans and 2-mercaptobenzimidazole in the presence of bases occur differently, depending on the nature of the base: (a) in the presence of triethylamine, the sole products are 2-substituted 4,5-dihydro-[1,3]-thiazoles; (b)



Scheme 32

in the presence of K_2CO_3 in dimethylformamide, as shown for butylmercaptan, the product of formal substitution of the isothiocyanate group in **13** by the alkylthio group can form in addition to 2-substituted 4,5-dihydro-[1,3]-thiazole.

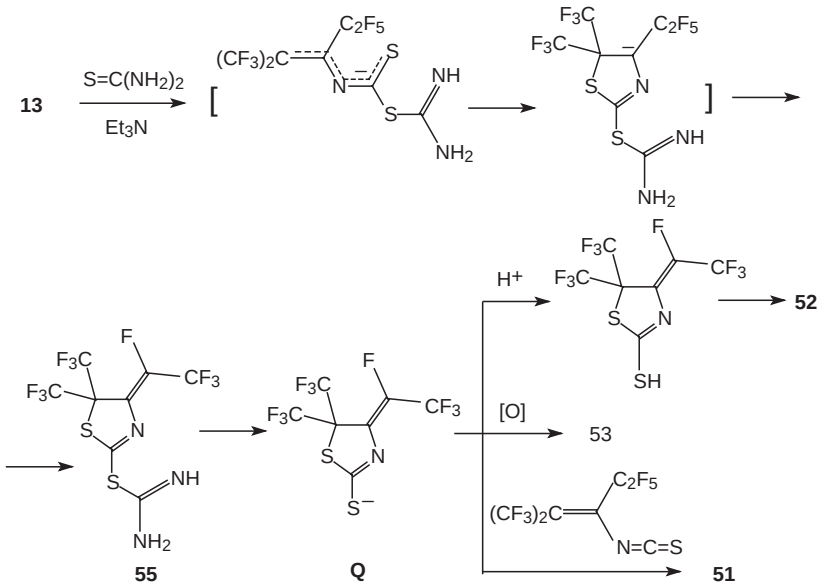
The reaction of perfluoro-2-methylpent-2-en-3-yl isothiocyanate with thiourea in the presence of triethylamine affords a mixture of reaction products containing both the expected derivatives of 4,5-dihydro-[1,3]-thiazole (perfluoro-[bis(4-ethylidene-5.5-dimethyl-4,5-dihydrothiazol-2-yl)]sulfide **51** and perfluoro[bis(4-ethylidene-5,5-dimethyl-4,5-dihydro-thiazol-2-yl)]disulfide **52**) and compounds **53** and **54** [**52** (97ZOB1708)] (Scheme 32).

Scheme 33 is proposed for the reaction of **13** with thiourea. The primary product is the 2-substituted thioether **55**. S-anion **Q** is generated by C–S bond cleavage under the action of bases. The reaction of S-anion **Q** with the starting compound **13** gives sulfide **51**. Protonation forms thiol, which either dimerizes into disulfide **52**, or isomerizes into more stable thione **54**.

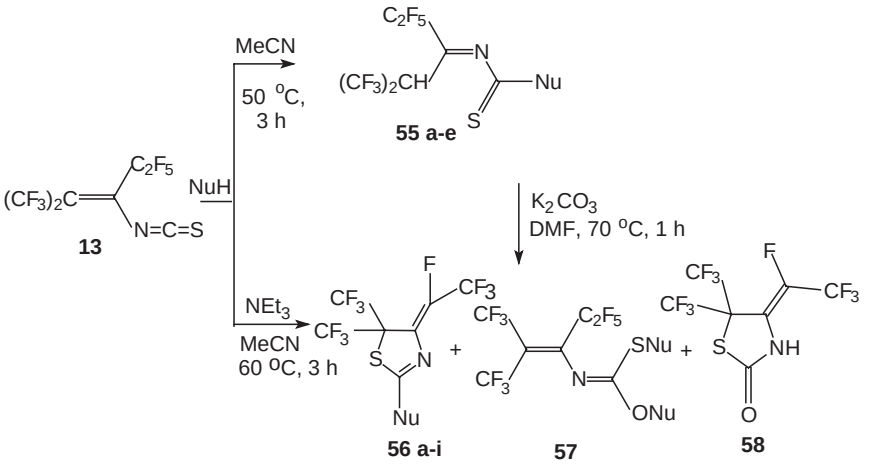
The reaction of perfluoro-2-methylpent-2-en-3-yl isothiocyanate **13** with alcohols in the absence of bases leads to adducts **55**; in the presence of KOH or triethylamine, the products are 2-alkoxy derivatives of 5,5-bis(trifluoro-methyl)-4-(2,2,2-trifluoro-1-trifluoromethylethylidene)-4,5-dihydro-[1,3]-thiazoles **56a–f** and **57** (Scheme 34). Another product of this reaction is 4-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoro-methyl)-thiazolin-2-one **58**, whose structure is confirmed by X-ray analysis (97ZOB1560, 98IZV2021, 99ZOB1499).

4-(1,2,2,2-Tetrafluoroethylidene)-5,5-bis(tri-fluoromethyl)-thiazolin-2-one **58** was confirmed by X-ray data (Figure 9) (99ZOB1499).

A more complex mixture of products is obtained in the reaction of **13** with isopropanol in the presence of triethylamine (98IZV2021) (Scheme 35). The structure was confirmed by X-ray data.



Scheme 33



Scheme 34

For the formation of compounds of **57a–i**, one can suggest Scheme 35. The O-nucleophile initially attacks the carbon atom of the C═N bond to form anion **60** in which a rearrangement takes place. This leads to anion **R**, which on protonation

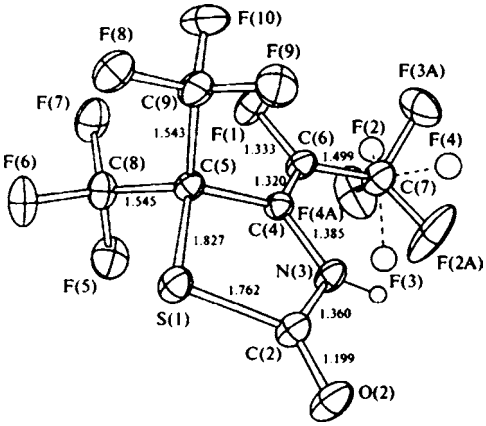
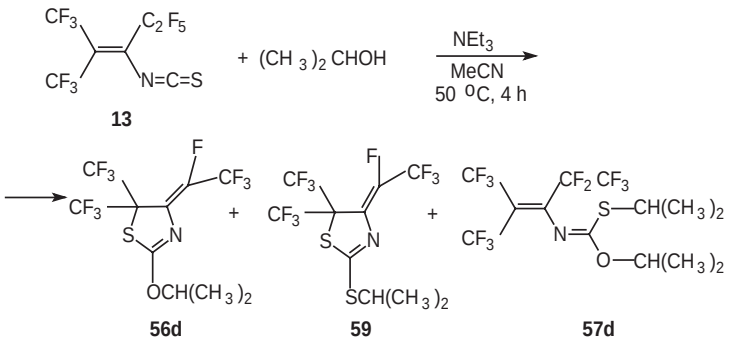


Figure 9. Structure of 3-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoro-methyl)thiazolidin-2-one **58** according to X-ray analysis (99ZOB1499).



Scheme 35

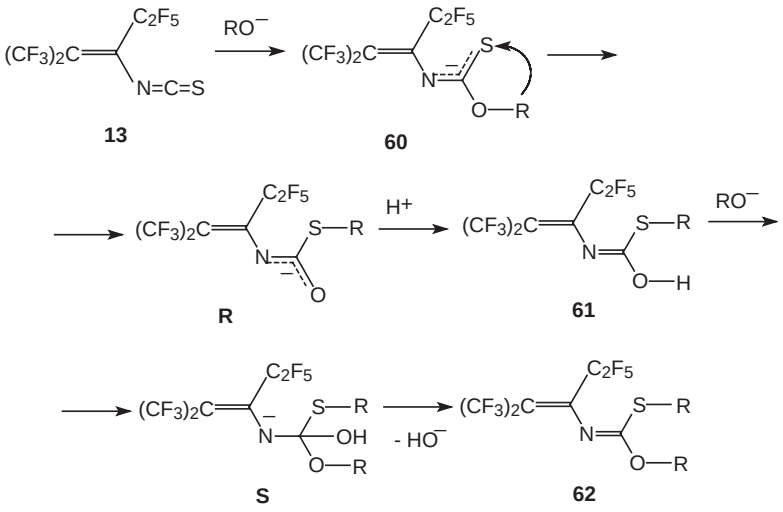
gives compound **61**. Further action of the O-nucleophile at the C═N carbon yields anion **S**, which is transformed into reaction product **62** (98IZV2021) (Scheme 36).

The 2-substituted derivatives of 4,5-dihydro-[1,3]-thiazoles are probably formed in the same way as S-nucleophiles. The key step is generation of the S-nucleophilic center in the course of the formation of the terminal double bond involving the CF_3 group.

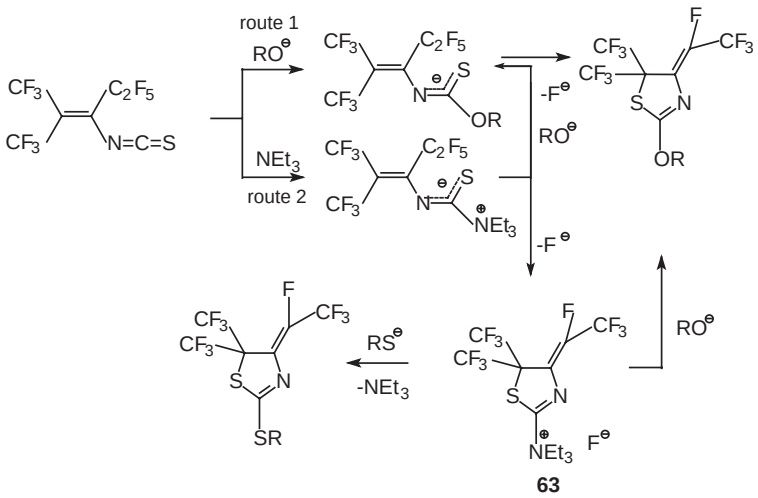
Triethylamine acts as an active nucleophile reacting at the carbon atom of the N═C═S group in these processes (98IZV2021) (Scheme 37).

Thus, triethylamine reacts with compound **13** with formation of triethyl-ammonium salts and 4,5-dihydrothiazole **63** (Scheme 37) that reacts with S- and O-nucleophiles to replace the triethylammonium group and give final products.

An interesting method for the preparation of 2-phosphorus-substituted fluorinated thiazolines involves reactions of perfluoro-2-methyl-3-isothio-cyanato-2-pentene with trivalent phosphorus derivatives possessing nucleophilic properties in analogy with the above reactions, with O-, S-, and N-nucleophiles. On the one hand,



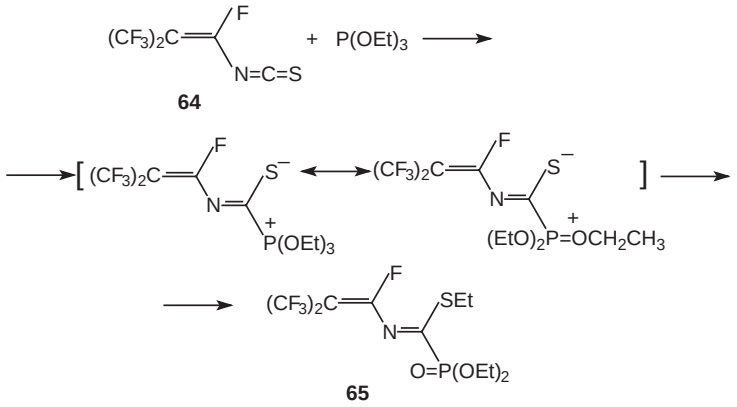
Scheme 36



Scheme 37

one would expect increase in biological activity due to the presence of the P–C═N–C═CF – fragment in these compounds. On the other hand, because of their superlypophilic groups, the resulting phosphonium salts and phosphonates are good potential extractants and phase-transfer catalysts (62JOC3651, 82OK(3)660, 63HOU(12/1)110).

There are at least two obstacles to the realization of this synthetic scheme. First, the most typical reaction of isothiocyanates with trivalent phosphorus compounds is desulphurization of the isothiocyanate group (62JOC3651, 82OK(3)660, 63HOU(12/1)110).



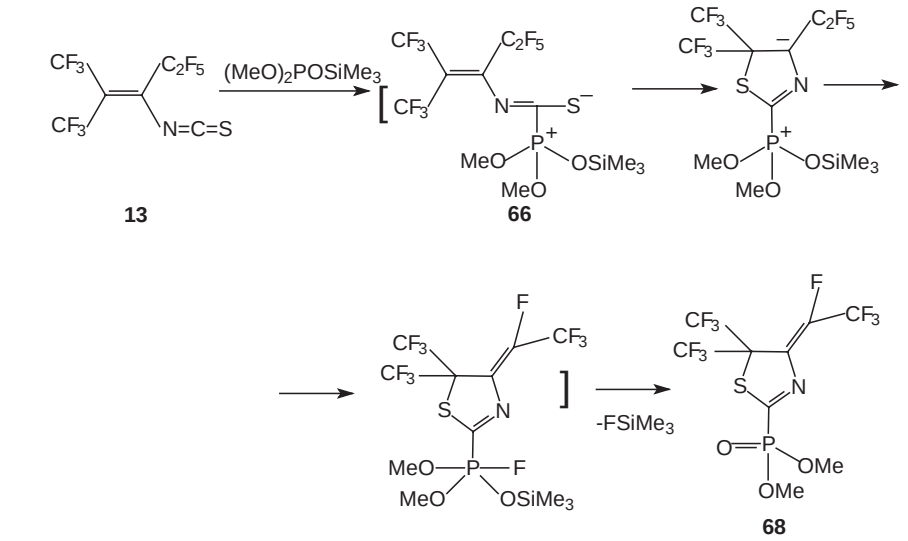
Scheme 38

The second obstacle is the high energy of the P–F bond, which is especially important in compounds with P–O bonds. For these reasons, the reactions occur with fluoride ion elimination to yield complex mixtures of products in which the oxygen atoms are partly substituted by the fluorine atoms (P–F bonds) (98ZOB798). Moreover, the exchange of fluorine for oxygen can take place until the PF_5^- anion has formed (90UP3). Nevertheless, as shown in (69IZV1176), interaction of perfluoro-2-methyl-1-isothiocyanato-1-propene **64** with triethylphosphite can occur without desulfurization. No heterocycles were formed in this case, and the formation of **65** was explained by intramolecular alkylation of the sulfur atom of the intermediate zwitterion (Scheme 38).

In the reaction of dimethyl(trimethylsilyl) phosphite with perfluoro-2-methylpent-2-en-3-yl isothiocyanate, less desulfurization is expected, because the trimethylsilyl group leads to greater stabilization of the positive charge on oxygen in the suggested intermediate **66** compared with an alkyl group (02ZOB1024). To avoid van der Waals repulsion between the sulfur atom and the pentafluoroethyl group, the =C–N=C–S fragment tends to adopt the cisoid conformation, favoring heterocycle formation. Due to the repulsion between the $SiMe_3$ and C_2F_5 groups, the S–C–P–OMe fragments prefer the transoid conformation, which must hinder desulfurization and intramolecular alkylation. After ring closure, trimethylfluorosilane and dimethyl-phosphonate **68** are formed in excellent yields due to the high stability of the Si–F bond (02ZOB1024) (Scheme 39).

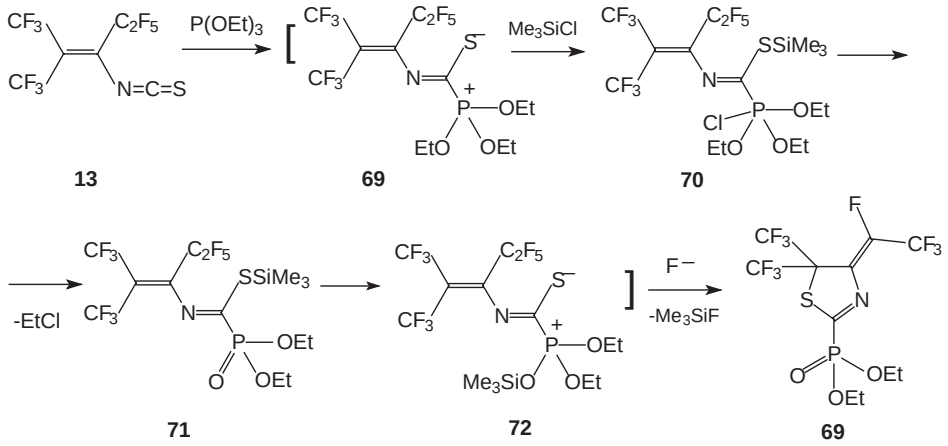
If perfluoro-2-methylpent-2-en-3-yl isothiocyanate is allowed to react with electrophilic trimethylchlorosilane and triethylphosphite (which do not react with each other under the reaction conditions), trimethylchlorosilane will temporarily block the S-nucleophilic center and act as a fluoride ion acceptor. Indeed, this reaction occurs smoothly, giving diethylphosphonate **69** in an almost quantitative yield. The suggested scheme of the reaction is shown in Scheme 40 (02ZOB1024).

At first, zwitterion **69** reacts with trimethylchlorosilane, giving phosphorane **70**, which decomposes with liberation of EtCl into phosphonate **71**. Probably because of the greater stability of its Si–O bond, the latter converts into compound **69** via intermediate **72**. After the S-nucleophilic attack at the double bond of the olefin and



13 66 68

Scheme 39



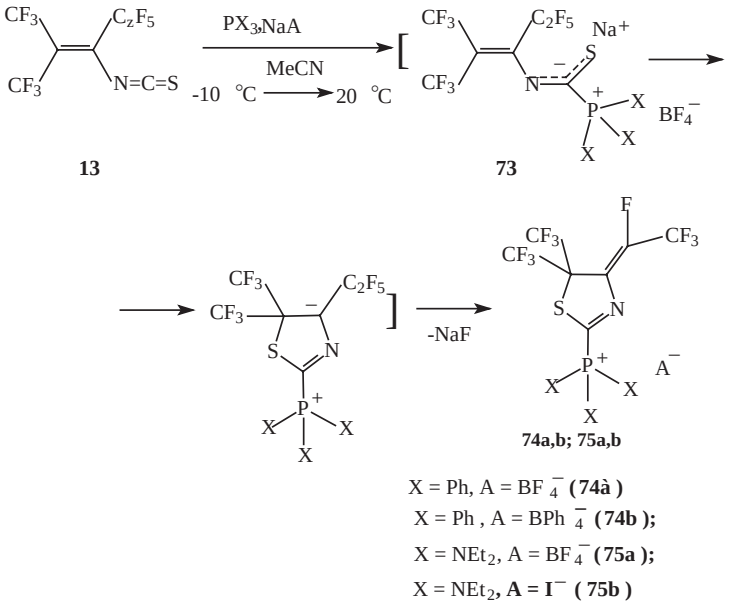
13 69 70 71 72 69

Scheme 40

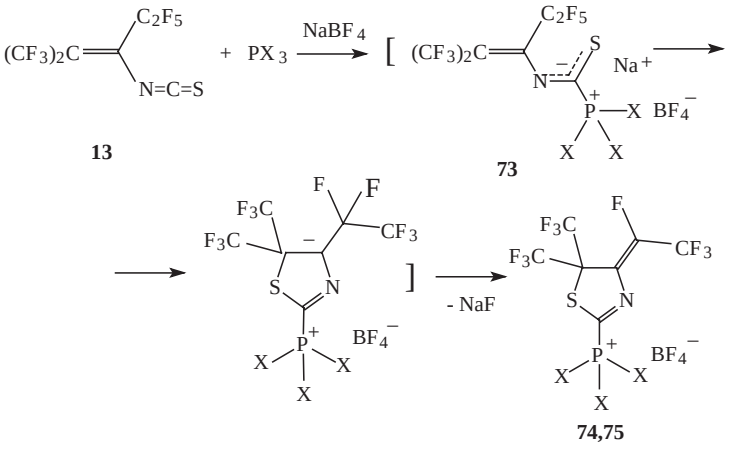
elimination of trimethylfluorosilane, phosphonate **69** is produced in a quantitative yield (^{19}F-NMR data).

A different strategy was chosen to obtain phosphonium salts by the action of triphenylphosphine and tris(dimethylamino)phosphine. In this case, the liberated fluoride ion makes the reaction reversible due to the high solubility of phosphonium salts in acetonitrile.

The relatively lypophilic KI and $NaBF_4$ salts, whose cations form insoluble fluorides, were used for stabilization of the zwitterions and scavenging the fluoride ion. In this case, compound **13** reacts smoothly with triphenylphosphine and



Scheme 41



Scheme 42

hexaethyltriamidophosphite [$P(NEt_2)_3$] (02ZOB1024), forming (in quantitative yields) the corresponding phosphonium salts with perfluorinated thiazoline as substituents (**74a,b**)–(**75a,b**) (Scheme 41). These salts are stable when their acetonitrile solutions are heated to at least 50 °C (02ZOB1024).

At the same time, the reaction of **13** with tris(pentafluorophenyl)phosphine did not produce the corresponding salt. The reaction occurs as shown in Scheme 42.

The P-nucleophilic attack at the carbon atom of the N═C═S group leads to the formation of zwitterion **73**, which is stabilized by the corresponding counterions

from $NaBF_4$, KI, or $NaBPh_4$ salts, hindering desulfurization and intramolecular alkylation. After heterocycle closure, the fluoride ion is eliminated in the form of NaF or KF.

Because of their general character, these methods are expected to be successful when used with other P-nucleophilic reagents and hydrocarbon and fluorocarbon electrophiles. These compounds are of interest from the viewpoint of their potential biological activity.

The data presented in this section lead us to conclude that perfluoroolefin α,β-unsaturated thiocyanates and isothiocyanates provide good opportunities for syntheses of various substituted fluorinated heterocyclic compounds with N and S atoms. Among them, compounds with high biological activity have already been found, and prospects for finding new compounds in this series look good.

III. The Use of Fluoroolefins with a Carbonyl-Containing Substitutent for the Construction of Heterocyclic Systems

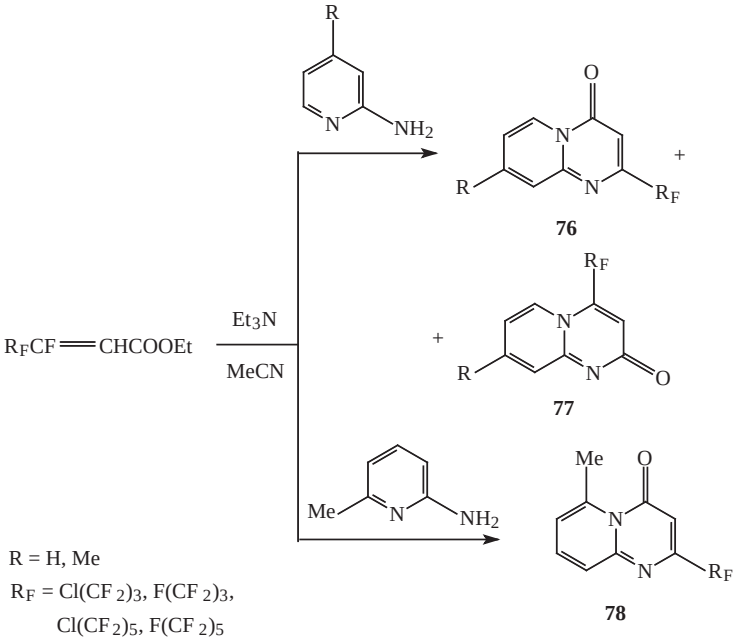
Apart from compounds with SCN and N=C=S groups at the double bond, some other perfluoroolefins (in particular, those with the carbonyl group) were employed for the construction of heterocyclic systems. It is not necessary that a double bond exists in the starting substrate; it may be generated in the course of the nucleophilic reaction. For the formation of heterocyclic systems some researchers used derivatives of perfluoroolefins (particularly those containing a carbonyl group) including both polyfluorinated aldehydes and carboxylic acids having in the CH and CH_2 fragments α-position (93JOC6671). It is essential that a bond be formed and that the nucleophilic reagent be a binucleophile.

Moreover, the new double bond should have a dominant reactivity. There may be two cases: one with a fluorine atom or a good-leaving anionic group, and the other with an electron acceptor (e.g. perfluoroalkyl) group at the multiple bond. Examples of such substrates are given below. Under these conditions, [3 + 2] cyclization, forming a CF=CRC(O)- conjugated system of bonds is possible.

Thus, in the presence of Et_3N, ethyl 2-hydropolyfluoroalk-2-enoates are transformed into polyfluoroalkylated pyrido[1,2-a]-pyrimidines **76** and **77** by reactions of 2-aminopyridines in acetonitrile at 90 °C for 50 h (97JCS(P1)981) (Scheme 43).

2-Amino-4-methylpyridine and 2-amino-6-methylpyridine reacted with ethyl 2-hydropoly-fluoroalk-2-enoates to afford only oxo products **78** in moderate yield apparently due to the steric effect of the 6-methyl group, which hinders the Michael addition of the ring nitrogen to the unsaturated esters.

For the synthesis of polyfluoroalkenylimidazo[1,2-*a*]pyridine, the reaction may be accelerated by applying ultrasonic conditions. In the presence of K_2CO_3, a mixture of 1 equivalent of 2-hydropolyfluoroalk-2-enoate and 3 equivalents of 2-aminopyridine in acetonitrile under ultrasonic conditions (125 W) for 2 h gives a mixture of isomeric polyfluoroalkyled pyrido[1,2-*a*]pyrimidines **76** and **77** in a 33–59% yield (97JCS(P1)981). In a similar reaction, 2-amino-6-methylpyridine reacts with ethyl



Scheme 43

2-hydropolyfluoroalk-2-enoate to produce a heterocyclic compound **78** with a moderate yield.

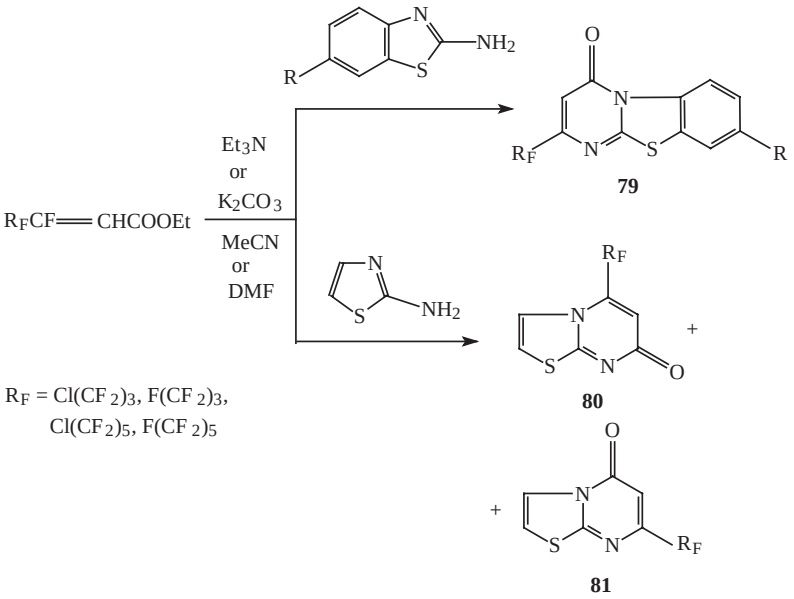
2-Aminobenzothiazole and 2-aminothiazole were used in a similar procedure for the preparation of 2-perfluoroalkyl-4*H*-pyrimido[2,1-*c*]benzothiazol-4-one **79** and a mixture of 7-fluoroalkyl-5*H*-1,4-thiazolo[3,2-a]pyrimidin-5-one **80** and 5-fluoroalkyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one **81**, respectively (97JCS(P1)981) (Scheme 44).

The 2-(ω-chloroperfluoropentyl)-2-enoates reacted with 2-mercaptobenzimidazole in the presence of $NaHCO_3$ to give 2-(ω-chloro-perfluoro-pentyl)-[1,3]-thiazino[3,2-*a*]benzimidazol-4-one (yield 78%) (97JCS(P)981).

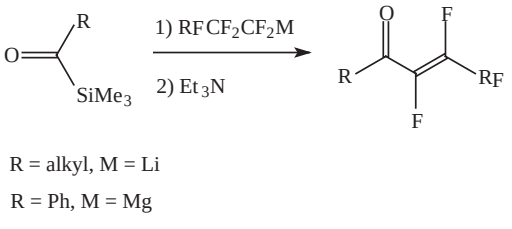
The perfluoroalkenyl ketones result from the reaction between acylsilanes and perfluoroorganometallic compounds in the presence of triethylamine. They have been shown (91TL83, 93JOC6669, 93JOC6673) to be excellent building blocks for the synthesis of polyfluorinated heterocycles (94TL4357, 01EJO187) (Scheme 45).

This cyclocondensation was then extended to acylsilane derivatives of a racemic xylitol and a protected D-xylofuranose to give pyrazole rings attached to carbo hydrate moieties (01EJO187) (Scheme 46).

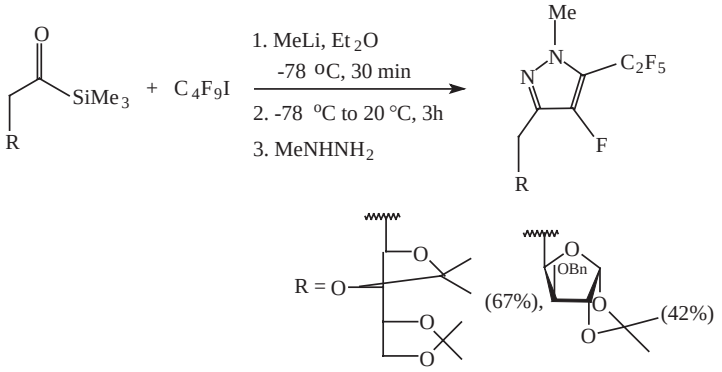
The presence of a multiple bond at the C═O group is not necessary, but under the reaction conditions with bases, this bond was generated. Thus in the presence of Et_3N, 2,2-dihydropolyfluoroalkoxides react with nucleophilic reagents such as aromatic amines and phenols; in the presence of polyphosphoric acid (PPA), the intermediates of these reactions cyclize into quinolines or chromones (92CCL583) (Scheme 47).



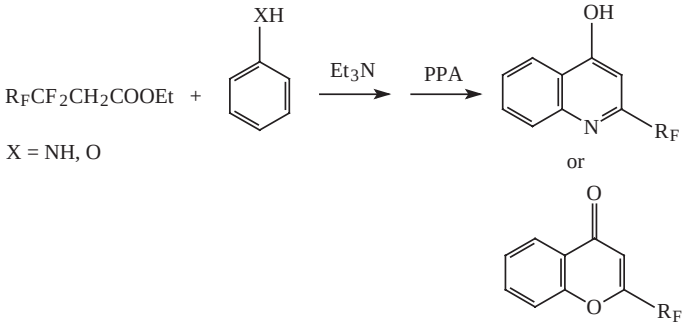
Scheme 44



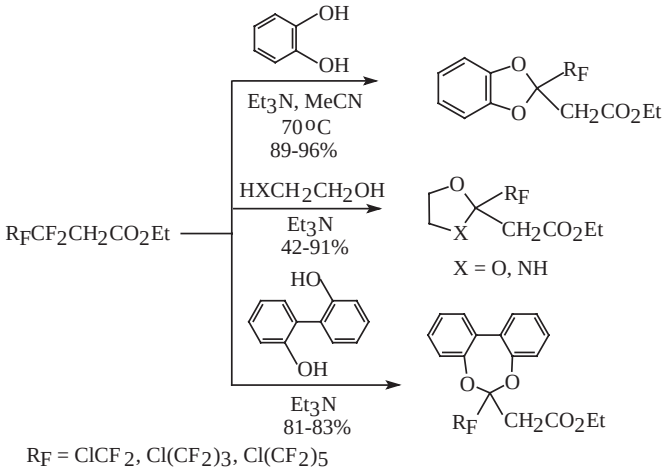
Scheme 45



Scheme 46



Scheme 47



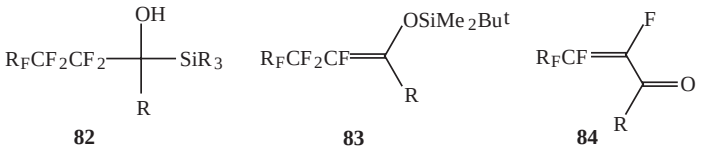
Scheme 48

Under similar conditions, this reaction occurs with other nucleophilic reagents such as catechol, 2,2-dihydroxydiphenyl, salicyl alcohol, ethylene glycol, and ethanolamine. The products are five- and seven-membered heterocycles (94CJC79) (Scheme 48).

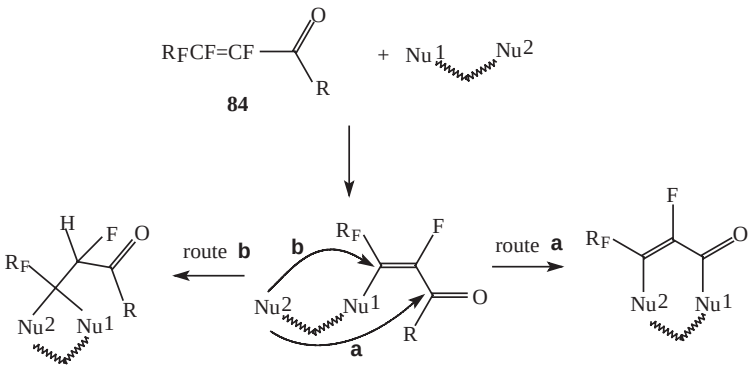
Synthetic equivalents of hemiperfluoroenones **84** (94TL409, 93JOC6675), 1-trialkylsilylperfluoroalkanols **82** (93JOC6671), and 1-alkyl 1(trialkylsilylo-xy)perfluoroalk-1-enes **83** (94TL409, 93JOC6675, 01EJO187) (Scheme 49), which are synthetic equivalents of compounds with a C=C–C=O conjugate system, react with binucleophiles, giving heterocyclic compounds.

Conjugated substrate **84** with its C = C–C = O reacts with a binucleophilic reagent at the β-atom of the C=C bond that includes a formation of carbanion, which is stabilized by elimination of a fluoride ion from the same of carbon atom (Scheme 50).

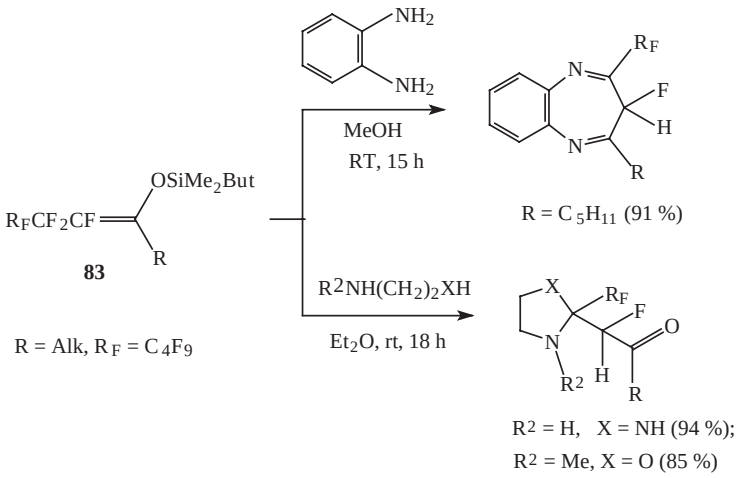
Subsequent intramolecular nucleophilic cyclization can proceed in several ways. In route **a**, nucleophilic attack on the carbonylcarbon proceeds with the elimination of



Scheme 49



Scheme 50

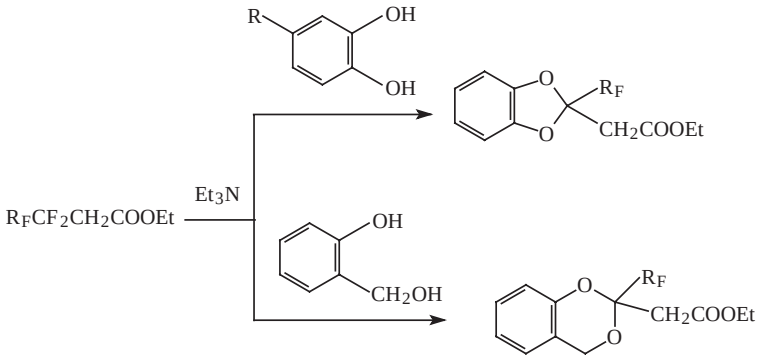


Scheme 51

group R. In route **b**, attack on the carbon of the alkenyl double bond with further proton atom leads to a new heterocyclic product.

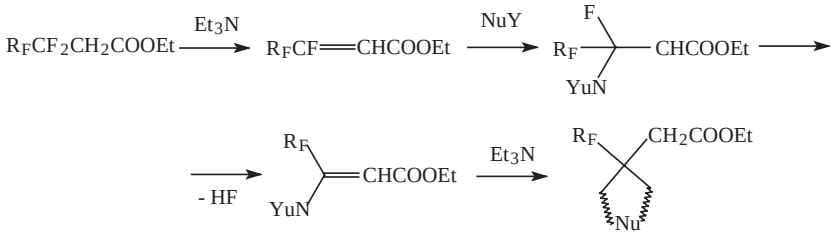
Thus compound **83** reacts with *ortho*-phenylenediamine, ethylenediamine, and *N*-methylethanolamine, forming five- or seven-membered heterocyclic compounds (Scheme 51).

These reactions proceed as addition eliminations. Regiospecific cyclization then occurs either at the carbon atom of the carbonyl group or at the β-carbon atom of the multiple bond.



R = H, CHO
X = O, NH
R_F = $ClCF_2$, $Cl(CF_2)_3$, $Cl(CF_2)_5$

Scheme 52



Scheme 53

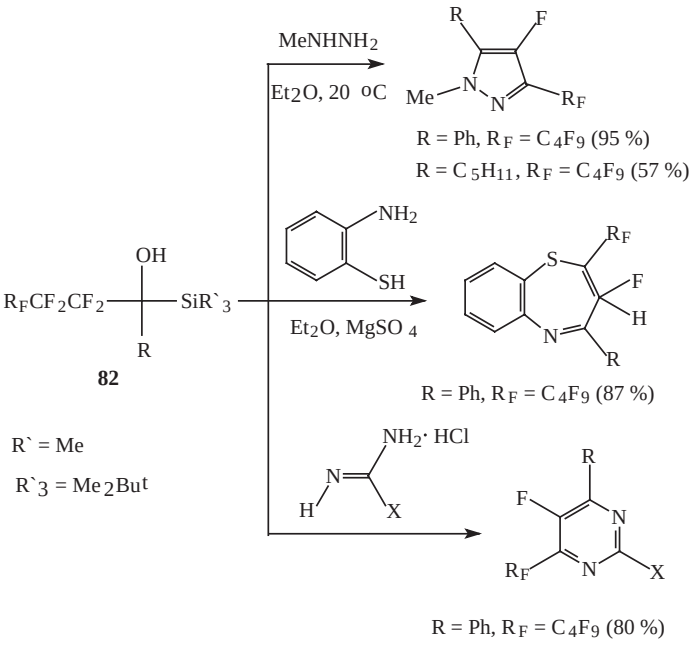
These processes can also involve carboxylic esters if there is a CF fragment in the β position relative to the carboxyl group (Scheme 52).

The reaction presumably occurs via the preliminary formation of the CF═CH double bond under the action of the base; the nucleophilic reagent adds at the carbon atom bearing the largest positive charge (Scheme 53).

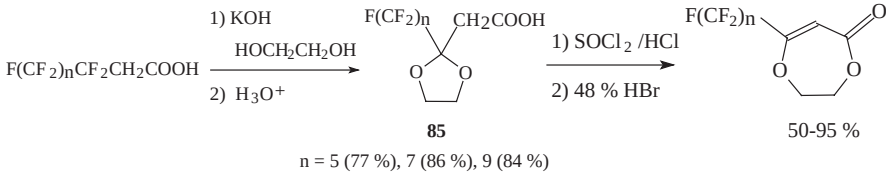
Five- (imidazolines and oxazolines), six- (pyrimidines), and seven- (diazepines and thiazepines) membered heterocycles are obtained with high yields from compound **82** under mild conditions (93JOC6671) (Scheme 54).

The compounds are preferably grouped into (1) compounds with an unsaturated functional group at the multiple bond and (2) compounds with a good leaving group and a multiple bond.

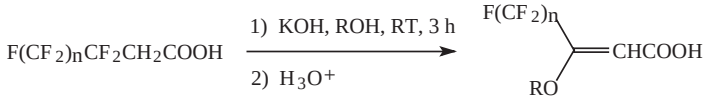
2,2-Dihydropolyfluoroalkanoic acids are easily prepared through the sodium dithionite-initiated addition of polyfluoroalkyl iodides with ethyl vinyl ether and subsequent oxidation (90CJC281, 91TL83, 93JOC6669, 93JOC6673). Heating partially fluorinated carboxylic acid in ethyleneglycol in the presence of KOH forms [2(perfluoroalkyl)-1,3-dioxolan-2-yl]acetic acids **85** (99JFC(95)141, 01TL2305) (Scheme 55). Treatment of compound **85** with thionyl chloride and a 45% HBr solution yields 7-polyfluoroalkyl-2,3-dihydro-5*H*-1,4-dioxepine-5-one (01TL2305).



Scheme 54



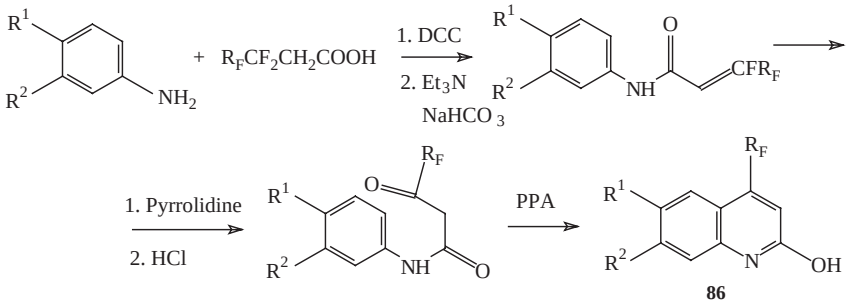
Scheme 55



n = 5, R = Et (65 %, Z/E = 95/5);
n = 7, R = Et (86 %, Z/E = 92/8);
n = 9, R = Et (95 %, Z/E = 100/0);
n = 7, R = $C_2H_4OC_2H_4OH$ (98 %, Z/E = 100/0)

Scheme 56

This reaction occurs with base-induced formation of the $F(CF_2)_nCF{=}CHCOOH$ unsaturated acid as an intermediate. The typical examples are reactions of the acid with alcohols (Scheme 56).



$X(CF_2)_n$	CF_3				$Cl(CF_2)_3$					$CF_3(CF_2)_4$				
R^1	Me	H	H	H	H	Br	H	Cl	Me	H	Br	Cl	H	Me
R^2	H	H	Me	Cl	H	H	Me	H	H	H	H	H	Me	H
Yield, %	85	84	82	80	70	59	58	61	62	68	56	65	56	66

Scheme 57

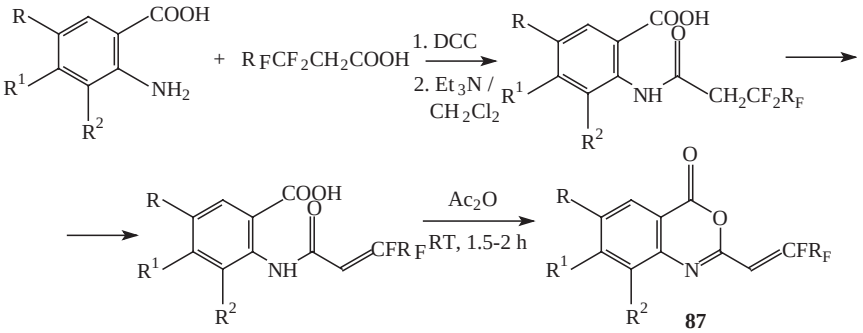
In the presence of *N*,*N*′-bicyclohexylcarbodiimide (DCC), 2,2-dihydropoly-fluoroalkanoic acids reacted with anilines to produce the corresponding amides, which eliminate hydrogen fluoride under the influence of Et_3N or $NaHCO_3$ to give *N*-aryl-3-fluoro-3-fluoroalkyl-2-propene-2-amides with a high yield. Michael addition of pyrrolidine to *N*-aryl-3-fluoro-3-fluoroalkyl-2-propene-2-amides followed by hydration of the adduct afforded *N*-aryl-2-oxa-polyfluoroalkanamides in the presence of PPA at 165–170 °C for 5–9 h. Then ring closure gave the corresponding 4-fluoroalkyl-2-quinolinols **86** regioselectively (92CCL583, 01JFC(111)207, 01JFC(111)213) (Scheme 57). Steric effect played an important role.

Similarly, a tricyclic compound was obtained from α-aminonaphthalene by similar reactions (01JFC(111)207).

DCC could also induce the condensation of these acids such as anthranilic acid or its derivatives giving corresponding amides. Subsequent treatment of the mixture with acetic anhydride afforded 2 [(*Z*)-1-hydropolyfluoro-1-alkenyl]-4*H*-3,1-benzoxazin-4-one **87** with good to excellent yields and stereoselectivity (92CCL583, 01JFC(111)213) (Scheme 58). These compounds have been known for more than a century (99JHC563) and show interesting pharmacological properties.

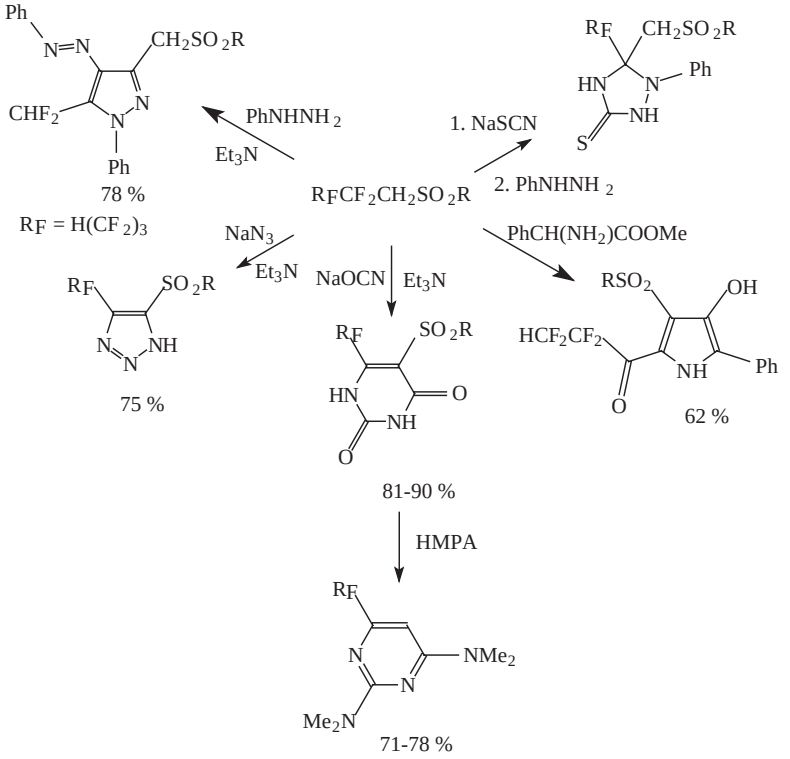
1,1-Dihydropolyfluoroalkylsulphones are very useful reagents for the synthesis of fluoro-containing heterocycles (02JFC(114)157) (Scheme 59). For example, in the reaction with *N*-phenylhydrazine they give pyrazolosulfones (01ZOR666). Fluoro-containing pyrrole was produced during the reaction of sulfones with α-phenylglycine. Another heterocycle, triazole, was obtained in the reaction of sulfones with sodium azide in the presence of Et_3N (01CHC518). 6-Polyfluoro-alkylsubstituted pyrimidine derivatives were obtained in the reaction of sulfones with sodium cyanate in the presence of Et_3N in HMPA (02JFC(114)157).

The first stage is dehydrofluorination with formation of fluoroalkenylsulphones. Dehydrofluorination is an equilibrium process such as a reaction with triethylamine in benzene (01ZOR666) (Scheme 60).

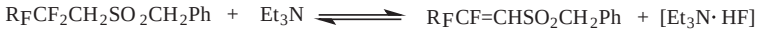


$(CF_2)_nX$	C_5F_{11}			C_3F_6Cl		CF_2Cl			C_3F_7		CF_2Br		CF_3	
R^1	H	H	OMe	H	H	H	H	OMe	H	OMe	H	OMe	OMe	H
R^2	Br	Cl	OMe	Cl	H	Cl	H	OMe	Cl	OMe	H	OMe	OMe	H
R^3	H	H	H	H	Cl	H	H	H	H	H	H	H	H	H
Yield, %	75	90	95	88	93	68	75	78	88	95	75	78	78	75

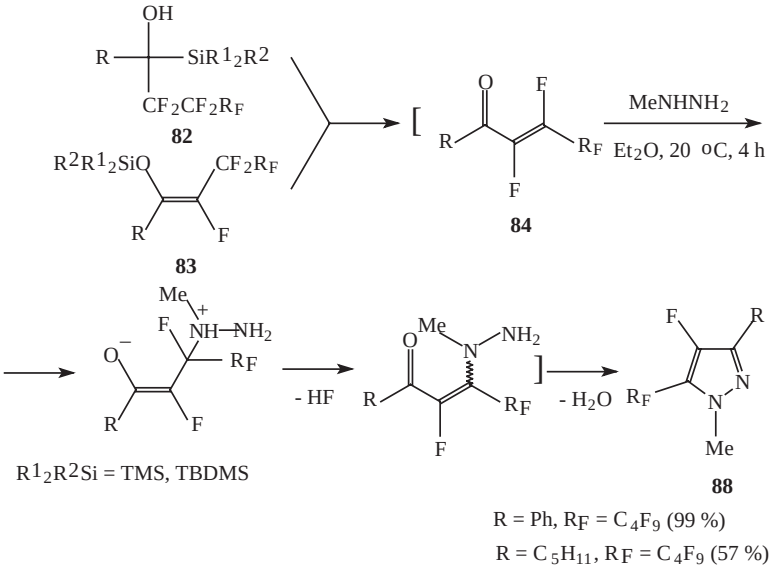
Scheme 58



Scheme 59



Scheme 60



Scheme 61

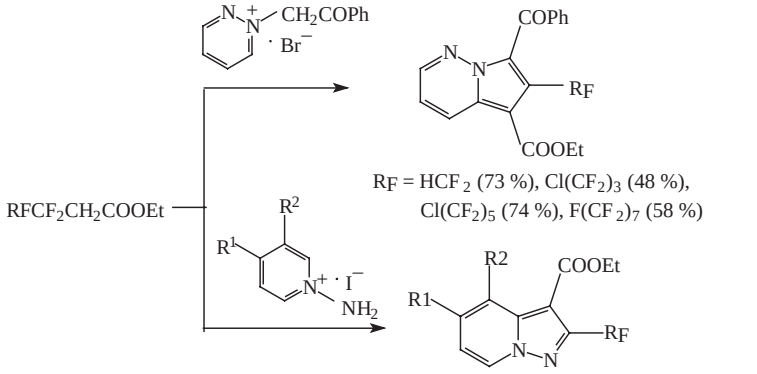
The reaction of urea with α-(perfluoroalkyl)acrylic acid in acetic acid anhydride leads to the formation of 5-(perfluoroalkyl)-5,6-dihydrouracil (99PDE19835866).

Various 4-fluoro-1-methyl-5-perfluoroalkylpyrazoles **88** may be synthesized by the reactions of methylhydrazine with acylsilanes **82** and **83** following a two-step route (93JOC6675, 01EJO187) (Scheme 61). The first step is the formation of the intermediate olefin, which reacts further with methylhydrazine, forming a pyrazole derivative.

In the presence of bases, ethyl 2,2-dihydropolyfluoroalkanecarboxylic ester reacts with *N*-aminopyridinium iodide, *N*-amino-γ-picolinium iodide, *N*-phenacylpyridiazinium bromide, *N*-phenacylpyridinium bromide, and *N*-phenacylisoquinolinium bromide in dimethylformamide at 50 °C, forming polyfluoroalkyl-substituted pyrazolo[1,5-*a*]pyridine, pyrrolo-[1,2-*a*]pyridazine, and indolizine derivatives, respectively (94CJC79, 95JFC(75)51) (Scheme 62).

One can also employ a compound with a double bond bearing no fluorine atoms, but having a perfluoroalkyl substituent (99JFC(99)41). For example, 1-iodo-2(polyfluoroalkyl)ethylenes react with *N*-ylides of isoquinolinium, pyridinium, 4-methylpyridinium, and pyridazinium ions giving pyrrolo[2,1-*a*]-isoquinoline and pyrrolo[1,2-*b*]pyridazine derivatives (99S51, 99JFC(99)41) (Scheme 63).

Isoquinolinium *N*-ylides, generated from the corresponding isoquinolinium salt and sodium hydride, were reacted with perfluoroalkynyl phosphonate to give of perfluoroalkylated pyrrolo[2,1-*a*]isoquinolinyl phosphonates (02JFC(116)157)



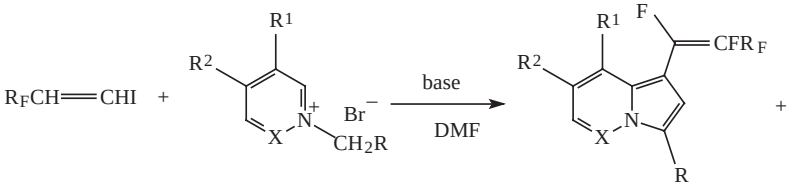
R_F = HCF_2 (73 %), $Cl(CF_2)_3$ (48 %), $Cl(CF_2)_5$ (74 %), $F(CF_2)_7$ (58 %)

R^1 = R^2 = H; R_F = HCF_2 (80 %), CF_3 (70 %), $Cl(CF_2)_3$ (80 %), $F(CF_2)_7$ (95 %)

R^1 = Me, R^2 = H; R_F = HCF_2 (65 %), CF_3 (70 %), $Cl(CF_2)_3$ (54 %), $F(CF_2)_7$ (75 %)

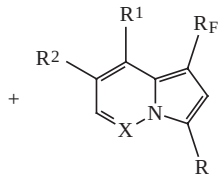
R^1, R^2 = -$(CH_2)_4$-; R_F = HCF_2 (77 %), $Cl(CF_2)_5$ (65 %), $F(CF_2)_7$ (77 %)

Scheme 62



X = CH, R = CN, R^1,R^2 = −$(CH_2)_4$−

R_F = $Cl(CF_2)_2$ (81 %), $Cl(CF_2)_4$ (70 %), $Cl(CF_2)_6$ (60 %)



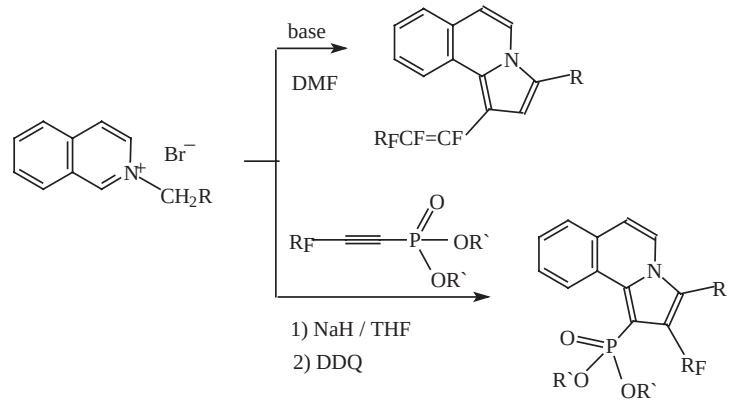
X = CH, R = CN, R^1,R^2 = −$(CH_2)_4$−

R_F = $Cl(CF_2)_2$ (55 %), $Cl(CF_2)_4$ (33 %), $Cl(CF_2)_6$ (50 %)

Scheme 63

(Scheme 64). The structure of diisopropyl-(2-trifluoromethyl-1-cyano-pyrrolo[2,1-*a*]isoquinolin-3-yl) phosphonates was confirmed by X-ray analysis (02JFC(116)157).

5,5,5-Trifluoro-4-trifluoromethyl-2-methylpenta-1,3-diene and 5,5,5-trifluoro-2,4-dimethylpenta-1,3-diene react with elemental sulfur or selenium, forming



DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

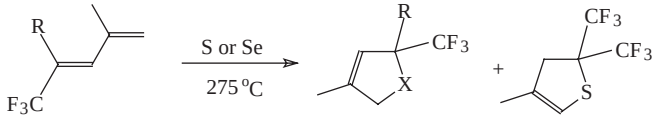
48-78 %

$R_F = CF_3, C_2F_5$

R = Ph, CO, CN, CO_2Er

R` = Et, i-Pr

Scheme 64



R, X (Yield, %): CF_3, S (71); Se (68); Me, S, Se

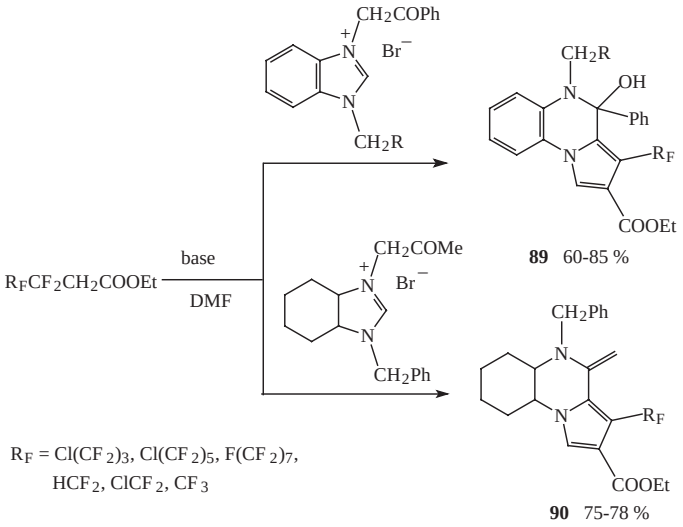
Scheme 65

2,2-bis(trifluoromethyl)-4-methyl-2,5-dihydrothiophene, 2,2-bis(trifluoromethyl)-4-methyl-2,5-dihydroselenophene, 2-trifluoromethyl-2,4-dimethyl-2,5-dihydrothiophene, and 2-trifluoromethyl-2,4-dimethyl-2,5-dihydroselenophene (97JFC(84)75) (Scheme 65).

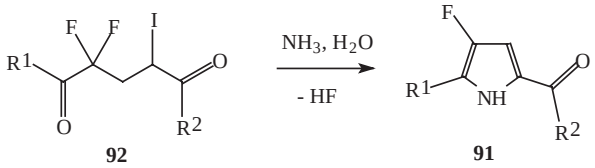
In the reactions of ethyl 2,2-dihydropolyfluoroalkanoate with 1-alkyl-benzimidazolium-3-ylides, the products are tricyclic heterocycles **89** and **90** with two nitrogen atoms (98JFC(87)57, 98T12465) (Scheme 66).

Fluorine-containing derivatives pyrrole **91** have been formed by the interaction of α,α-difluoro-γ-iodoketones **92** with aqueous ammonia at room temperature (94TL4319) (Scheme 67).

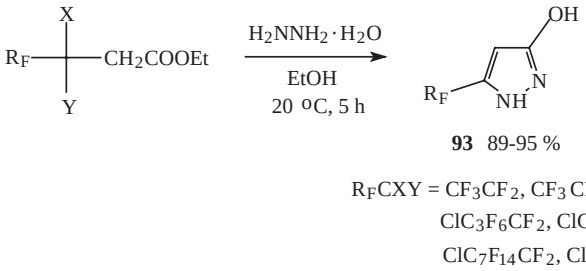
Pyrazoles and their substituted derivatives with perfluoroalkyl groups are important heterocyclic compounds widely employed in industries and in agriculture as biostatics, insecticides, and psychopharmacological agents. In the recent years, several procedures for the preparation of pyrazoles have been developed. Thus ethyl α-perfluoroalkylacetates react with hydrazine in ethanol, forming 3-hydroxy-5-perfluoroalkylpyrazoles **93** with excellent yields (95JFC(75)51) (Scheme 68). The solvent



Scheme 66



Scheme 67

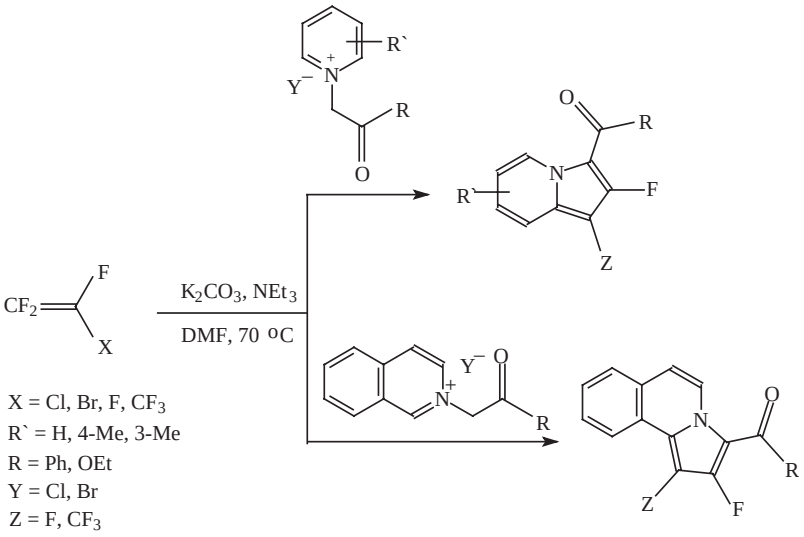


Scheme 68

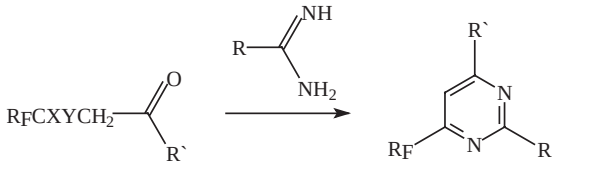
and the temperature as well as the length of the perfluoroalkyl chain do not have a pronounced effect on the reaction. This approach is very attractive due to the simple experimental procedure and the high product yields.

The reaction of fluoroolefins with pyridine *N*-ylides in the presence K_2CO_3 in DMF form indolizine and 4*H*-pyrrolo[1,2-*a*]benzimidazoles (03S35) (Scheme 69).

α-Fluoroalkyl alkyl ketones or α-fluoroalkyl aldehyde reacted with benzamidine or acetamidine to give 2(and 4)-substituted 6-fluoroalkyl pyrimidines **94** and **95** in high yields (96S997) (Scheme 70).



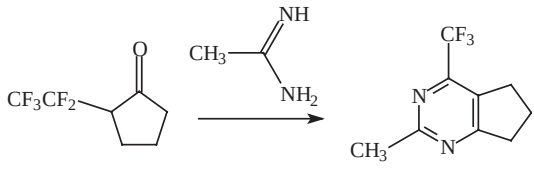
Scheme 69



94

R` = $C(CH_3)_3$

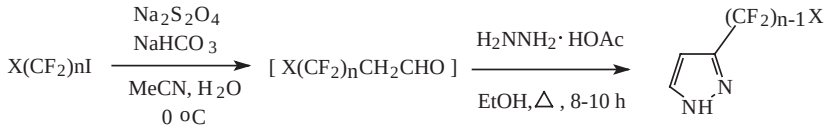
R_FCXY	R	Yield,%
CF_3CF_2	Ph	89
CF_3CF_2	Me	80
$Cl(CF_2)_3CF_2$	Ph	85
$Cl(CF_2)_3CF_2$	Ph	85



95 80 %

Scheme 70

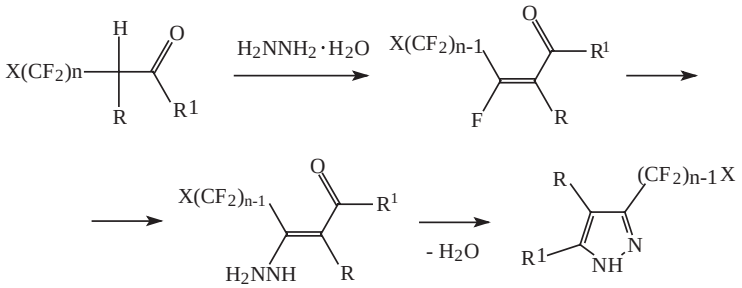
α-Perfluoroalkylaldehydes are important building blocks with fluorine atoms, synthesized from simple and accessible starting materials (91CJC167, 96JFC(79)77) and widely used in synthesis of various aromatic heterocycles (91CJC167). High yields of fluoroalkylaldehydes are obtained in reactions of fluoroalkyl iodides with



96

X	F	F	F	F	Cl	Cl	Cl
n	2	4	6	8	4	6	8
Yield, %	91	85	90	91	86	90	93

Scheme 71



97

Scheme 72

ethyl vinyl ether in the presence of sodium dithionite and sodium carbonate. Fluoro alkylaldehydes react with hydrazine in acetic acid forming 3-(fluoroalkyl)pyrazoles **96** (94JCS(P1)2161, 95JCS(P1)1039) (Scheme 71).

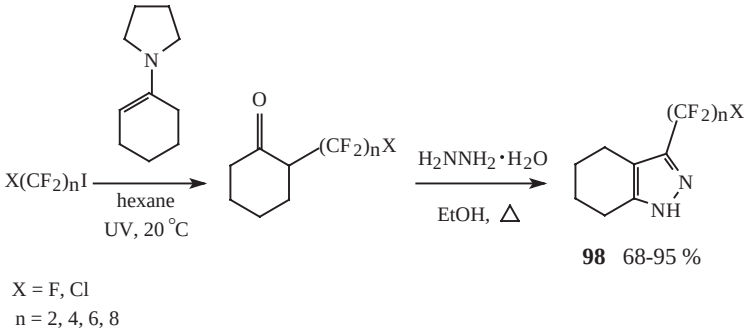
Interaction of α-polyfluoroalkylketones and hydrazine monohydrate forms 3-(polyfluoroalkyl)pyrazoles **97**. This reaction possibly occurs according to the Scheme 72 (92CCL583).

2-Polyfluoroalkylcyclohexanones, obtained by the reaction of polyfluoroalkyl iodides and 1-pyrrolidin-1-yl cyclohex-1-ene, react similarly with hydrazine hydrate, giving 3-polyfluoroalkyl-4,5,6,7-indazoles **98** (94JCS(P1)2161, 95JCS(P1)1039) (Scheme 73).

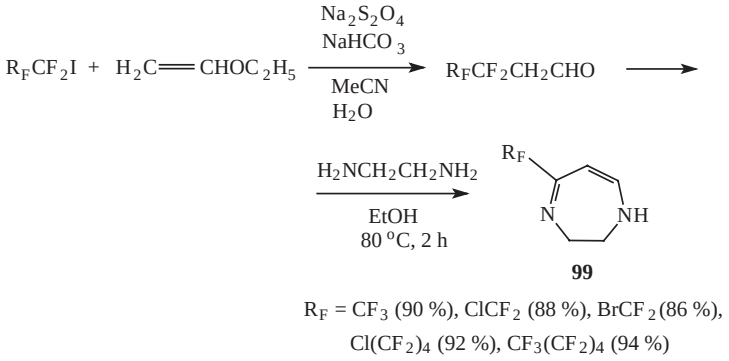
α-Perfluoroalkyl aldehydes may be prepared from ethoxyethylene in the presence of $Na_2S_2O_4/NaHCO_3$ in solvent $MeCN/H_2O$ and then condensed with ethylenediamine to give 5-perfluoroalkyl-2,3-dihydro-1,4-diazepines **99** (91CJC167, 96JFC(79)77, 94JCS(P1)2161, 95JCS(P1)1039, 98TL2377) (Scheme 74). The structure of the compound with $R_F = CF_3$ is confirmed by X-ray analysis (99JFC(94)79, 98TL2377).

The above reaction possibly proceeds via the intermediate enamine (99JFC(94)79) (Scheme 75).

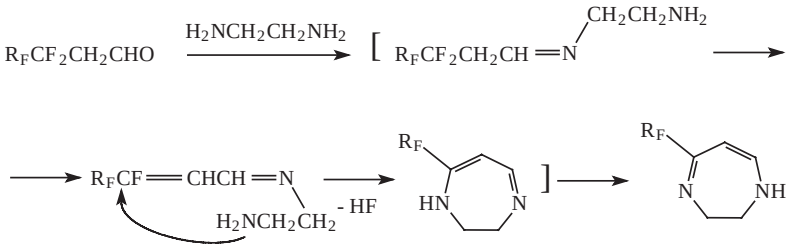
Using other dinucleophiles such as $H_2(CH_2)_3NH_2$, $H_2N(CH_2)_4NH_2$, $HOCH_2CH_2OH$, $HOCH_2CH_2NH_2$, and $HSCH_2CH_2NH_2$, none produced the corresponding ring products (98TL2377). Polyfluoroalkyl iodides reacted with 2,2-dimethyl-4-methylidene-1,3-dioxolane to provide the corresponding ketones **100**, which were in



Scheme 73



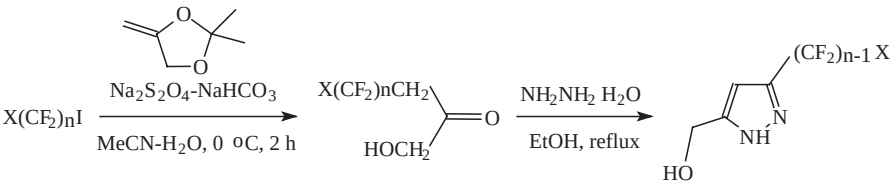
Scheme 74



Scheme 75

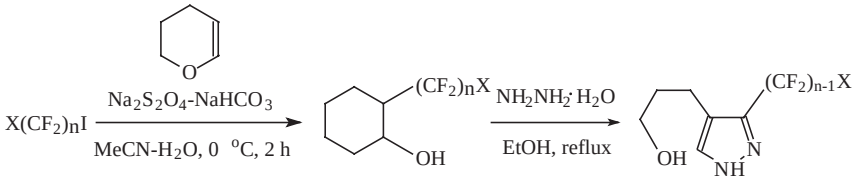
turn treated with hydrazine monohydrate in refluxing ethanol to give 3-(polyfluoroalkyl)-pyrazoles **101** (95JCS(P1)1039) (Scheme 76).

This reaction was also applied to a series of α-polyfluoroalkyl hemiacetals that were prepared conveniently from polyfluoroalkyl iodides and 3,4-dihydro-2*H*-pyran. A mixture of α-polyfluoroalkyl hemiacetals and hydrazine monohydrate was refluxed in ethanol for several hours and was then stirred to produce **102** in excellent yields (Scheme 77).



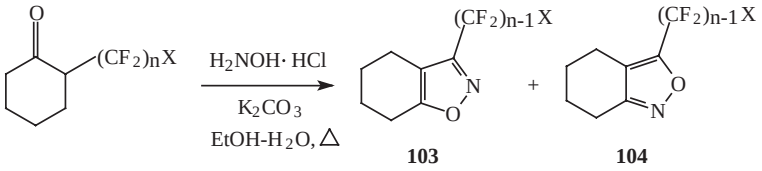
100 **101** 72-92 %

Scheme 76



102 81-96 %

Scheme 77



103 **104**

X = F, n = 2 (90 %), 4 (80 %), 6 (79 %), 8 (75 %);
X = Cl, n = 4 (82 %), 6 (81 %), 8 (85 %)

Scheme 78

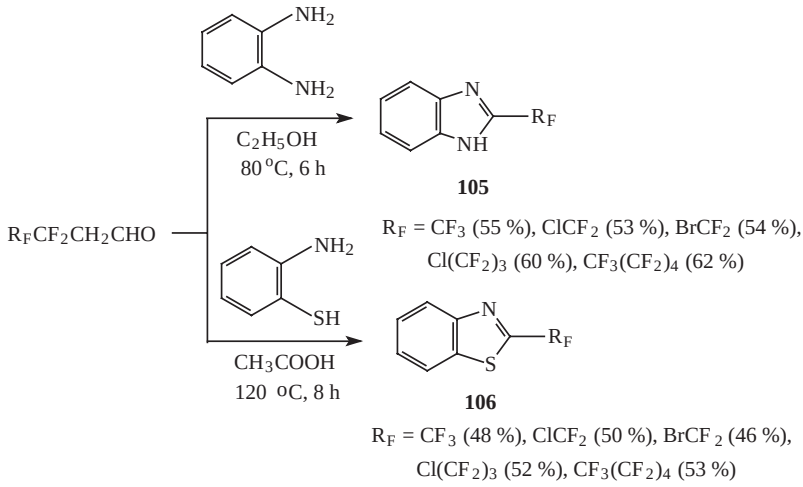
The reaction of hydroxylamine with α perfluoroalkyl-cyclohexanones leads to 4,5-(1,4-butylene)-3-perfluoroalkylisoxazolines **103** and **104** (95JFC(74)9) (Scheme 78).

Isomeric 5-perfluoroalkylisoxazoles are also formed; the reaction occurs via the formation of the corresponding oximes with quantitative yields.

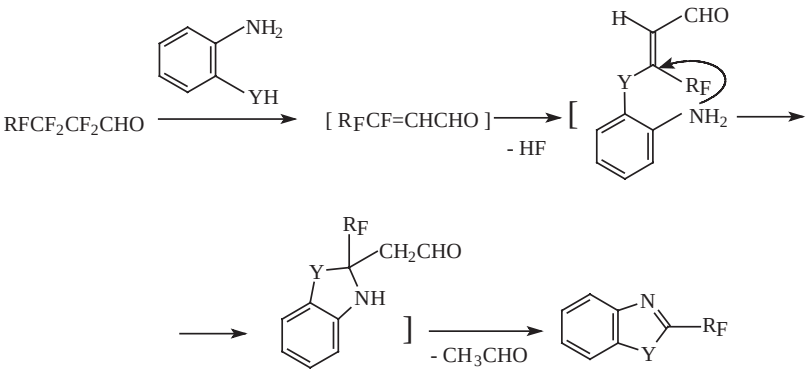
The reaction of *o*-phenylenediamine with α-perfluoroalkylaldehydes in ethanol produces 2-perfluoroalkyl-1H-benzimidazole **105** (99JFC(95)141) (Scheme 79). As a solvent, one can use acetonitrile, dioxane, or tetrahydrofuran. In the reaction with 2-aminothiophenol in acetic acid, the products are 2-perfluoroalkylbenzothiazoles **106**.

A possible reaction mechanism is suggested in Scheme 80 (99JFC(95)141).

The 1:1 adducts of perfluoroalkyl iodides with alkynes (97JFC(83)133, 94JCS(CC)631) or vinyl acetate (95CCL281) smoothly react with hydrazine hydrate or hydroxylamine, producing 3-perfluoroalkylpyrazoles **107** and 5-trifluoromethy-lisoxazoles **108**, respectively (Scheme 81). Synthesis of 3-trifluoromethylated pyrazoles is based on a sequence of two processes: (1) free-radical reaction of pentafluoroethyl iodide with alkyne, leading to the 1:1 adduct; (2) nucleophilic reaction of hydrazine with this adduct, forming the pyrazole ring.



Scheme 79

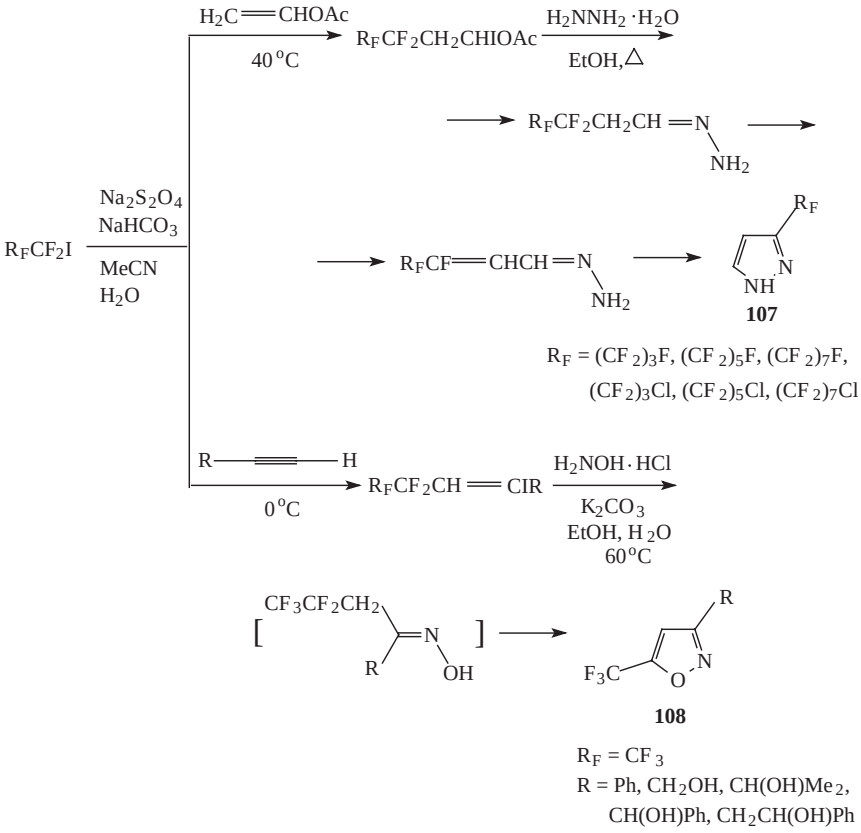


Scheme 80

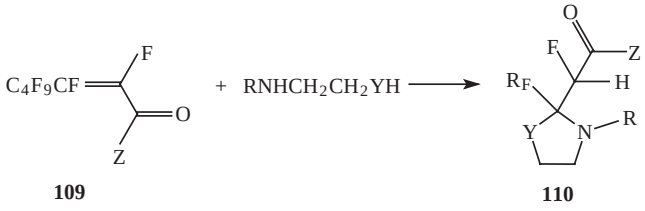
However, the presence of a C═C double bond in the molecule is not necessary for the intramolecular nucleophilic cyclization. The role of this bond can be played by other groups, for example, C═O carbonyl group. Thus synthetic equivalents of perfluoroenones (93JOC6675), 1-trialkylsilylperfluoroalkanols (94TL409), and 2-perfluoroenoxysilanes (93JOC6675) are known to react with binucleophiles, forming heterocyclic systems. The five-(imidazolines, oxazolines), six- (pyrimidines), and seven-(diazepines, thiaazepines) membered heterocycles can actually be obtained under mild conditions with high yields.

For example, the reaction of compound **109** with binucleophilic reagents follows Scheme 82 forming five-membered heterocycles **110** (94TL4357).

β-Polyfluoroalkylenaminones **111**, obtained by nucleophilic substitution of *N*-arylpolyfluoroalkylimidoyl iodides with a carbanion generated from α-methylketones, perform an important role in the synthesis of heterocyclic compounds. Thus in



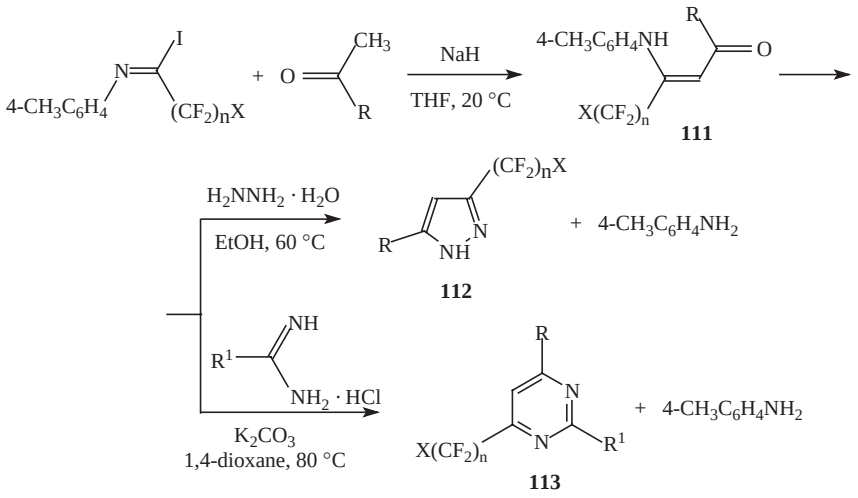
Scheme 81



Scheme 82

the reaction of compound **111** with hydrazine, the products are 3-polyfluoroalkyl-5-substituted pyrazoles **112**, whereas the reaction with benzamidine gives 2-phenyl-4-substituted 6-polyfluoro-alkylpyrimidines **113** (97JFC(84)65) (Scheme 83).

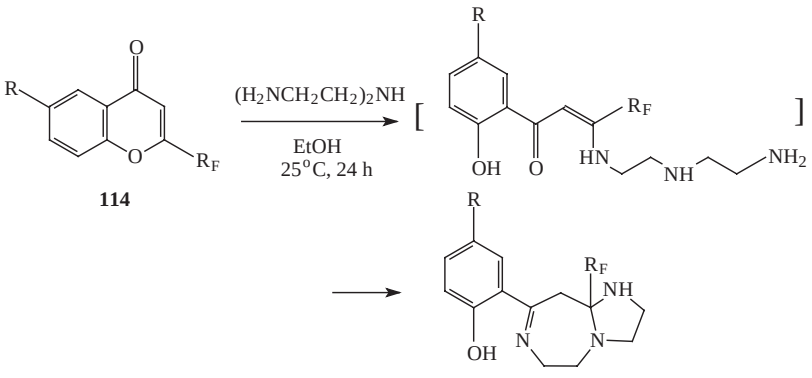
Heterocycle-forming reactions with binucleophilic reagents also occur with cyclic systems containing a double bond activated with a perfluoroalkyl substituent and a



112 R, n, X (Yield, %) : Ph, 2, Cl (93); Ph, 4, Cl (86); Ph, 1, F (90); 2-furyl-, 2, Cl (79); 2-furyl-, 4, Cl (50); 2-furyl-, 1, F (72); ^{t}Bu, 2, Cl (71); Me, 2, Cl (72).

113 R, n, X (Yield, %) : Ph, 2, Cl (90); Ph, 4, Cl (93); Ph, 1, F (96); Me, 2, Cl (96); Me, 4, Cl (94); Me, 1, F (70).

Scheme 83

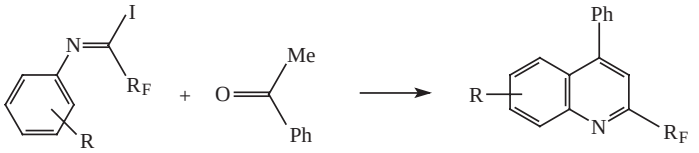


115

R	H	5-Me	H	5-Me	H
R_F	CF_3	CF_3	$(CF_2)_2H$	$(CF_2)_2H$	CHF_2
Yield, %	80	67	54	65	54

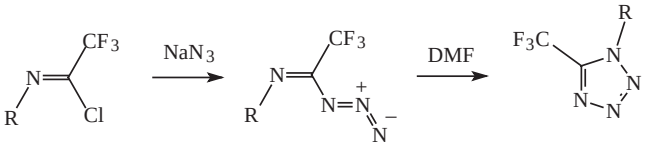
Scheme 84

carbonyl group. Indeed, the reactions of 2-polyfluoroalkyl-chromones **114** with diethylenetriamine in ethanol at 25 °C lead to 2-hydroxyaryl derivatives of 1,4,8-triazabicyclo-[5.3.0]-dec-4-ene **115** (99IZV1825) (Scheme 84).



R = 4-Me, 2-Cl, 4-Cl, 4-I
$R_F = C_2F_4Cl, C_4F_8Cl$

Scheme 85



R = Ph (80 %), 4-MeC_6H_4 (91 %),
3,4-Me$_2C_6H_3$ (68 %), 4-ClC_6H_4 (53 %),
3,4-Cl$_2C_6H_3$ (50 %), 4-BrC_6H_4 (55 %),
4-$NO_2C_6H_4$ (70 %), 2-$NO_2C_6H_4$ (53 %),
4-MeOC_6H_4 (94 %), $PhCH_2CH_2CH_2$ (61 %)

Scheme 86

At first, the nucleophilic attacks the C(2) atom of the pyrone ring, accompanied by ring cleavage the N-substituted aminoenones intermediate subsequently cyclized into the triazabicycles with the participation of both electrophilic centers and liberation of water (99IZV1825).

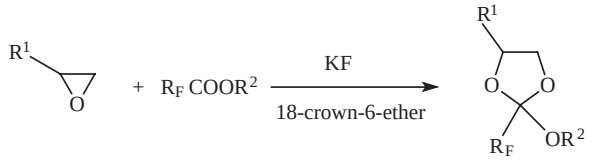
The reactions of *N*-arylpolyfluoroalkylimidoyl iodides with acetophenone produce 2-polyfluoroalkylquinolines (97CJC278) (Scheme 85).

N-substituted trifluoroacetimidoyl chlorides are often used as building blocks for syntheses of heterocyclic compounds with trifluoromethyl groups (95JFC(74)279, 96S511, 86TL4821). For example, 1-substituted 5-tri-fluoromethyltetrazoles were synthesized in this way (99JFC(99)83) (Scheme 86).

Condensation of perfluorocarboxylates with oxiranes in the presence of tetrabutylphosphonium bromide (TBPB) or KBr/18-crown-6-ether as catalysts gives heterocyclic compound **116** (95TL2781) (Scheme 87).

Pyrroles are obtained from perfluorocarboxylic acid amides reacting with substituted olefins in the presence of mineral acids (98PEP816337).

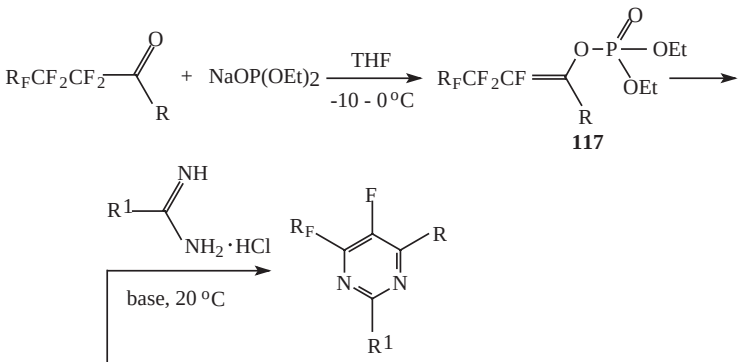
Ishihara et al. (89JKKP01 22856, 88CL819) found that 1-substituted perfluoro-1-alkenyl phosphates **117** obtained from perfluoroalkylketones (84JFC(25)47) may be used as powerful precursors for synthesis of various fluorine-containing pyrimidines and pyrazoles. For example, enolphosphate **117** reacts with amidines (Ph and Me) in the presence of bases in tetrahydrofuran for 3–12 h at room temperature. The reaction leads to 4-alkyl-6-perfluoroalkyl-5-fluoropyrimidines **118**; with methylhydrazine, pyrazoles **119** are formed in almost quantitative yields (Scheme 88).



116 50-85 %

R^1 = $MeOCH_2$, $PhOCH_2$
R^2 = Et, ^{i}Pr, $PhCH_2$, Me
R_F = CF_3, C_2F_5

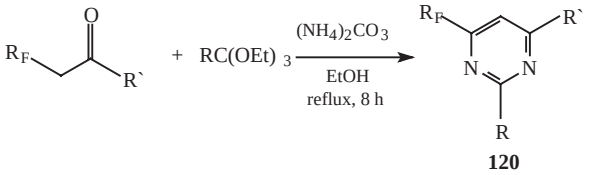
Scheme 87



Scheme 88

α-Fluoroalkyl-substituted carbonyl compounds react with triethylorthoacetals in the presence of ammonium carbonate to form fluoroalkylpyrimidines **120**; with cyclic ketones, the products are condensed pyrimidines **121** (97SL1261) (Scheme 89).

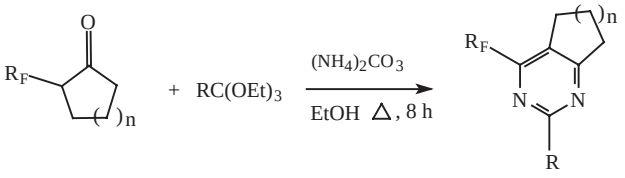
Fluorine-substituted heterodienes undergo a Diels-Alder reaction with dienophiles, generally forming six-membered heterocycles, for example, pyrroles (81JOC147, 81JOC153, 81T1779, 81JOC144) (Scheme 90).



120

R = Me, Et

$R_F = Cl(CF_2)_4$, R` = $^t$Bu (90 %); $R_F = Cl(CF_2)_4$, R` = Me (85 %);
$R_F = Cl(CF_2)_4$, R` = H (71 %); $R_F = BrCF_2CF_2$, R` = H (70 %);
$R_F = CF_3(CF_2)_5$, R` = ^{t}Bu (40 %)



121

R = Me, Et

$R_F = Cl(CF_2)_4$, n = 2 (85 %); $R_F = C_2F_5$, n = 1 (82 %);
$R_F = ClCF_2CF_2$, n = 2 (85 %)

Scheme 89

An interesting method using 1,5-diazapentadienium salts **122** has been described. (For detailed synthetic procedures, see review (00JFC(105)295)). These salts possess high reactivity and form five- and six-membered heterocyclic compounds in reactions with bifunctional heteronucleophiles. Thus trifluoromethyl derivatives of pyrimidine **123** and pyrazole **124**, respectively, in 65–69% yield, are formed in the reaction of 3,3,3-trifluoropropionic acid with amidines and hydrazines in the presence of $POCl_3$/Me_2NCHO (96TL1829) (Scheme 91).

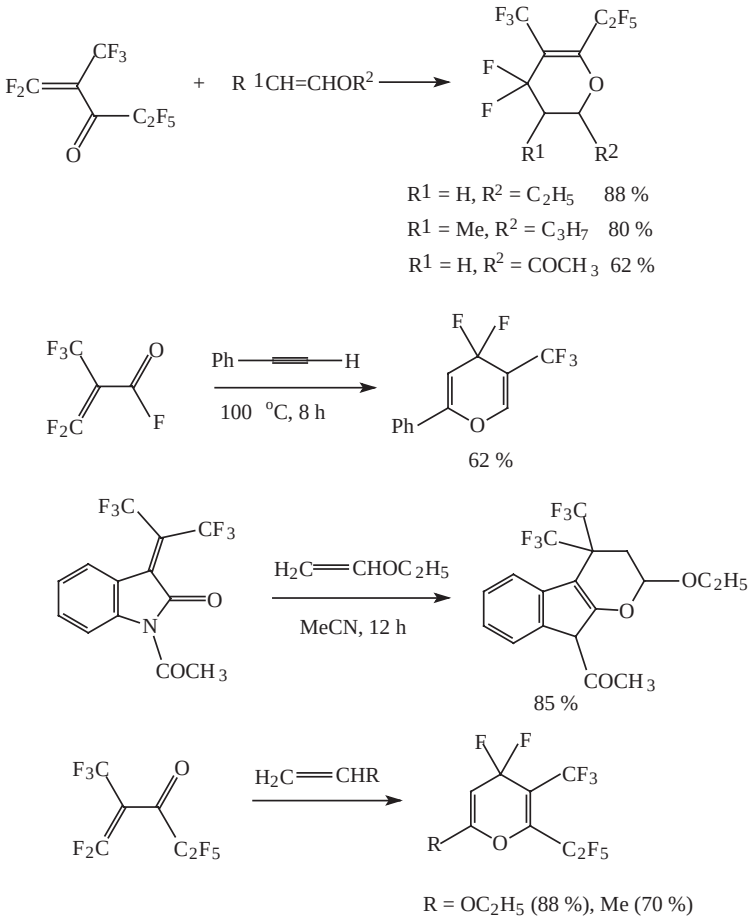
The reaction occurs following Scheme 92:

The free amino group of the amidine attacks the carbon atom of salt **122**. The intermediate imine undergoes intramolecular cyclization, forming dihydropyrimidines, transformed into pyrimidines **123** by dialkylamine elimination.

1,1-Dicyano-2,2-bis(trifluoromethyl)ethylene **125** has been successfully applied in heterocyclic chemistry (93BAU512, 90JFC59, 91JFC(51)323, 92BAU2068, 97JFC(83)133). It served as a precursor for the synthesis of different classes of CF_3-containing nitrogen heterocycles, in particular, for 1,4-dihydropyridines and 1,4-dihydropyrimidines possessing arthropodicidal activity (97WO9711057). Current interest in the synthesis of condensed pyrazoles (90ZN1675, 98JHC333, 87AHC319, 90AHC223) due to their biological activity explains the focus on these heterocycles.

5-Amino-3,3-bis(trifluoromethyl)-1-phenyl-4-cyano-4-pyrazole **126** was obtained by the reaction of 2,2-bis(trifluoromethyl)-1,1-dicyanoethylene with phenylhydrazine (88IZV2417, 88IZV1917) (Scheme 93). The structure is confirmed by X-ray analysis.

The reaction of olefin **125** with 1,2-phenylenediamine in absolute diethyl ether at 20 °C forms 2-amino-4,4-bis(trifluoromethyl)-3-cyano-4,5-dihydro-1H-1,

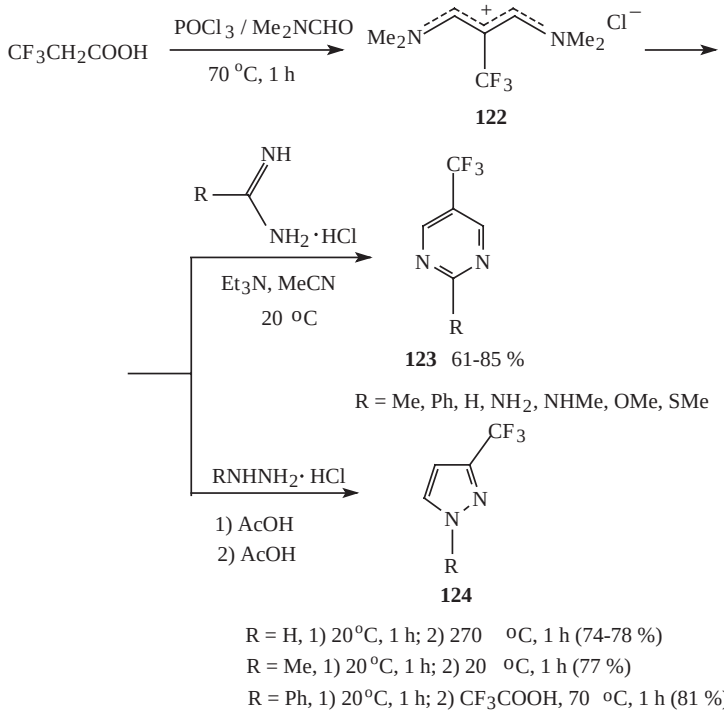


Scheme 90

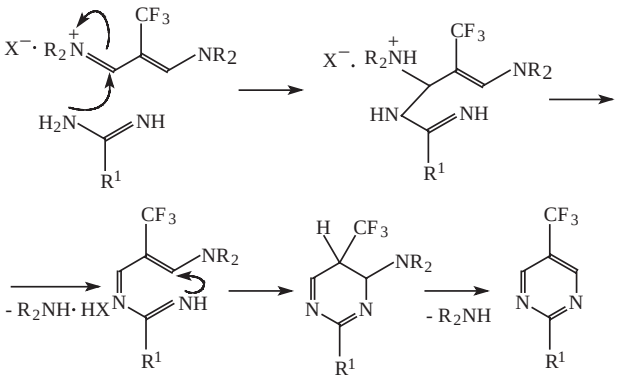
5-benzodiazepine **127** (yield 55%) (88IZV1920, 88IZV1451). The reaction with α-naphthylamine at 20 °C gives 2-amino-4,4-bis(trifluoromethyl)-3-cyano-1,4-dihydrobenzo[*h*]quinoline **128** (91% yield) (00IZV1261) (Scheme 93). The structure of compound **128** was determined from X-ray data (00IZV1261).

The reaction of 2-trifluoromethyl-2-chloro-1,1-dicyanoethylene with 2-aminopyridine and 2-aminopicolines at room temperature leads to 4-amino-2-trifluoromethyl-3-cyano-4*H*-pyrido[1,2-*a*]pyrimidines **129** (00IZV1261) (Scheme 94). The structure of 4-imino-7-methyl-2-trifluoromethyl-3-cyano-4*H*-pyrido[1,2-*a*]pyrimidine (56% yield) is confirmed by X-ray analysis (00IZV1261). The reaction probably occurs via alkenylation of the amino group of aminopyridine with 2-chloroethylene and subsequent intramolecular cyclization.

Under similar conditions 1-methoxycarbonyl-2-trifluoromethyl-2-chloro-1-cyanoethylene gives 2-trifluoromethyl-3-cyano-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **130** (23–53% yield). The structure of 4-imino-7-methyl-2-trifluoromethyl-3-cyano-4H-pyrido



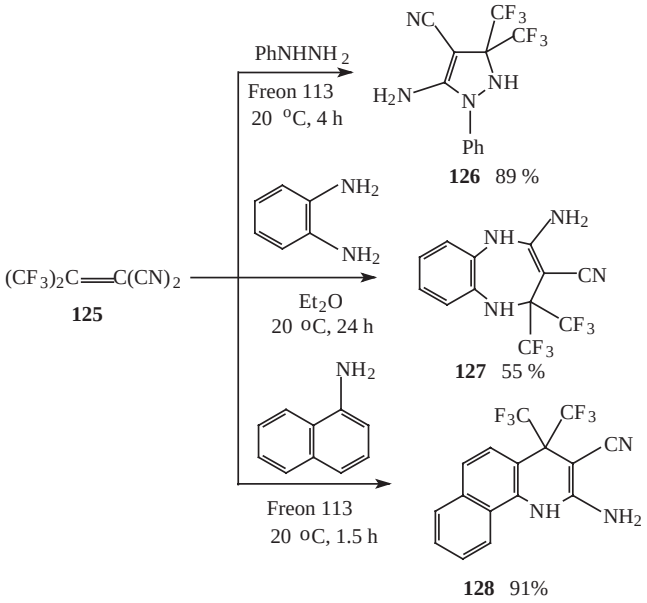
Scheme 91



Scheme 92

[1,2-*a*]pyrimidine (56% yield) is confirmed by X-ray data (00IZV1261). In reactions with aromatic amines and diamines, various nitrogen-containing heterocyclic compounds are formed (02JFC(114)63) (Scheme 95).

Alkenes-containing CN groups reacted with N-unsubstituted amidines (benzamidine, acetamidine, and trifluoroacetamidine) to give 1,4-dihydropyrimidines in fair



Scheme 93

to good yields (97WO9711057, 02JFC(114)63). These alkenes reacted with 3(5)-aminopyrazole and 3(5)-amino-5(3)-methylpyrazole to give (1:1) adducts **132** in good yields. According to X-ray analysis, this adduct is a pyrazolo-[1,5-*a*]pyrimidine (97WO9711057, 02JFC(114)63).

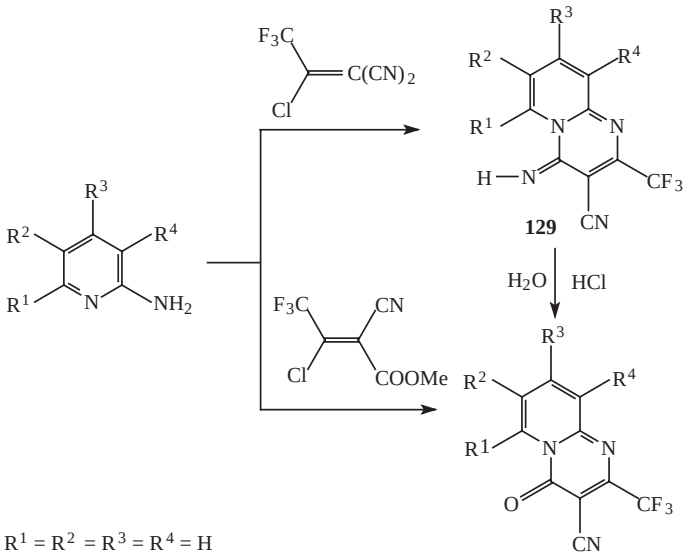
Reacting these alkenes with 3-methyl-1-phenyl-2-pyrazolin-5-one and 3-methyl-1(4-fluoro-phenyl)-2-pyrazolin-5-one gave pyrano[2,3-*c*]pyrazoles. The structure of 6-amino-5-cyano-4,4-bis(chlorodifluoromethyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole were proved by X-ray analysis (02JFC(114)63).

These examples prove that using fluoroolefins with electron-accepting substituents is a general technique leading to various heterocyclic compounds.

IV. The Use of Alkynes Containing Perfluoroalkyl Groups in the Synthesis of Heterocyclic Compounds

A similar route would be expected for O-, S-, and N-binucleophilic reagents in reactions with perfluorinated alkenes or perfluoroalkyl-substituted alkynes (91RCR501), forming a series of perfluoroalkyl-substituted heterocycles with high-potentially biological activities.

Perfluoroalkylacetylenes have been found to act as good electrophiles since the perfluoroalkyl group R_F significantly enhances the electrophilic character of the triple bond (91JSOCJ612, 91AHC1). Indeed, with various binucleophilic reagents (1,2-ethanedithiol, 2-mercaptoethanol, ethyleneglycol, and ortho-phenylenediamine),



Scheme 94

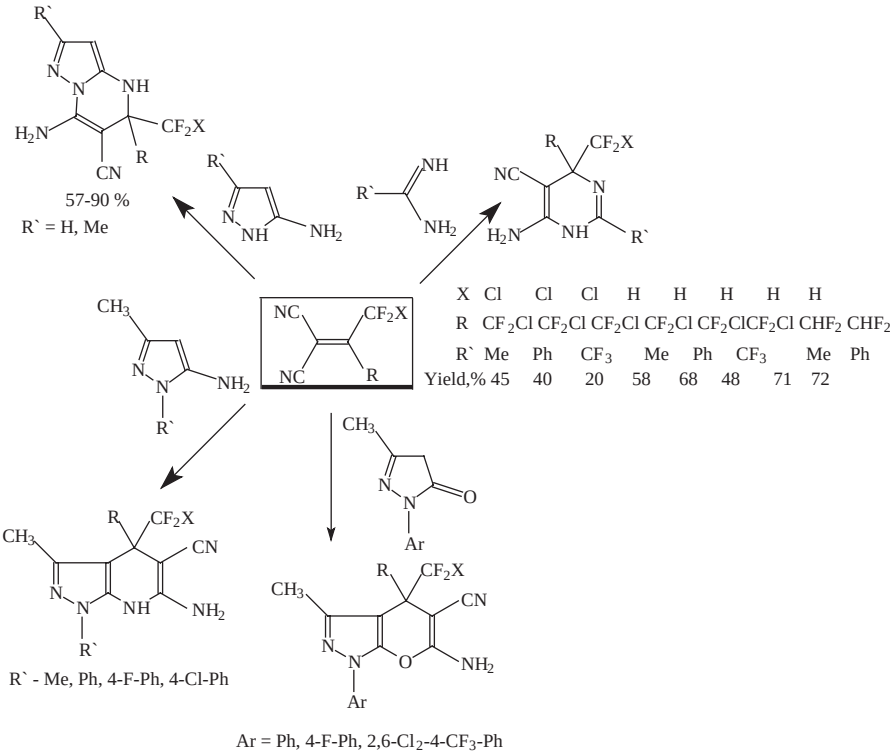
perfluoro- and polyfluoroalkylacetylenecarboxylic acids $R_FC{=}C{-}COOH$ ($R_F = CF_3$, CHF_2, and $CHF_2CF_2CF_3$) undergo inter- and intramolecular Michael reactions, giving heterocyclic compounds with two heteroatoms (imidazolidine, thiazolidine, and oxazolidine) (98NKK1321, 89NKK1864, 94BCS3021, 92JFC(57)177, 88JFC(41)227, 85S970, 86T663).

Thus, 4,4-difluoro-2-butynoic acid was allowed to react with ethylenediamine in ethanol water (1:3) at room temperature for 0.5 h to give to 2(difluoromethyl)imidazolidine-2-acetic acid in 97% yield (94BCS3021) (Scheme 96).

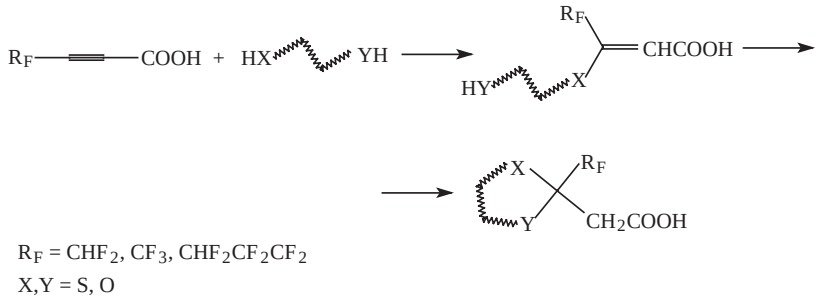
The reaction of perfluoroalkylacetylenecarboxylic acid with 1,2-dithioethane in the presence of alkalies at room temperature leads to the Michael product, a mixture of *E*- and *Z*-isomer acids of 3-(2-mercapto-ethylthio)perfluoroalk-2-enes **133**. The latter are capable of nucleophilic cyclization, leading to the formation of 2-(carboxymethyl)-2-perfluoroalkyl-1,3-dithiolane **134**; the product of intermolecular nucleophilic addition is formed as an impurity (94BCS3021) (Scheme 97).

1,3-Dithiolpropane reacts similarly, producing 4,4,5,5,6,6-hexafluoro-3-(3-mercaptopropylthio)hex-2-enic acid **135** as a Michael adduct and cyclic product **136** (Scheme 98).

When stored with 2-mercaptoethanol in the presence of equimolar amounts of KOH at room temperature in a 1:3 ethanol water mixture, perfluoroalkylacetylenecarboxylic acid gives Michael adduct **137** (1:1 mixture of *E*- and *Z*-isomers) in >85% yield. At 60 °C, the adduct undergoes cyclization, forming 2-(carboxymethyl)-2-polyfluoroalkyl-1,3-oxathiolane **138** (Scheme 99).



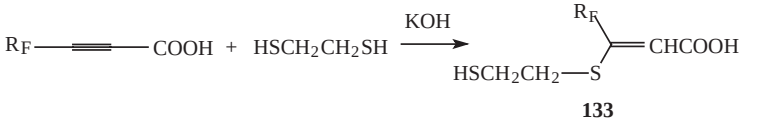
Scheme 95



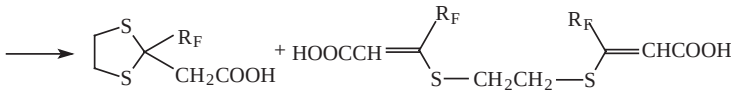
Scheme 96

Under more rigid conditions, the reaction with ethyleneglycol gives 2-(carboxymethyl)-2-polyfluoroalkyl-1,3-dioxolane **139** and the corresponding acid, 3-ethoxy-3-polyfluoroalkylbut-2-enylic acid **140** (Scheme 100).

The reaction with ethylenediamine also gives a five-membered heterocyclic compound, 2-polyfluoroalkyl-2-methylimidazolidine **141**. Its formation is explained by decarboxylation of enamine **143**, formed as an intermediate with **142** (94BCS3021) (Scheme 101).



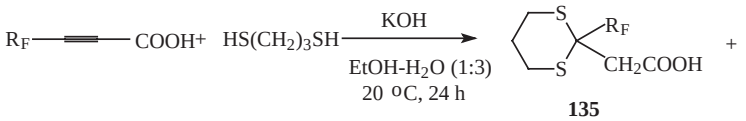
133



134

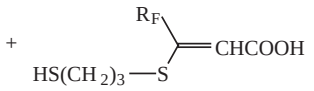
$R_F = CF_3, CHF_2, H(CF_2)_3$

Scheme 97



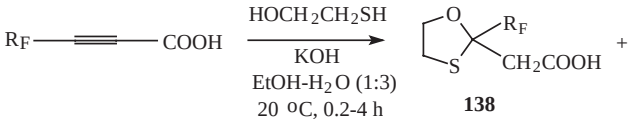
135

$R_F = CHF_2$ (74 %), $CHF_2(CF_2)_2$ (26 %)



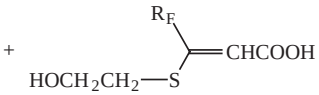
136

Scheme 98



138

$R_F = CHF_2$ (80 %), CF_3 (76 %)

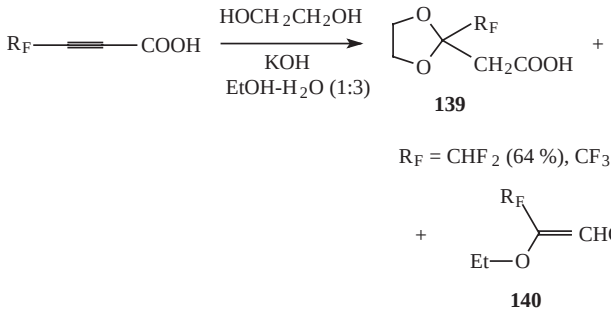


137

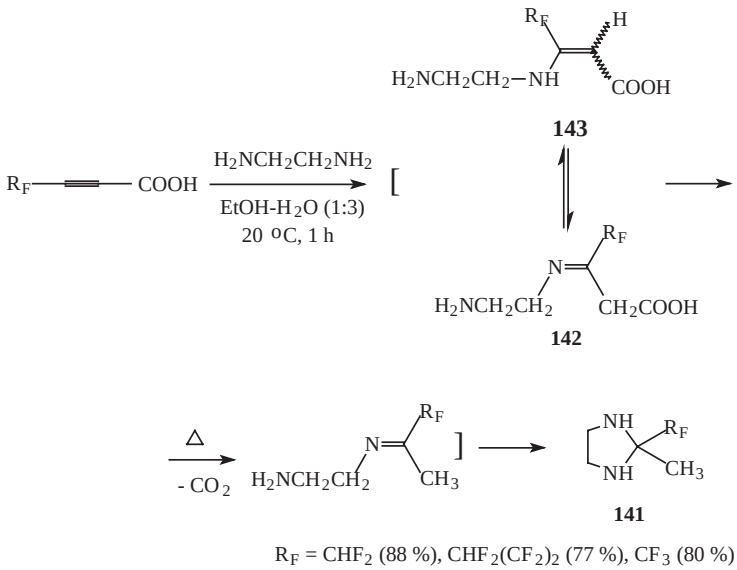
Scheme 99

The intermediate formation and decarboxylation of enamine **143** also takes place in the reaction with *o*-phenylenediamine (product **144**) (Scheme 102). This is a general reaction for N-nucleophiles.

For example, the reaction with 2-aminoethanethiol occurs with decarboxylation of intermediate **145**, leading to 2-difluoromethyl-2-methyl-1,3-thiazolidine **146** (94BCS3021) (Scheme 103).



Scheme 100

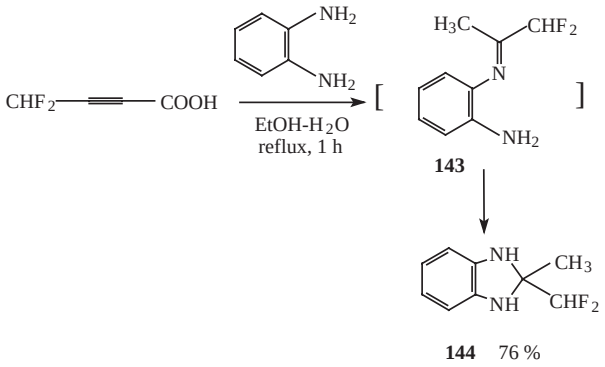


Scheme 101

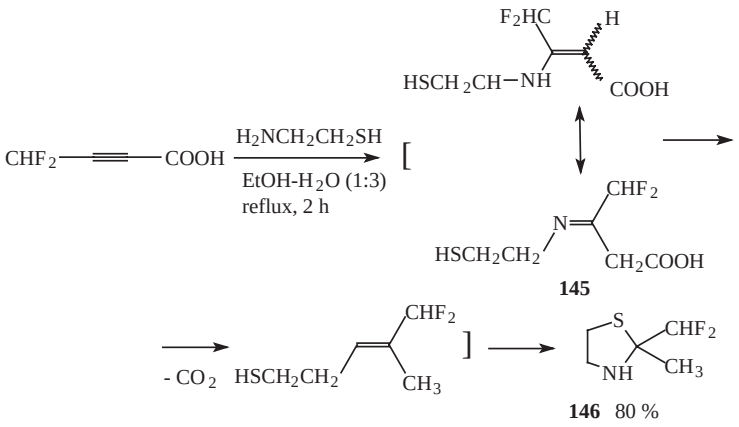
In the reaction of methyl mercaptoacetate with ethyl perfluoroalkyl-acetylenic ester, the products are thiophene **147** and a mixture of *Z*- and *E*-isomers of ethyl 3-perfluoroalkyl-3(carbomethoxymethylthio)prop-2-enate. When the mixture is treated with sodium methoxide, thiophene **148** is formed (86T663) (Scheme 104).

Fluorinated alkynes have been found to be good dipolarophiles as exemplified by the reaction of aromatic nitrile oxides with hexafluoro-2-butyne (85S970). The reaction of aromatic nitrile oxides with methyl perfluoro-2-alkynoates gave fluoroalkylisoxazoles **149** and **150** (Scheme 105).

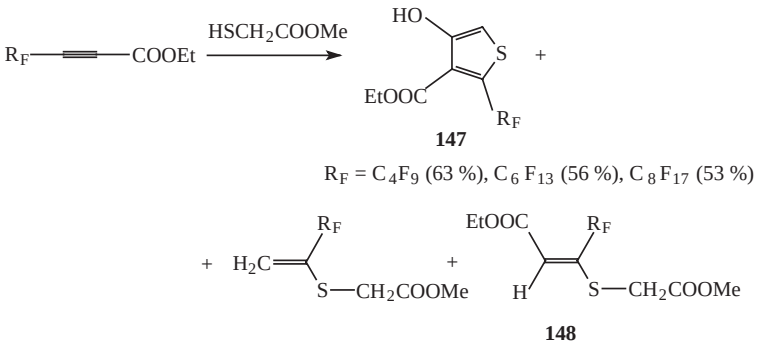
The addition of monosubstituted alkylhydrazines to perfluoroalkylacetylenic esters gives 5-substituted 1-alkyl-3-hydroxypyrazoles as major products (92JOC5680). Thus, methylhydrazine yields 1-methyl-5-pentafluoroethyl-1*H*-pyrazol-3-ole (92JOC5680). Regiospecific cyclocondensation of the ethyl ester of



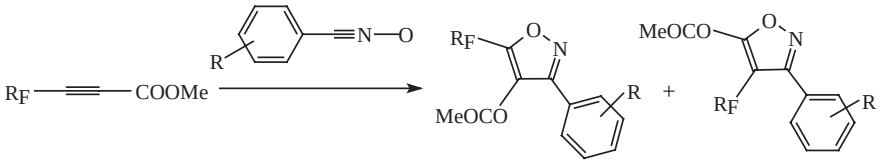
Scheme 102



Scheme 103



Scheme 104

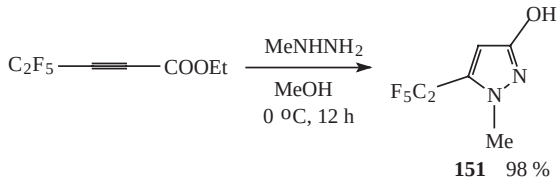


149 89-97 % 90:10 **150**

$R_F = CF_3, C_2F_5, C_3F_7$

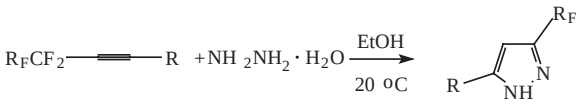
R = H, 2-Cl, 4-Cl, 4-Me

Scheme 105



151 98 %

Scheme 106



152

R_F	$F(CF_2)_3$	$Cl(CF_2)_3$	$F(CF_2)_5$	CF_3	CF_3	CF_3	$Cl(CF_2)_3$	$Cl(CF_2)_5$	$Cl(CF_2)_3$
R	Ph	Ph	Ph	Ph	CH_2OH	CH(OH)Me	$C(OH)Me_2$	CH_2OH	CH_2OH
Yield,	96	95	98	94	95	92	94	96	95

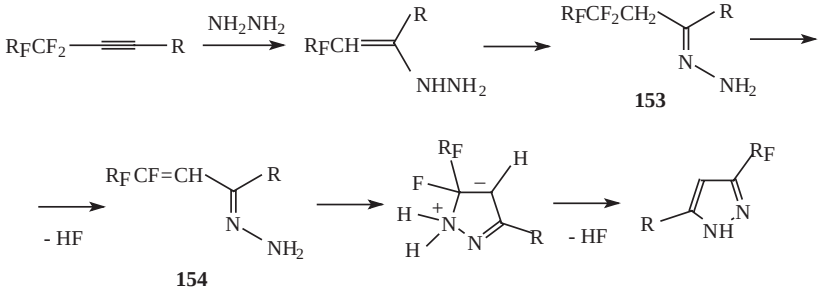
Scheme 107

pentafluoroethylacetylenic acid with methylhydrazine afforded 3-hydroxy-5(pentafluoroethyl)-1-methylpyrazole **151** (Scheme 106).

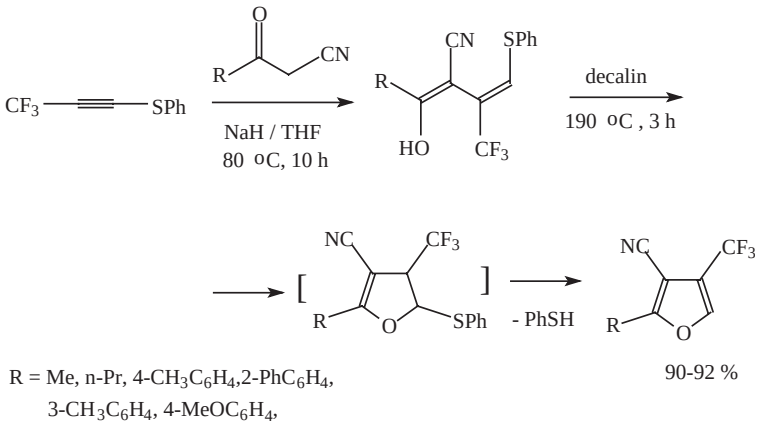
It was shown (95JFC(73)129) that the reactions of perfluoroalkylacetylenes with hydrazine hydrate form 3-perfluoroalkylpyrazoles **152** in high yields (Scheme 107).

These reactions serve as examples of a convenient route to 3-perfluoro-alkyl-substituted pyrazoles, emerging as a new type of fluorine-containing compound possessing high biological activities such as herbicides, fungicides, insecticides, etc. (90PJJ02 129171, 87GP3713774, 88EPA295117).

This reaction is assumed to proceed via nucleophilic attack of hydrazine monohydrate on perfluoroalkylacetylenes to give hydrazone intermediate **153**, which eliminates HF to form the intermediate **154**. Such intramolecular nucleophilic addition, followed by elimination of another molecule of HF to give the 3-perfluoroalkyl pyrazoles, occurs as shown in Scheme 108 (95JFC(73)129).



Scheme 108



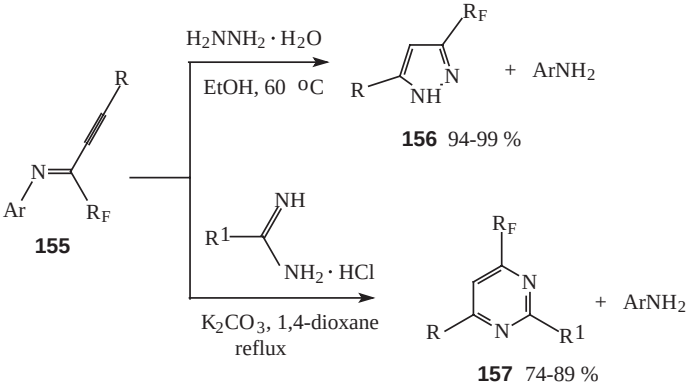
Scheme 109

When trifluoromethyl phenylthio acetylene was treated with an active methylene (e.g. benzoylacetonitrile) it gave (1*E*,3*E*)-2-trifluoro-methylbutadienyl phenyl sulfides regio- and stereoselectively. These then underwent intramolecular cyclization in decalin at 190 °C or in acetic acid with 1,4-benzoquinone oxidant and sodium acetate to afford 3-trifluoromethyl-substituted furans in high yields (02TL665) (Scheme 109).

1-Perfluoroalkyl-*N*-arylacetyleneimines **155**, obtained by the reactions of acetylenes with *N*-arylperfluoroalkylimidoyl iodide in the presence of $Pd(PPh_3)_2Cl_2/CuI$ in Et_3N/MeCN, react with hydrazine hydrate in ethanol (or CH_3OH, DMF, MeCN) at 60 °C or with benzamidine in dioxane in the presence of boiling K_2CO_3 to give pyrazoles **156** and pyrimidines **157** (98JFC(87)69) (Scheme 110).

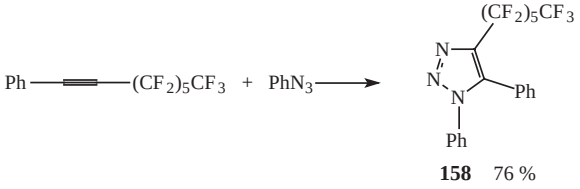
The reaction of phenyl azide with fluorinated phenylacetylenes gives triazoles **158** in 76% yields (75JOC810, 92LA947, 91JFC(55)199, 85ZOR979, 83ZOR221, 84JFC(26)47, 83JCS(P1)1) (Scheme 111).

Some examples demonstrate the dipolarophilic properties of perfluoroalkyl-substituted acetylenes (Scheme 112). The high regioselectivity of the reactions of perfluoroalkylacetylene with 4-methoxyphenyl azide (85ZOR979), benzonitrile oxide (83JCS(P1)1, 83ZOR221), and diphenyldiazomethane (83JCS(P1)1, 83JCS(P1)1)

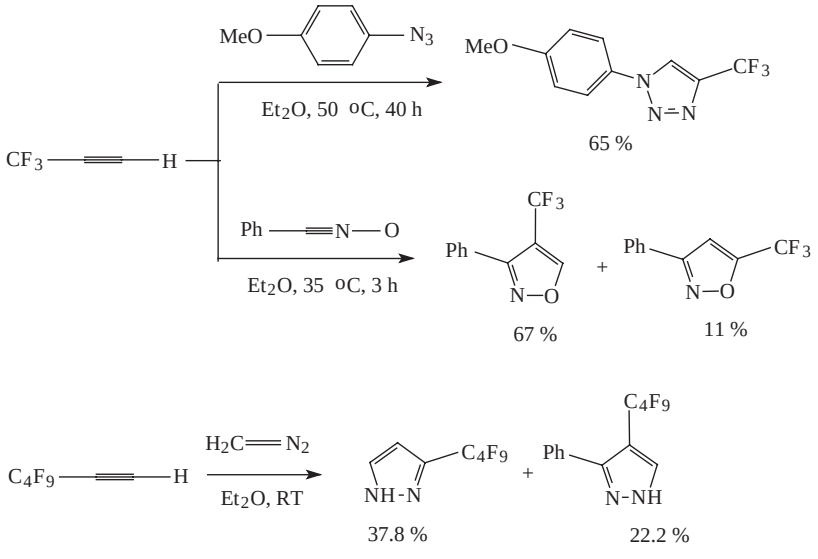


R = Ph, Me_3Si, n-Bu, CH_3COO
R^1 = Ph, Me
R_F = CF_3, C_4F_9, C_4F_8Cl, C_2F_4Cl

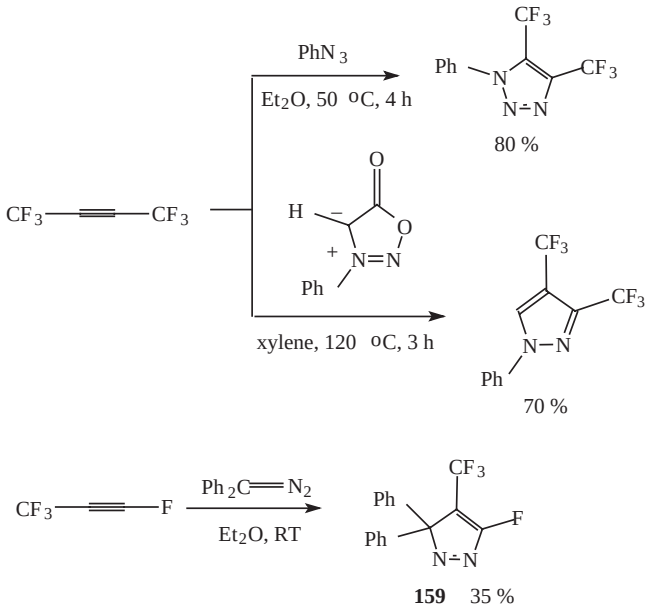
Scheme 110



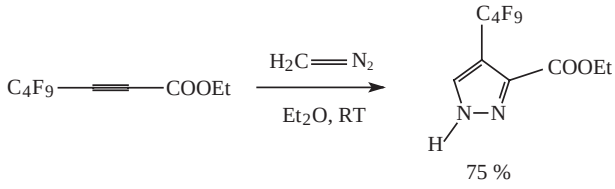
Scheme 111



Scheme 112



Scheme 113



Scheme 114

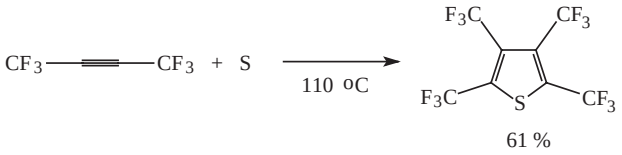
leads to the formation of five-membered heterocyclic compounds. The latter gives 5-fluoro-3,3-diphenyl-4-trifluoromethyl-3*H*-pyrazole as a single product **159**, although the regiochemistry is undetermined (Scheme 113).

In a similar procedure, perfluoro-2-butyne reacts with various 1,3-dipoles (85ZOR979), and perfluoropropyne reacts with diphenyldiazomethane (83JCS(P1)1).

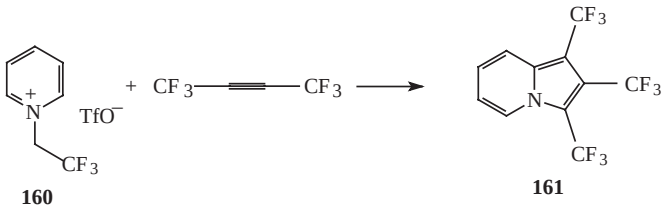
Regiospecific addition of diazomethane takes place with an ethyl acetylenecarboxylate (84JFC(26)47) (Scheme 114).

N,*N*-dibutyl(3,3,3-trifluoro-1-propyne)amine ($CF_3C{=}CNBu_2$) and $CH_2{=}CHCOMe$ undergo cycloaddition, resulting in a Diels–Alder adduct, 2-dibutylamino-6-methyl-3-trifluoromethyl-4*H*-pyrane (97% yield) (00CL666). This is a common property of fluorinated acetylenes, affording heterocycles with perfluoroalkyl groups.

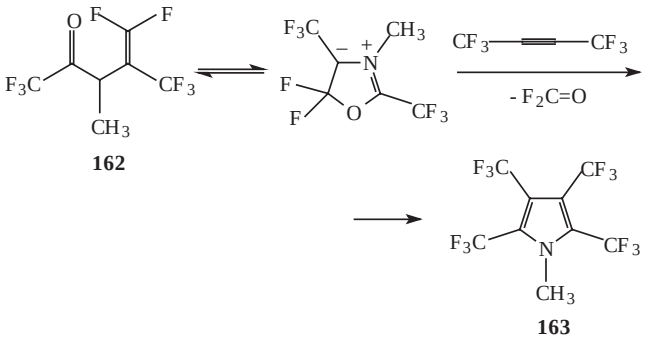
Perfluoro-2-butyne and elemental sulfur react on heating, forming tetrakis(trifluoromethyl)thiophene (sulfolane at 110 °C) (84JFC(26)47) (Scheme 115). However, the mechanism is unknown.



Scheme 115



Scheme 116



Scheme 117

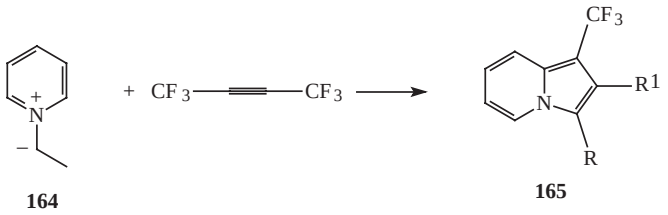
The partially fluorinated azomethine ylides precursor **160** possess high reactivity; they are capable of [3 + 2] cycloaddition with alkynes, giving indolizines **161** (86JFC(34)275, 88JFC(38)289, 91JFC(51)407) (Scheme 116).

N-methyl-*N*-(2-perfluoropropenyl)trifluoroacetamide **162** is a valence tautomer of the cyclic ylide azomethine; it is capable of reacting with various dipolarophiles. Thus [3 + 2] cycloaddition with alkynes leads to the trifluoromethyl derivative of pyrrole **163** (89BAU1325) (Scheme 117).

Perfluoro-2-butyne reacts with pyridine ylide **164** in the presence of sodium hydride, and [3 + 2] cycloaddition yields the trifluoromethyl derivative of indolizine **165** (91JFC(51)407) (Scheme 118).

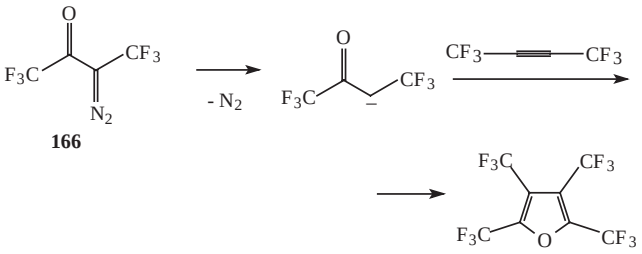
Photolysis of hexafluoro-3-diazobutan-2-one **166** and perfluoro-2-butyne affords the trifluoromethyl derivative of the five-membered heterocycle (tetrakis-(trifluoromethyl)furan) (77CZ402, 79BAU1688, 86JFC(34)275) (Scheme 119).

Hexafluoro-2-butyne is used increasingly as a definitive acetylenic dienophile in Diels–Alder reactions. For example, to prepare bicycloalkanes via its reaction with



R = COOEt, COPh
R1 = H, CF_3

Scheme 118



Scheme 119

cis,trans-1,3-undecadiene (79TL3401) and to do a tendem Diels–Alder reaction with a 1,1-bis(pyrrole)methane (85JCS(CC)1621). Its reactions with pyrrole derivatives and furan have been used in the synthesis of 3,4-bis(trifluoromethyl)pyrrole (83S313, 82JOC4779) and 1,4-bis(trifluoromethyl)benzene-2,3-oxide (86CB589), respectively (Scheme 120).

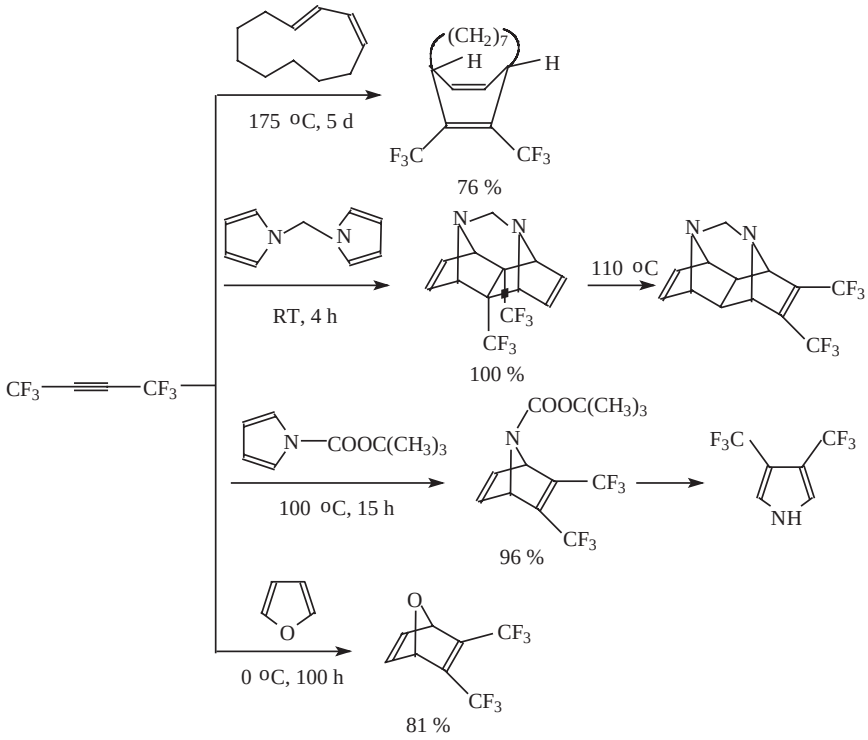
γ-Rays induced addition an reaction of propionaldehyde with hexafluoro-2-butyne in Freon 113 and the product was treated with sulfuric acid to give 2,5-diethyl-3,4-bis(trifluoromethyl)furan (94% yield) (91JHC225).

The intermediates formed from α-halo-hydrazones nitrileimines **167**, 1,3-dipoles, undergo [3 + 2] cycloaddition with various substituted 1-aryl-3,3,3-trifluoro-1-propynes, resulting in triaryl-substituted trifluoromethyl-pyrazoles **168** (94JFC(67)183) (Scheme 121).

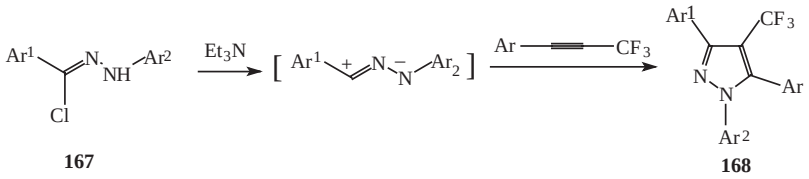
Hexafluoro-2-butyne and ethyl 4,4,4-trifluorobut-3-ynoate react with 2,5-dialkyl-3,4-bis(trifluoromethyl)furan gave to 1,4-dialkyl-7-oxa-2,3,5,6-tetrakis(trifluoromethyl)bicyclohepta-2,5-diene. The UV irradiation of compound **169** in CCl_4 afforded a mixture of compounds (92JHC113).

Perfluoroalkylacetylenes react with furans giving adduct Diels–Alder **169**. The subsequent heating results in a thermal retro Diels–Alder reaction with the formation of 3-trifluoro-methylfuran **170** in high yield (91JFC(53)285, 91JFC(53)297, 92SFC359, 92JFC(56)359, 95JFC(70)59, 94HCA1826, 97SL197) (Scheme 122).

Diels–Alder reaction of ethyl perfluoroalkylpropyneoates with different substituted pyrroles gave perfluorinated alkyl pyrroles (91JFC(53)285) (Scheme 123).



Scheme 120



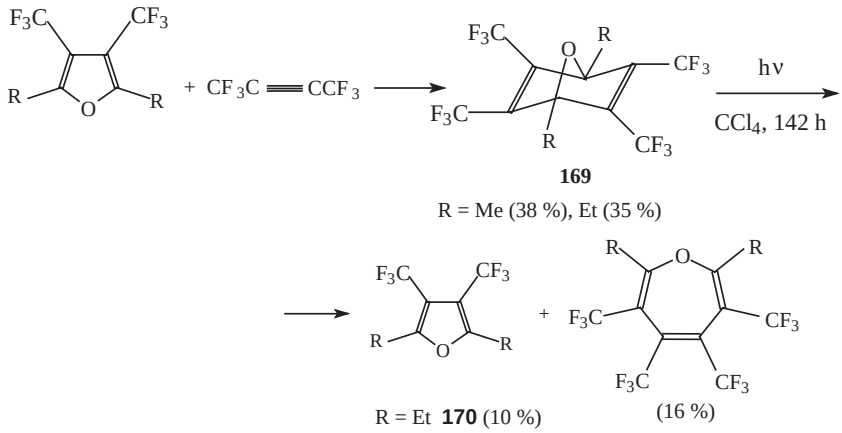
Scheme 121

Compound **171** derivatives of acetylene form with isoxazole **172** and 1,3-oxazine **173** (89ZN1298) (Scheme 124).

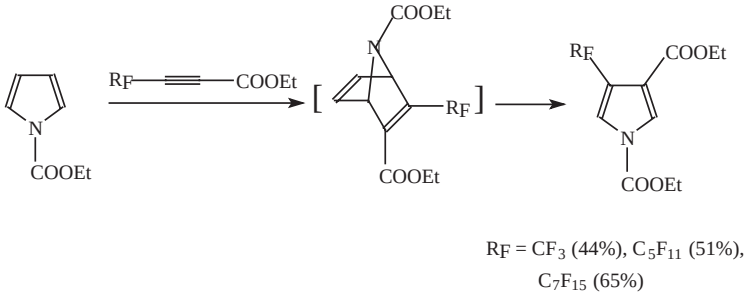
The reaction of β-perfluoroalkylacetylenic esters **175a–g** with benzohydroximinoyl chloride **174** in the presence of base gave the 5-perhaloalkylisoxazoles **176a–g** as the major product and small amounts (2–18%) of the 4-perhaloisoxazoles **177a–g** (Table 2) (03JHC575).

The reaction of trifluoromethyl acetylenic ketones with hydroxylamine under basic conditions gave 5-trifluoromethylisoxazole (89TL2049).

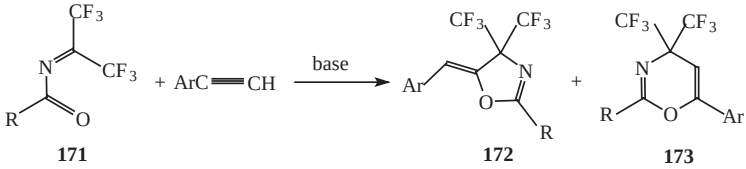
Haloalkyl and trifluoromethyl isoxazoles have been reported as antiviral agents (01WO0164755), anti-inflammatory agents (00DDR273, 97USP5633272), tissue factor Xa inhibitors (00BMCL685, 98WO9828282), immunosuppressents



Scheme 122



Scheme 123

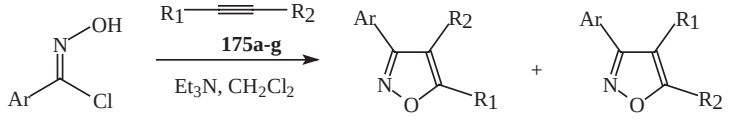


Scheme 124

(94WO9424095), herbicides (89JPP01009978) and antifugal agents (88JPP63238006). Often the trifluoromethyl-substituted isoxazoles are included along with non-fluorinated analogs as patent examples of biologically active compounds. However, in some cases trifluoromethylisoxazoles have been shown to have particularly enhanced activity and selectivity compared with non-fluorinated analogs, as in the case of anti-inflammatory COX-2 inhibitors (00DDR273) and herbicidal protoporphyrin-9 oxidase inhibitors (95JAFC219).

These examples indicate that the multiple bond is effectively employed in the formation of the heterocyclic ring. Intramolecular nucleophilic cyclization involves

Table 2. Ratio of 1,3-dipolar cycloaddition products obtained from acetylenes **175** and hydroximinoyl chloride **174** (03JHC575)



174 **176a-g** **177a-g**

Compound	R_1	R_2	Product ratio (%) **176**	Product ratio (%) **177**	Reaction temperature (°C)
a	CF_3	CO_2CH_3	80 (49)	20 (3)	0
b	CF_2CF_3	CO_2Et	79 (38)	21 (18)	0
c	CF_2Cl	CO_2CH_3	87 (68)	13 (5)	RT
d	CF_2H	CO_2Et	85 (76)	15 (2)	RT
e	CF_3	H	77 (41)	23	0
f	CF_3	CF_3	(60)		RT
g	CF_3	Ph	—	33 (11)	40

RT, room temperature.

both the electrophilic center at the multiple bond of the functional fragment and the heteronucleophile generated in the course of the reaction.

V. Conclusions

The synthesis of heterocyclic compounds from accessible perfluoroolefins and their derivatives is of great interest to researchers. The aim of this attempt to analyze the available data is to attract the chemists' attention to this actively developing section of organic chemistry and provide help to the specialists engaged in the design of new compounds useful in the field of medicine and agriculture. The materials on methods for the synthesis of heterocyclic compounds with perfluoroalkyl groups has been collected and treated systematically. Many new heterocycles are accessible and this will give impetus to biological screening of the many new compounds with fluorine atoms. Some new heterocyclic compounds may also be used for the construction of complexons, which are potentially important for metal ion extraction and separation as well as for the synthesis of high-temperature dielectrics, heat carriers, etc.

References

62JOC3651 T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, **27**, 3651 (1962).

63HOU(12/1)110 Houben-Weyl, in "*Methoden der Organischen Chemie*" Bd. 121/1, p. 110, Thieme Verlag, Stuttgart (1963).

69IZV1176 S. Z. Sterlin, B. L. Dyatkin, L. G. Zhuravkova, and I. L. Knunyants, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1176 (1969).

75JOC810 R. J. De Pasquale, C. D. Padgett, and R. W. Rosser, *J. Org. Chem.*, **40**, 810 (1975).

77CZ402 K. Burger and R. Ottlinger, *Chem.-Ztg.*, **101**, 402 (1977).

77M3 S. Pata, (ed.), in "*The Chemistry of Cyanates and their Thio Derivatives*", Wiley, Chichester (1977).

78JFC193 T. Kitazume, S. Sasaki, and N. Ishikawa, *J. Fluorine Chem.*, **12**, 193 (1978).

78JOC950 D. S. Matteson, M. S. Bierbaum, R. A. Bechtold, J. D. Cambell, and R. J. Wilcsee, *J. Org. Chem.*, **43**, 950 (1978).

79BAU1688 Z. V. Safranova, L. A. Simonyan, Y. V. Zeifman, and N. P. Gambaryan, *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, **28**, 1688 (1979).

79TL3401 P. G. Gassman, S. R. Korn, T. F. Bailey, T. H. Johnson, J. Finer, and J. Clardy, *Tetrahedron Lett.*, 3401 (1979).

79TSC(4)373 S. Scheithauer and R. Mayer, in *"Topics in Sulfur Chemistry"* (A. Senning ed.), vol. 4, p. 373, Georg Thieme Verlag, Stuttgart (1979).

81AHC1 R. D. Chambers and C. R. Sargent, in *"Advances in Heterocyclic Chemistry"* (A. R. Katritzky and A. J. Boulton, eds.), vol. 28, p. 1, Academic Press, Inc., NewYork (1981).

81JOC144 D. C. England, E. A. Donald, and F. J. Weigert, *K. Org. Chem.*, **46**, 144 (1981).

81JOC147 D. C. England, *J. Org. Chem.*, **46**, 147 (1981).

81JOC153 D. C. England, *J. Org. Chem.*, **46**, 153 (1981).

81T1779 P. P. Righetti, A. Gambra, G. Tacconi, and G. Desimoni, *Tetrahedron*, **37**, 1779 (1981).

82BAFC R. Filler and Y. Kobayashi, in "*Biomedical Aspects of Fluorine Chemistry*", Elsevier Biomedical Press, Kodansha, Tokyo, NY (1982).

82JMC956 F. Watjen, O. Bachardt, and E. Lang, *J. Med. Chem.*, **25**, 956 (1982).

82JOC4779 R. W. Kaesler and E. Le Goff, *J. Org. Chem.*, **47**, 4779 (1982).

82OK(3)660 D. Barton and D. D. Ollis, eds., in "*Organic Chemistry*" Nitrogen-containing compounds (I. O. Sazerlent ed.), Translated in English by N. K. Kochetrov, L. V. Bachinovskii, Khimia, Moscow, vol. 3, p. 660 (1982).

83JCS(P1)1 G. B. Blackwell, R. N. Haszeldine, and D. R. Taylor, *J. Chem. Soc., Perkin Trans. 1*, **N 1**, 1 (1983).

83JCS(P1)1235 S. Bartlett, R. D. Chambers, J. R. Kirk, , et al., *J. Chem. Soc., Perkin Trans. 1*, 1235 (1983).

83S313 J. Leroy, D. Cantacuzene, and C. Wakselman, *Synthesis*, 313 (1983).

83ZOR221 E. S. Tusbanova, N. P. Stepanova, V. A. Lebedev, V. A. Galishev, and A. A. Petrov, *Zh. Org. Khim.*, **19**, 221 (1983).

84JFC(25)47 R. D. Chambers, C. G. P. Jones, M. J. Silvester, and D. B. Speight, *J. Fluorine Chem.*, **25**, 47 (1984).

84JFC(26)47 J. Froissard, J. Greiner, R. Pastor, and A. Cambon, *J. Fluorine Chem.*, **26**, 47 (1984).

84M2 N. Ishikawa, ed., in "*Fluorine Compounds, Modern Technology and Applications*", p. 592, Mir, Moscow, (1984).

85JCS(CC)1621 M. Visnick and M. A. Battiste, *J. Chem. Soc., Chem. Commun.*, 1621 (1985).

85S970 Y. -C. Shen, J. -H. Zheng, and Y. -Z. Huang, *Synthesis*, 970 (1985).

85ZOR979 N. P. Stepanova, N. A. Orlova, V. A. Galishev, E. S. Turbanova, and A. A. Petrov, *Zh. Org. Khim.*, **21**, 979 (1985).

86CB589 H. Prinzbach, H. Bingmann, J. Markiert, G. Gischer, L. Knowthe, W. Eberbach, and J. Brokawzky-Geiger, *Chem. Ber.*, **119**, 589 (1986).

86JFC(34)275 R. E. Banks and S. N. Mohialdin, *J. Fluorine Chem.*, **34**, 275 (1986).

86NKK1321 H. Yamanaka, T. Araki, M. Kuwabara, K. Fukunishi, and M. Norura, *Nippon Kagaku Kaishi.*, 1321 (1986).

86T663 A. Chauvin, J. Greiner, R. Pastor, and A. Camson, *Tetrahedron*, **42**, 663 (1986).

86TL4821 K. Uneyama, O. Morimoto, and F. Yamashita, *Tetrahedron Lett.*, **36**, 4821 (1986).

87AHC319 M. H. Elnagdi, M. R. H. Elmoghayar, and G. E. H. Elgemeie, *Adv. Heterocycl. Chem.*, **41**, 319 (1987).

87GP3713774 H. Shimotori, T. Ishii, H. Yamazaki, T. Kuwatsuka, Y. Yanase, and Y. Tanaka, Ger. Pat. 3713774 (1987); *Chem. Abstr.*, 108, 112445d (1988).

87M73 F. S. Babichev, Yu. A. Sharanin, V. K. Promorenko, et al., in "*Intramolecular* interaction nitrilic and amino groups" p. 73 Kiev: Naukova Dumka, (1987).

88CL819 T. Ishihara, M. Kuroboshi, T. Shinozaki, and T. Ando, *Chem. Lett.*, 819 (1988).

88EPA295117 I. G. Buntain, L. R. Harton, D. W. Hawkins, C. J. Person, and D. A. Roberts, *Eur. Pat. Appl.*, 295117 (1988) [*CA* **112**, 35845n (1990)].

88IZV1451 K. V. Komarov, N. D. Chkanikov, M. V. Galokhov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1451 (1988) [*CA* **110**, 57444s (1989)].

88IZV1917 K. V. Komarov, N. D. Chkanikov, S. V. Sereda, M. Tu. Antipin, M. Yu. Struchkov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1917 (1988) [*CA* **110**, 114659s (1989)].

88IZV1920 K. V. Komarov, N. D. Chkanikov, S. V. Sereda, M. Tu. Antipin, M. Yu. Struchkov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1920 (1988) [*CA* **110**, 231590y (1989)].

88IZV2417 K. V. Komarov, N. D. Chkanikov, S. V. Sereda, M. Tu. Antipin, M. Yu. Struchkov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 2417 (1988) [*CA* **110**, 192703r (1989)].

88JFC(38)289 R. E. Banks and S. N. Mohialdin, *J. Fluorine Chem.*, **38**, 289 (1988).

88JFC(41)227 M. Kawabara, K. Fukunishi, M. Nomura, and H. Yamanaka, *J. Fluorine Chem.*, **41**, 227 (1988).

88JPP63238006 T. Hatsuta, A. Takase, and T. Maeda, *Jpn. Kokai Tokkyo Koho JP*, 63238006 (1988) [*CA* **111**, 57717 (1989)].

89BAU1325 V. M. Koshelev, T. D. Truskanova, A. N. Chekhlov, N. V. Vasil'ev, and A. F. Gontar, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **38**, 1325 (1989).

89JKKP01 22856 T. Ishihara, Jpn. Kokai Tokkyo Koho JP 01 22855 (1989) [*CA* **111**, 134144u (1989)]

89JPP01009978 S. Sumimoto, I. Ishizuka, S. Ueda, A. Takase, and K. Okuno, Jpn. Kokai Tokkyo Koho JP 01009978 (1989) [*CA* **111**, 57722 (1989)]

89NKK1864 H. Yamanaka, A. Murakami, M. Kuwabara, K. Fukunishi, and M. Norura, *Nippon Kagaku Kaishi.*, 1864 (1989) [*CA* **112**, 197575b (1990)].

89TL2049 R. J. Linderman and K. S. Kirollos, *Tetrahedron Lett.*, **30**, 2049 (1989).
89ZN1298 K. Burger, N. Sewald, E. Huber, and R. Ottlinger, *Z. Naturforsch.*, **44B**, 1298 (1989).
90AHC223 M. H. Elnagdi, M. R. H. Elmoghayar, and K. U. Sadek, *Adv. Heterocycl. Chem.*, **48**, 223 (1990).
90CJC281 W. -Y. Huang, L. Lu, and Y. F. Zhang, *Chin. J. Chem.*, 281 (1990).
90IZV2599 V. Ya. Popkova, E. I. Mysov, M. V. Galakhov, V. K. Osmanov, and L. S. German, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2599 (1990).
90JOC4448 D. W. Reynolds, P. E. Cassidy, C. G. Jahnson, and M. L. Cameron, *J. Org. Chem.*, **55**, 4448 (1990).
90PJJ02 129171 S. Ishii, K. Yagi, T. Umehara, M. Kudo, T. Nawamaki, and S. Watanabe, *Jpn. Pat.*, **02**, 129171 (1990) [*CA* **113**, 172014a (1990)].
90UP3 S. A. Lermontov, I. M. Rakov, and I. V. Martinov, Tez. Report VI Symposium on Fluorine Compounds, Novosibirs, Russia (1990), p. 193.
90YGK16 K. Tanaka, *Yuki Gosei Kagaku Kyokai Shi.*, **48**, 16 (1990) [*CA* **112**, 355077a (1990)].
90ZN1675 F. F. Abdel-Latif, *Z. Naturforsch.*, **45b**, 1675 (1990).
91CJC167 W. -Y. Huang and L. Lu, *Chinese J. Chem.*, **9**, 167 (1991).
91FBC J. T. Welch and S. Eswarakrishnan, in *"Fluorine in Bioorganic Chemistry"*, Wiley, New York (1991).
91IZV2366 V. Ya. Popkova, L. E. Vinogradova, L. A. Leites, and V. K. Osmanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2366 (1991) [*CA* **116**, 6461m (1992)].
91JFC(53)285 A. Nezis, J. Fayn, and A. R. Cambon, *J. Fluorine Chem.*, **53**, 285 (1991).
91JFC(53)297 A. Nezis, J. Fayn, and A. R. Cambon, *J. Fluorine Chem.*, **53**, 297 (1991).
91JFC(51)323 V. Y. Tyutin, N. D. Chkanikov, A. F. Kolomiets, and A. V. Fokin, *J. Fluorine Chem.*, **51**, 323 (1991).
91JFC(51)407 R. E. Banks and S. N. Khaffaff, *J. Fluorine Chem.*, **51**, 407 (1991).
91JFC(55)199 G. Meazza and G. Zanardi, *J. Fluorine Chem.*, **55**, 199 (1991).
91JHC225 M. Nishida, Y. Hayakawa, M. Matsui, K. Shibata, and H. Muramatsu, *J. Heterocycl. Chem.*, **28**, 228 (1991).
91JSOCJ612 K. Uneyama, *J. Synth. Org. Chem. Japan*, **49**, 612 (1991).
91AHC1 R. D. Chambers and C. R. Sargent, *Adv. Heterocyl. Chem.*, **60**, 1 (1991).
91RCR501 E. S. Turbanova and A. A. Petrov, *Russ. Chem. Rev.*, **60**, 501 (1991).
91TL83 C. Portella and B. Dondy, *Tetrahedron Lett.*, **32**, 83 (1991).
92AHC101 V. Ya. Popkova, M. Yu. Antipin, L. E. Vinogradova, L. A. Leites, and Yu. T. Struchkov, *Heteroatom. Chem.*, **3**, 101 (1992) [*CA* **118**, 147498 (1993)].
92BAU2068 A. S. Golubev, V. Y. Tyutin, N. D. Chkanikov, A. F. Kolomiets, and A. V. Fokin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **41**, 2068 (1992).
92CCL583 W. -Y. Huang, Y. -S. Liu, and L. Lu, *Chin. Chem. Lett.*, **3**, 583 (1992).
92IZV343 A. B. Zolotoy, V. Ya. Popkova, M. Yu. Antipin, and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 343 (1992) [*CA* **118**, 123825k (1993)].
92JFC(56)359 A. B. Abubakar, B. L. Booth, N. N. Suliman, and A. E. Tipping, *J. Fluorine Chem.*, **56**, 359 (1992).

92JFC(57)177 H. Yamanaka, K. Tamura, K. Funabiki, K. Fukunishi, and T. Ishihara, *J. Fluorine Chem.*, **57**, 177 (1992) [*CA* **117**, 233950 (1992)].
92JFC(58)343 V. Ya. Popkova, *J. Fluorine Chem.*, **58**, 343 (1992).
92JHC113 M. Nishida, Y. Hayakawa, M. Matsui, K. Shibata, and H. Muramatsu, *J. Heterocycl. Chem.*, **29**, 113 (1992).
92JOC5680 B. C. Hamper, M. L. Kurtzweil, and J. P. Beck, *J. Org. Chem.*, **57**, 5680 (1992).
92LA947 N. Seewald and K. Burger, *Liebigs Ann. Chem.*, 947 (1992).
92M1 G. A. Olah, R. D. Chambers, and G. K. S. Prakash, eds., in "*Synthetic Fluorine Chemistry*", John Wiley & Sons, New York (1992).
92SFC359 R. D. Chambers, *Synth. Fluorine Chem.*, 359 (1992).
93BAU512 V. Y. Tyutin, N. D. Chkanikov, V. N. Nesterov, M. Yu. Antipin, Yu. T. Struchkov, A. F. Kolomiets, and A. V. Fokin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **41**, 512 (1993).
93JOC6669 B. Dondy and C. Portella, *J. Org. Chem.*, **58**, 6669 (1993).
93JOC6671 B. Dondy and C. Portella, *J. Org. Chem.*, **58**, 6671 (1993).
93JOC6673 P. Doussot and C. Portella, *J. Org. Chem.*, **58**, 6675 (1993).
93JOC6675 B. Dondy and C. Portella, *J. Org. Chem.*, **58**, 6675 (1993).
93JPP05 04979 T. Obata, K. Fujii, Y. Fukuda, K. Tsutsuminchi, Y. Yamanaka, Jpn. Pat. 05 04979 (1993) [*CA* **118**, 207578 (1993)]
93KGK253 G. G. Furin and Yu. V. Gatilov, *Khim. Geterotsikl. Soedin.*, 253 (1993) [*CA* **120**, 8510h (1994)].
93M3 R. Filler, Y. Kobayashi, L.M. Yagupolskii, eds., in "*Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*", Studies in Organic Chemistry, Vol. 48, p. 386, Elsevier Science Publishers, Netherlands B.V., Amsterdam (1993)
94AHC1 K. Burger, U. Wucherpfenning, and E. Brunner, *Adv. Heterocycl. Chem.*, **60**, 1 (1994) [*CA* **122**, 187423 (1995)].
94BCS3021 K. Funabiki, K. Tamura, T. Ishihara, and H. Yamanaka, *Bull. Chem. Soc. Jpn.*, **67**, 3021 (1994).
94CJC79 W. -Y. Huang, Y. -S. Liu, and L. Lu, *Chin. J. Chem.*, **12**, 79 (1994).
94H1015 V. Ya. Popkova, F. M. Dolgushin, M. Tu. Antipin, A. I. Yanovsky, Yu. T. Struchkov, and K. Burger, *Heterocycles*, **40**, 1015 (1994) [*CA* **123**, 111920 (1995)].
94HCA1826 P. Muller and Z. Miao, *Helv. Chim. Acta*, **77**, 1826 (1994).
94JCS(CC)631 X. -Q. Tang and C. -M. Hu, *J. Chem. Soc., Chem. Commun.*, 631 (1994).
94JCS(P1)2161 X. -Q. Tang and C. -M. Hu, *J. Chem. Soc., Perkin Trans. 1*, 2161 (1994).
94JFC(67)183 G. Meazza and G. Zanardi, *J. Fluorine Chem.*, **67**, 183 (1994).
94PWO9424095 M. J. Coghlan, J. R. Luly, and P. E. Wiedeman, PCT Int. App;. WO 9424095 (1995) [*CA* **123**, 285992 (1995)].
94TL409 B. Dondy, P. Doussot, and C. Portella, *Tetrahedron Lett.*, **35**, 409 (1994).
94TL4319 Z. M. Qiu and D. J. Barton, *Tetrahedron Lett.*, **35**, 4319 (1994).
94TL4357 D. Dondy, P. Doussot, M. Iznaden, M. Muzard, and C. Portella, *Tetrahedron Lett.*, **35**, 4357 (1994).
94ZOR1704 G. G. Furin, *Zh. Org. Khim.*, **30**, 1704 (1994) [*CA* **123**, 339774u (1995)].
95CCL281 X. -Q. Tang and C. -M. Hu, *Chin. Chem. Lett.*, **6**, 281 (1995).
95CEN39 S. K. Ritter and C. Washington, *Chem. Eng. News*, **73**, 39 (1995).
95JAFC219 B. C. Hamper, K. L. Leschinsky, S. M. Massey, C. L. Bell, L. H. Brannigan, and S. D. Prosch, *J. Agric. Food Chem.*, **43**, 219 (1995).

95JCS(P1)1039 X. -Q. Tang and C. -M. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1039 (1995).

95JFC(70)59 M. G. Barlow, N. N. Suliman, and A. E. Tipping, *J. Fluorine Chem.*, **70**, 59 (1995).

95JFC(73)129 X. -Q. Tang and C. -M. Hu, *J. Fluorine Chem.*, **73**, 129 (1995).

95JFC(74)9 X. -Q. Tang and C. -M. Hu, *J. Fluorine Chem.*, **74**, 9 (1995).

95JFC(74)279 W. -S. Huang, C. -Y. Yuan, and Z. -Q. Wang, *J. Fluorine Chem.*, **74**, 279 (1995).

95JFC(75)51 Q. -S. Hu, H. -P. Guan, and C. -M. Hu, *J. Fluorine Chem.*, **75**, 51 (1995).

95JFC(75)131 V. Ya. Popkova, K. Burger, and E. Herdtweck, *J. Fluorine Chem.*, **75**, 131 (1995).

95OPPI33 J. Elguero, A. Fruchier, N. Jogerovic, and A. Werner, *Org. Prep. Proded. Int.*, **27**, 33 (1995) [*CA* **122**, 187437 (1995)].

95TL2781 A. Kameyama, Y. Hatakeyama, and T. Nishikubo, *Tetrahedron Lett.*, **36**, 2781 (1995).

95ZOR508 G. G. Furin, *Zh. Org. Khim.*, **31**, 508 (1995).

96CR1 G. G. Furin, in "*Chemistry Review*", **20**, Part 4, 1 (1996); Overseas Publishers Association, Amsterdam B.V., Horwood Academic Publishers GmbH., The Netherlands.

96JFC(79)77 S. -Z. Zhu, C. -Y. Qin, and B. Xu, *J. Fluorine Chem.*, **79**, 77 (1996).

96JFC131 V. Ya. Popkova, K. Burger, and E. Herdtweck, *J. Fluorine Chem.*, **75**, 131 (1996).

96S511 W. -S. Huang and C. -Y. Yung, *Synthesis*, 511 (1996).

96S997 H. -P. Guan, Q. -S. Hu, and C. -M. Hu, *Synthesis*, 997 (1996).

96TL1829 H. Yamanaka, T. Takekawa, K. Morita, T. Ishihara, and J. T. Gupton, *Tetrahedron Lett.*, **37**, 1829 (1996).

97CJC278 H. -B. Yu, Q. -S. Zhang, and W. -Y. Huang, *Chin. J. Chem.*, **15**, 278 (1997) [*CA* **127**, 248004 (1997)].

97IZV831 A. V. Rogoza and G. G. Furin, *Izv. Akad. Nauk. Ser. Khim.*, 831 (1997).

97IZV1355 G. G. Furin, I. Yu. Bagryanskay, and Yu. V. Hatilov, *Izv. Akad. Nauk. Ser. Khim.*, 1355 (1997).

97JCS(P1)981 Y. -S. Liu and W. -Y. Huang, *J. Chem. Soc., Perkin Trans. 1*, 981 (1997).

97JFC(83)133 A. Haas, M. Lieb, and M. Schelvis, *J. Fluorine Chem.*, **83**, 133 (1997).

97JFC(84)75 H. Abele, A. Haas, M. Lieb, and M. Schelvis, *J. Fluorine Chem.*, **84**, 75 (1997).

97JFC(84)65 H. -B. Yu and W. -Y. Huang, *J. Fluorine Chem.*, **84**, 65 (1997).

97SL197 R. N. Warrener, D. Margetic, E. R. Tiekink, and R. A. Russel, *Synlett*, 197 (1997).

97SL1261 B. -H. Luo, H. -P. Guan, and C. -M. Hu, *Synlett*, 1261 (1997).

97USP5633272 J. J. Talley, D. L. Brown, S. Nagarajan, J. S. Carter, R. M. Weier, M. A. Stealey, P. W. Collins, R. S. Rogers, and K. Seibert, US Pat. 5633272 (1997) [*CA* **127**, 65756 (1997)].

97WO9711057 D. A. Frasier, C. W. Holyoke, M. H. Howard, G. E. Lapone, J. E. Powell, and R. J. Pasteris, WO Pat. US 97, 11057 (1995) [*CA* **126**, 305586f (1997)].

97ZOB782 G. G. Furin, L. S. Pressan, A. V. Rogoza, and I. A. Salmanov, *Zh. Obshch. Khim.*, **33**, 782 (1997) [*CA* **132**, 92841v (2000)].

97ZOB1560 G. G. Firin and E. L. Zhuzhgov, *Zh. Obshch. Khim.*, **67**, 1560 (1997) [*CA* **129,** 67727t (1998)].

97ZOB1708 G. G. Furin and E. L. Zhuzhgov, *Zh. Obshch. Khim.*, **67**, 1708 (1997) [*CA* **129**, 67726s (1998)].

97ZOR777 A. V. Rogoza and G. G. Furin, *Zh. Org. Khim.*, **33**, 777 (1997).
97ZOR787 G. G. Furin, A. V. Rogoza, I. Yu. Bagryanskay, and Yu. V. Gatilov, *Zh. Org. Khim.*, **33**, 787 (1997).
98IZV2021 G. G. Furin, I. Yu. Bagryanskay, Yu. V. Gatilov, and E. L. Zhuzhgov, *Izv. Akad. Nauk. Ser. Khim.*, 2021 (1998) [*CA* **130**, 182397t (1999)].
98JFC(87)57 X. -C. Zhang and W. -Y. Huang, *J. Fluorine Chem.*, **87**, 57 (1998).
98JFC(87)69 H. -B. Yu and W. -Y. Huang, *J. Fluorine Chem.*, **87**, 69 (1998).
98JHC333 J. Quiroga, B. Insuasty, S. Cruz, P. Hermandez, A. Bolanos, R. Moreno, A. Hormaza, and R. H. de Almeida, *J. Heterocycl. Chem.*, **35**, 333 (1998).
98PEP816337 V. Kameswaran, Eur. Pat. Appl. EP 816337 (1998) [*CA* **128**, 127929 (1998)].
98T12465 X. -C. Zhang and W. -Y. Huang, *Tetrahedron*, **54**, 12465 (1998).
98THS(2)355 G. G. Furin, in "*Targets in Heterocyclic Systems. (Chemistry and Properties)*" (O. A. Attanasi and D. Spinell eds.), Italian Society Chemistry, Roma, **2**, 355 (1998) [*CA* **131**, 87838z (1999)].
98TL2377 Q. -F. Wang, D. Hu, B. -H. Luo, and C. -M. Hu, *Tetrahedron Lett.*, **39**, 2377 (1998).
98UP1 G. G. Furin and E. L. Zhuzhgov, in *"Abstracts of 12th European Symposium on Fluorine Chemistry"*, Berlin, Germany (1998) p. 1–11.
98WO9828282 J. R. Pruitt, J. M. Fevig, M. L. Quan, and D. J. P. Pinto, PCT Int. Appl. WO 9828281 (1998) [*CA* **129**, 95486 (1998)].
98ZOB798 A. V. Rogoza and G. G. Furin, *Zh. Obshch. Khim.*, **68**, 798 (1998).
99IZV1825 V. Y. Sosnovskich, Yu. G. Yatluk, and V. A. Kuzenko, *Izv. Akad. Nauk. Ser. Khim.*, 1825 (1999).
99JHC563 G. M. Coppola, *J. Heterocycl. Chem.*, 563 (1999).
99JFC(94)79 Q. -F. Wang, Y. -Y. Mao, and C. -M. Hu, *J. Fluorine Chem.*, **94**, 79 (1999).
99JFC(95)141 Q. -F. Wang, Y. -Y. Mao, S. -Z. Zhu, and C. -M. Hu, *J. Fluorine Chem.*, **95**, 141 (1999).
99JFC(99)41 C. Zuczek, C. Gerardin-Charbonnier, S. Rocca, S. Thiebaut, and C. Selve, *J. Fluorine Chem.*, **99**, 41 (1999).
99JFC(99)83 J. -B. Xiao, X. -M. Zhang, D. -I. Wang, C. -G. Yuan, *J. Fluorine Chem*. **99**, 83 (1999).
99PDE19835866 K. Kato, M. Takemitsu, H. Mizumoto, K. Tokoyoda, and S. Arai, Ger. Offen DE 19835866 (1999) [*CA* **130**, 168166 (1999)].
99S51 X. -C. Zhang and W. -Y. Huang, *Synthesis*, 51 (1999).
99ZOB1491 A. V. Rogoza and G. G. Furin, *Zh. Obshch. Khim.*, **69**, 1491 (1999) [*CA* **132**, 334387w (2000)].
99ZOB1499 G. G. Furin, L. S. Pressman, I. A. Salmanov, and E. L. Zhuzhgov, *Zh. Obshch. Khim.*, **69**, 1499 (1999) [*CA* **132**, 334388x (2000)].
99ZOR1481 G. G. Furin, Yu. V. Gatilov, V. G. Kiriyanko, T. V. Rybalova, and E. L. Zhuzhgov, *Zh. Org. Khim.*, **35**, 1481 (1999) [*CA* **133**, 222655w (2000)].
00BMCL685 J. R. Pruitt, D. J. Pinto, M. J. Estrella, L. L. Bostrom, R. M. Knabb, P. C. Wong, M. R. Wright, and R. R. Wexler, *Bioorg. Med. Chem. Lett.*, **10**, 685 (2000).
00CL666 T. Mantani, T. Konno, T. Ishihara, and H. Yamanaka, *Chem. Lett.*, 666 (2000).
00DDR273 A. G. Habeeb, P. N. P. Rao, and E. E. Knaus, *Drug Dev. Res.*, **51**, 273 (2000).

00IZV1261 A. F. Shidlovskii, A. Yu. Sizov, L. N. Kuleshova, V. V. Nesterov, M. Yu. Antipin, A. S. Peregudov, and Chkanikov, *Izv. Akad. Nauk Ser. Khim.*, 1261 (2000) [*CA* **134**, 29379b (2001)].

00JFC(105)295 H. Yamanaka and T. Ishihara, *J. Fluorine Chem.*, **105**, 295 (2000).

01CHC518 V. M. Timoshenko, Ya. V. Nikolin, E. B. Rusanov, A. N. Chernega, and Yu. G. Shermolovich, *Chem. Heterocycl. Compd.*, **4**, 518 (2001).

01EJO187 J. -P. Bouillon, B. Didier, B. Dondy, P. Doussot, R. Plantier-Royon, and C. Portella, *Eur. J. Org. Chem.*, 187 (2001).

01IZV1027 A. V. Rogoza, G. G. Furin, Yu. V. Gatilov, and I. Yu. Bagryanskay, *Izv. Akad. Nauk. Ser. Khim.*, 1027 (2001) [*CA* **136**, 167313t (2002)].

01JFC(111)207 J. -T. Liu and H. -J. Lu, *J. Fluorine Chem.*, **111**, 207 (2001).

01JFC(111)213 J. -T. Liu and H. -J. Lu, *J. Fluorine Chem.*, **111**, 213 (2001).

01TL2305 B. Villaume, C. Gerardin-Charbonnier, S. Thiebaut, and C. Selve, *Tetrahedron Lett.*, **42**, 2305 (2001).

01WO0164755 M. Brands, S. Nikolic, P. Eckenberg, M. Bauser, J. Kaulen, A. Paessens, E. Graef, O. Weber, S. Lottmann, and K. Schlemmer, PCT Int. Appl. WO 0164755 (2001) [*CA* **135**, 221261 (2001)]

01ZOR666 V. M. Timoshenko, Ya. V. Nikolin, N. P. Kolesnik, and Yu. G. Shermolovich, *Zh. Org. Khim.*, **37**, 666 (2001).

02JFC(114)63 A. S. Golubev, P. V. Pasternak, A. F. Shidlovskii, L. N. Saveleva, B. B. Averkiev, V. N. Nesterov, M. Yu. Antipin, A. S. Peregudov, and N. D. Chkanikov, *J. Fluorine Chem.*, **114**, 63 (2002).

02JFC(114)157 Yu. Shermolovich and V. Timoshenko, *J. Fluorine Chem.*, **114**, 157 (2002).

02JFC(116)157 Y. -C. Shen, Y. Zhang, and J. Sun, *J. Fluorine Chem.*, **116**, 157 (2002).

02TL665 B. Jiang, F. -J. Zhang, and W. Xiong, *Tetrahedron Lett.*, **43**, 665 (2002).

02ZOB1024 A. V. Rogoza and G. G. Furin, *Zh. Obshch. Khim.*, **72**, 1024 (2002) [*CA* **138**, 187828 j (2003)].

03AHC(86)129 G. G. Furin, *Adv. Heterocyclic Chem.*, **86**, 129 (2003).

03JHC575 B. C. Hamper and K. L. Leschinsky, *J. Heterocycl. Chem.*, **40**, 575 (2003).

03S35 K. Wu and Q. -Y. Chen, *Synthesis*, 35 (2003).

04AHC(87)273 G. G. Furin, *Adv. Heterocycl. Chem.*, **87**, 273 (2004).

Index