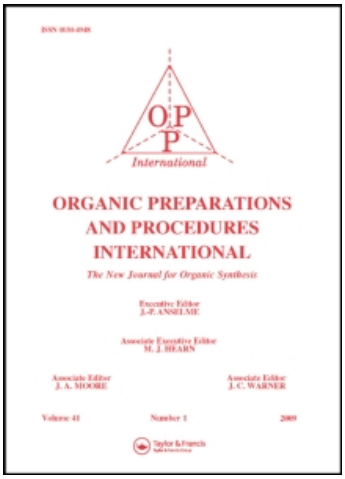

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

RECENT ADVANCES IN THE SYNTHESIS OF PYRROLES

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To cite this Article Ferreira, Vitor F. , de Souza, Maria Cecília B. V. , Cunha, Anna C. , Pereira, Letícia O. R. and Ferreira, Maria L. G.(2001) 'RECENT ADVANCES IN THE SYNTHESIS OF PYRROLES', Organic Preparations and Procedures International, 33: 5, 411 — 454
To link to this Article: DOI: 10.1080/00304940109356613
URL: http://dx.doi.org/10.1080/00304940109356613

ORGANIC PREPARATIONS AND PROCEDURES INT., 33 (5), 411-454 (2001)

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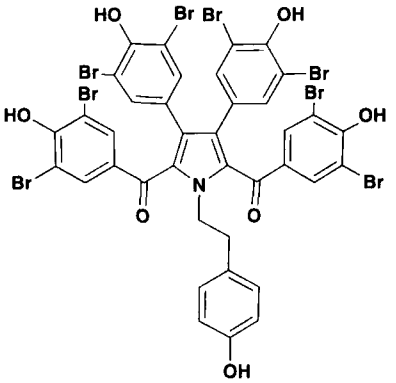
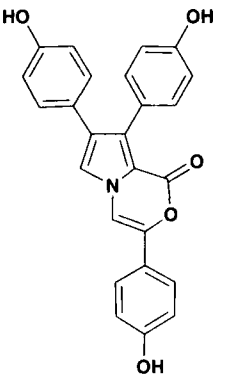
INTRODUCTION

The pyrrole unit occurs in a diversity of synthetic pharmaceutical agents, conducting polymers,[1] molecular optics,[2] electronics,[3] gas sensors for organic compounds[4] and, as building blocks in many physiologically interesting natural products, such as heme, chlorophyll, bile pigments, N-bridgehead pyrroles (pyrrolizidines and indolizidines alkaloids[5]) and, vitamin B_{12}.

Many substituted pyrroles show important biological activities. Recently, a number of alkaloids having the aryl or alkyl-substituted pyrrole framework were isolated from marine sources.[6] Compounds such as polycitone A and lukianol A illustrate some examples of these highly substituted pyrroles with important biological activities. For instance, lukianol A exhibits some activity against a cell line derived from human epidermatoid carcinoma.[7,8] Pharmacological studies on a series of 1,2-diarylpyrroles showed that these substances are very potent and selective inhibitors of the human cyclooxygenase-2 (COX-2) enzyme, which plays an important role in the inflammation process.[9] Other studies showed that 1-phenyl-3-(aminomethyl)pyrroles have high affinities for D2, D3, and D4 dopamine receptor subtypes,[10] while some other aroyl(aminoacyl)pyrroles displayed promising anticonvulsant activity.[11]

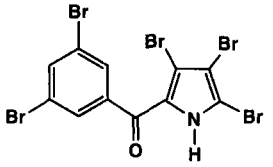


Polycitone A

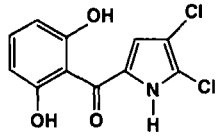


Lukianol A

Polyhalogenated pyrroles isolated from natural sources represent also a class of substituted pyrroles with important biological activities. 3-Halopyrroles have been shown to possess pronounced physiological activities in agrochemical. Pentabromopseudilin[12] and pyoluteorin[13] are antibacterial halopyrroles, which were isolated from the bacteria *Alteromonas luteo-violaceus* and *Pseudomonas aeroginosa*, respectively.



Pentabromopseudilin



Pyoluteorin

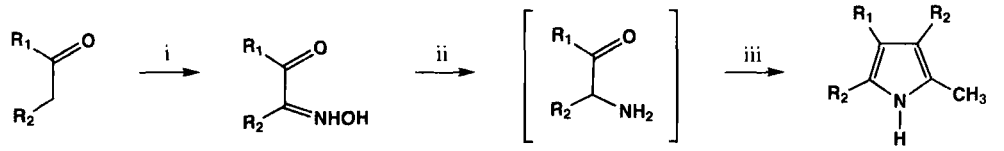
Due to these multiple uses and varieties of biological activities, the synthesis of this ring system has been subject of intense investigation. Several new synthetic methods and variations of the classical ones reported recently either give new types of pyrroles or result in better yields. The classical methods of constructing pyrrole ring system include mainly Knorr, Paal-Knorr and Hantzsch pyrrole syntheses, which have been summarized in a number of heterocycles review articles[14] and books.[15]

This review provides an update of significant advances since 1995 on the synthesis by the classical methods and on the new methodologies developed for preparation of highly substituted pyrroles. Although indoles are a very important class of organic compounds and represent a variation of the pyrrole ring, the focus of this survey is directed toward to the methods of preparing the pyrrole ring itself.

I. ADVANCES IN THE CLASSICAL METHODS

1. Knorr Pyrrole Syntheses

The Knorr pyrrole synthesis[16, 17] consists of the condensation of an α-aminoketone or α-amino-β-ketoester with a ketone or ketoester (*Scheme 1*), and has been widely used for the synthesis of pyrrole derivatives derivatives (e. g. 3-substituted-2,5-dicarbaldehyde pyrroles).[18] In most cases, symmetrical β-diketones are used, since this reaction sequence lacks regioselectivity with asymmetric β-diketones. Another major drawback of this reaction is the facile self-condensation of the starting α-aminoketones, which can be prepared *in situ* from α-oximinoketones or a masked amino group.



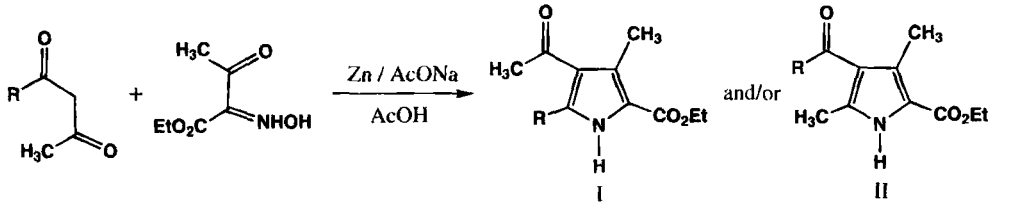
R_1 = Alkyl, $R_2 = CO_2Et$, CO_2Me

i) $NaNO_2$/AcOH; ii) Zn/ AcOH; iii) $H_3CCOCH_2R_2$

Knorr Pyrrole Synthesis using an α-Oximinoketone

Scheme 1

Recently a number of useful variations of the Knorr methodology have been reported. Fujii and coworkers devised optimum experimental conditions for preparing pyrroles starting from sterically hindered asymmetric β-diketones (*Scheme 2*).[19] The condensation of asymmetric β-diketones with ethyl α-oximinoacetoacetate in the presence of zinc dust and sodium acetate in acetic acid led to the pyrroles in reasonable yields. Only small R groups (*e. g.* Et) on the β-diketone led to a mixture of structural isomers, suggesting that steric effects are responsible for the selectivity.

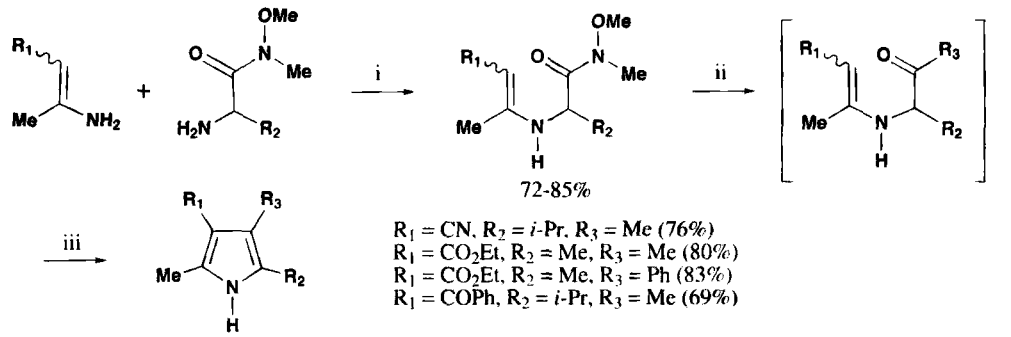


R = Et (38%), ratio I/II = 20/80 R = n-Pr (49%), ratio I/II = 17/83
R = i-Pr (45%), ratio I/II = 0/100 R = t-Bu (38%), ratio I/II = 0/100

Regioselectivity in Knorr Pyrrole Synthesis using Asymmetric β-Diketones

Scheme 2

The Weinreb α-aminoamides (N-methoxy-N-methyl-α-aminocarboxamides)[20] have been shown to be very useful reagents for the synthesis of pyrroles.[21] Ortega and coworkers devised a highly improved protocol for the Knorr pyrrole synthesis based on Weinreb α-aminoamides.[22] The method explored the low tendency of these amides to undergo self-condensation. Thus, N-methoxy-N-methyl-α-aminoamides are easily obtained from the appropriate enamines, which in a separate step react with an organometallic compound (RLi or RMgX) producing a carbonyl intermediate which cyclizes during the work-up. Some representative examples of pyrroles that have been prepared by this method are shown in *Scheme 3*.



R_1 = CN, R_2 = *i*-Pr, R_3 = Me (76%)
R_1 = CO_2Et, R_2 = Me, R_3 = Me (80%)
R_1 = CO_2Et, R_2 = Me, R_3 = Ph (83%)
R_1 = COPh, R_2 = *i*-Pr, R_3 = Me (69%)

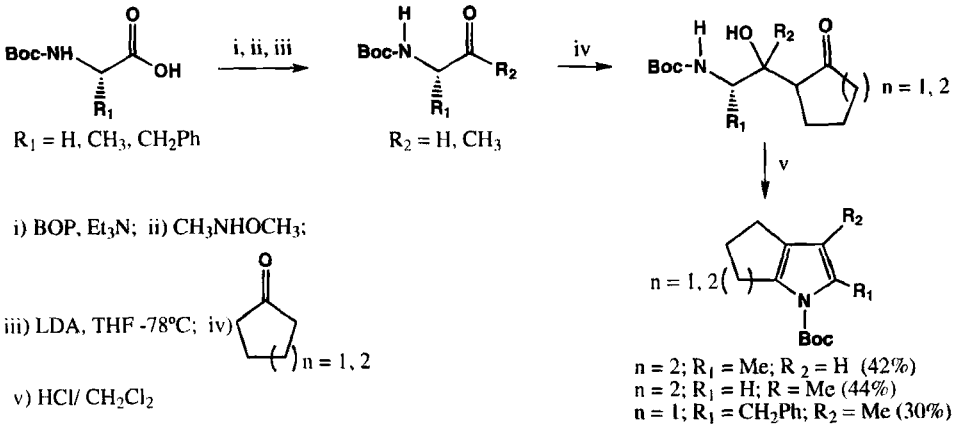
i) MeOH, 40°C; ii) R_3Li/THF; iii) EtONa/EtOH

Knorr Pyrrole Synthesis Based on Weinreb α-Aminoamides

Scheme 3

Aldol addition products of lithium enolates of ketones to Boc-α-aminoketones are quite suitable for cyclization under acidic conditions to pyrroles (*Scheme 4*). This methodology is conceptually similar to the Knorr pyrrrole synthesis and was applied successfully to the preparation of a large

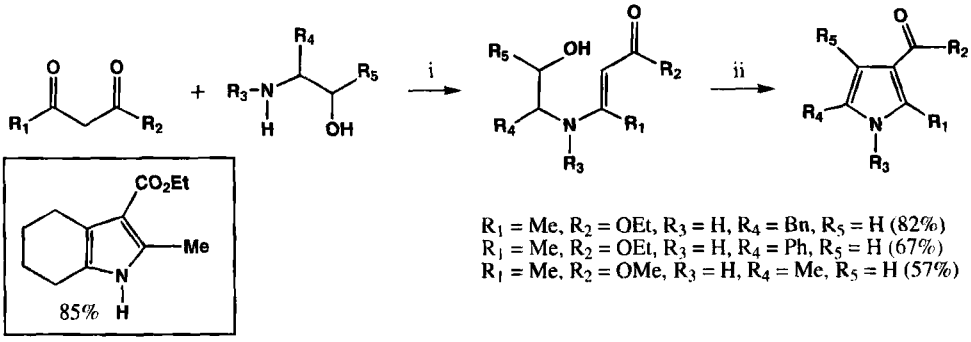
number of fused pyrroles.[23] It is especially noteworthy that the Boc-α-amino aldehydes and Boc-α-amino ketones used in this protocol were easily prepared by conversion of Boc-α-amino acids to Weinreb amides which are subsequently reduced with lithium aluminum hydride or treated with Grignard reagents, respectively. Some selected examples are shown below.



Use of Boc-α-amino Aldehyde and Ketones for the Synthesis of Pyrroles

Scheme 4

A new application for the key intermediate in the Knorr pyrrole synthesis was developed by Ohta and coworkers and involves the palladium-catalyzed oxidation and cyclization of β-hydroxy-enamines (*Scheme 5*).[24] The latter substances are easily obtained by the condensation between β-aminoalcohols and carbonyl compounds. Subsequent treatment with the palladium catalyst in the presence of mesyl bromide proceeded to give the corresponding polysubstituted pyrroles in good yields. This protocol can be applied also to produce pyrroles from cyclic enamines (see structure in the box). Despite the use of inexpensive and readily available starting materials, this method has been scarcely utilized.



i) THF, Molecular sieves 4 Å, 7 days; ii) $Pd(PPh_3)_4/K_2CO_3$, MsBr/DMF, 150°C.

Pd-catalyzed Oxidation of the Enamine-intermediate of Knorr Synthesis

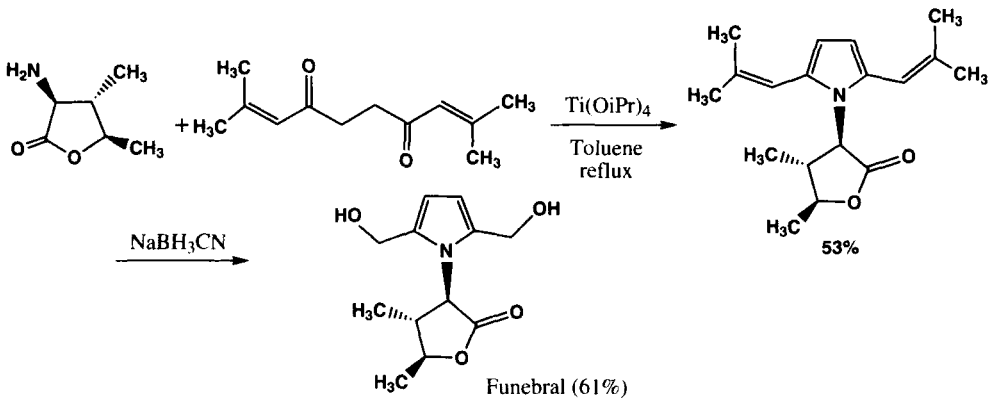
Scheme 5

2. Paal-Knorr Pyrrole Synthesis

The classical Paal-Knorr pyrrole synthesis is a well-established procedure[25] that involves an acid-catalyzed condensation of alkyl amines with 1,4-dicarbonyl compounds (or masked 1,4-dicarbonyl compounds) leading to polysubstituted pyrroles. This route has been used in a variety of preparations of pyrrole. Recently, a large series of pyrroles was prepared by this method.[26] In this work it was found that 3-pyridyl-2,5-diaryl-pyrroles are potent, orally bioavailable inhibitors of p38 kinase, showing the importance of this method in the synthesis of very useful compounds. In a similar work using Paal-Knorr synthesis, several 1-[2-(substituted pyrrol-1-yl)ethyl]-2-methyl-5-nitroimidazole derived from metronidazole were synthesized and their antibacterial and antifungal activities were assayed.[27] Also, conducting polymers having multi-ring aromatic monomers with electron-rich terminal heterocycles were prepared by this method.[28]

Several variations of this protocol which have been described recently deal mainly with masked (or potential) 1,4-dicarbonyl compounds. It is worth mentioning that when this synthesis is performed under classical (thermal) conditions the reaction requires at least 12 hours, but shorter times and much higher yields are obtained by microwave irradiation.[29]

Following the usual Paal-Knorr protocol, Le Quesne and coworkers described a short synthesis of (±)-funebral, an alkaloid isolated from the tree *Quararibea funebris* (liave) Visher (Bombacaceae), employing titanium isopropoxide as a weak Lewis acid for the addition of amines to a doubly unsaturated 1,4-dicarbonyl derivative. The use of the weak Lewis acid was the key step since it avoided degradation of the starting material (*Scheme 6*).[30]

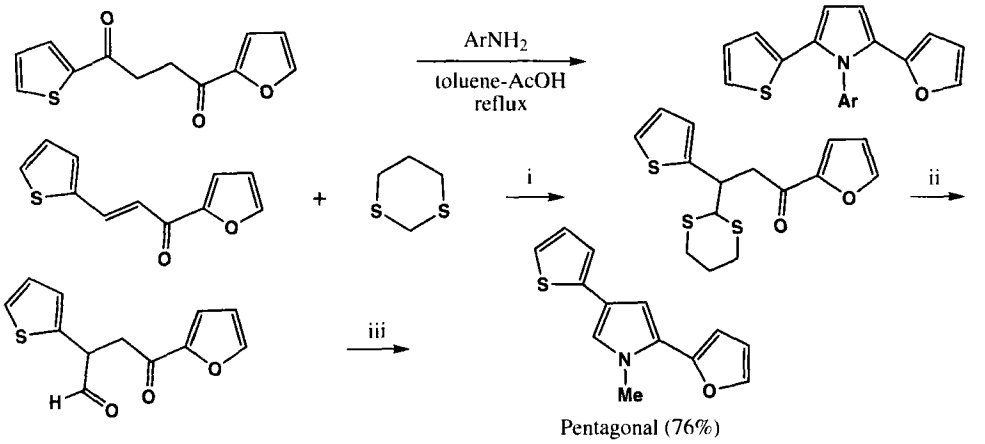


Addition of Amines to an Unsaturated 1,4-Dicarbonyl Compound Catalyzed by Ti(O*i*-Pr)4

Scheme 6

The development of π-conjugated pyrroles or mixed pyrrole-thiophene polymers or oligomeric compounds with optical, electrochemical and electrical properties is very important for the optical and electronic industries. The Paal-Knorr protocol has been used for the preparation of many of these of pyrrole-thiophene π-conjugated systems.[31] By a similar methodology, pentagonal 2,3':5',2"-triheterocyclic compounds, another π-conjugated system, have been produced in a series of consecutive reactions starting from 1,3-bis heterocyclic propenones in 76% yield.[32] Michael addition

involving one-carbon elongation with 2-lithio-1,3-dithiane, deprotection of dithiane, and amine addition to the 1,4-dicarbonyl compound was used for producing these pyrrole-thiophene π-conjugated systems with different substitution patterns (*e. g.* pentagonal). In fact, this sequence is an alternative procedure for transforming α,β-unsaturated derivatives into 1,4-dicarbonyl moieties, which is necessary for the Paal-Knorr protocol (*Scheme 7*).

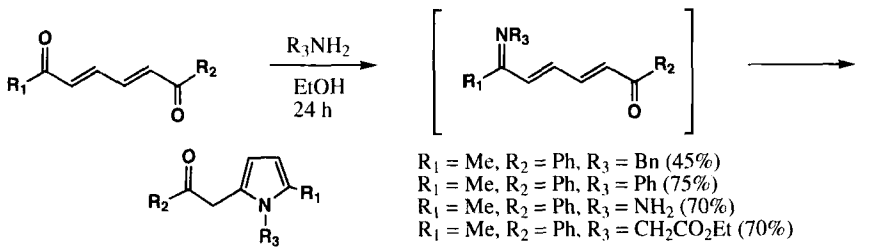


i) BuLi/THF, Ar, 6h, -78°C, 73%; ii) CuO/$CuCl_2$/acetone/H_2O, reflux (85%); iii) $MeNH_2$.HCl, NaOEt, EtOH, reflux.

Triheterocyclcic Compounds Produced from 1,3-*bis* Heterocyclic Propenones

Scheme 7

Ong and coworkers reported a further example which exploits vinylogous 1,6-dicarbonyl compounds for preparing 1,2,5-substituted pyrroles chemoselectively.[33] It was demonstrated that 1,6-dioxo-2,4-dienes react easily with primary amines, at the more reactive carbonyl center, forming an imine intermediate, which by olefin isomerization, intramolecular cyclization and aromatization led to 1,2,5-pyrrole derivatives (*Scheme 8*).



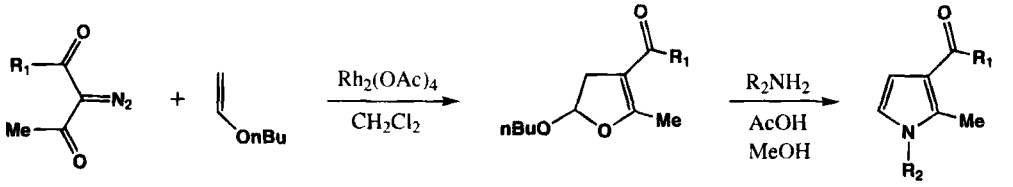
R_1 = Me, R_2 = Ph, R_3 = Bn (45%)
R_1 = Me, R_2 = Ph, R_3 = Ph (75%)
R_1 = Me, R_2 = Ph, R_3 = NH_2 (70%)
R_1 = Me, R_2 = Ph, R_3 = CH_2CO_2Et (70%)

The Use of Vinylogous 1,6-Dicarbonyl Compounds for Preparing 1,2,5-Substituted Pyrroles

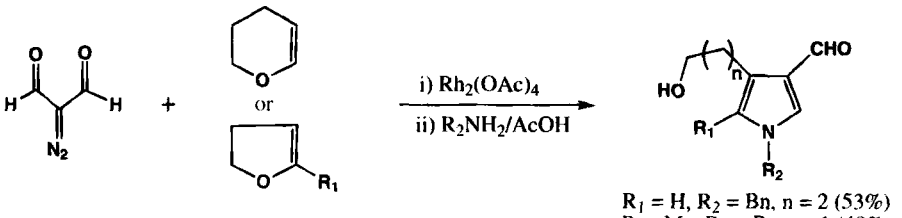
Scheme 8

2,5-Dimethoxytetrahydrofurans are masked 1,4-dicarbonyl compounds, which have been used in many reaction sequences for preparing pyrroles.[34] For example, their condensation with alkyl and arylamines, amides and sulfonamides in the presence of P_2O_5, easily produced *N*-substituted pyrroles in good yields.[35] Recently, Ferreira and coworkers[36, 37] reported the preparation of highly

substituted pyrroles in two steps from dihydrofurans obtained from α,α'-diazocarbonyl derivatives (*Scheme 9*). Dihydrofurans bearing a carbonyl group at the 3-position are suitable starting materials for the synthesis of substituted pyrroles, since they have the same oxidation state as pyrroles and bear an α,β-unsaturated carbonyl group. These compounds are very susceptible to ring opening by the attack of amine nucleophiles under mild conditions. This protocol represents an alternative route to produce substituted pyrroles presenting a carbonyl group at 3-position.



R_1 = Me, R_2 = Bn (70%) R_1 = Me, R_2 = n-decyl (80%) R_1 = Me, R_2 = n-butyl (78%)
R_1 = OEt, R_2 = n-decyl (70%) R_1 = OEt, R_2 = n-Bn (76%)

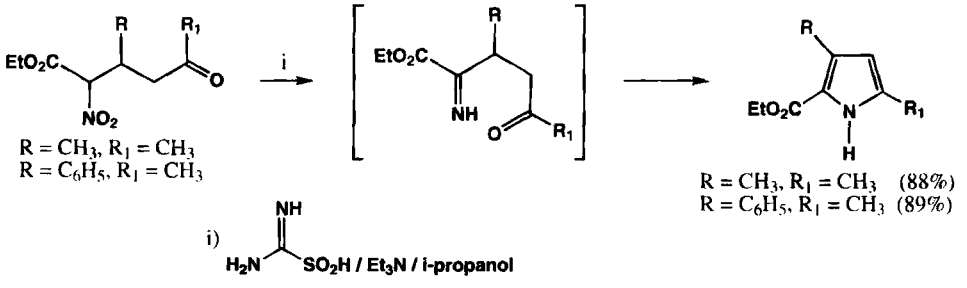


R_1 = H, R_2 = Bn, n = 2 (53%)
R_1= Me, R_2 = Bn, n =1 (49%)

Use of Dihydrofurans and Dihydropyrans for the Synthesis of Substituted Pyrroles

Scheme 9

Masked 1,4-dicarbonyl systems can also be obtained from γ-nitroketones, which are easily obtained from the Michael addition of α-nitro esters at α,β-unsaturated ketones. Heating these nitroketones with formamidinesulfinic acid and triethylamine in propanol produces pyrroles in good yields (*Scheme 10*).[38] The presence of an electron-withdrawing group appears to be necessary for the reduction to take place. It is speculated that the reaction proceeds through an imine or oxime-intermediate. Another alternative to obtain 1,4-dicarbonyl systems is the addition of nitroalkanes to α,β-unsaturated carbonyl compounds followed by oxidation of the nitro group to a ketone.[39]



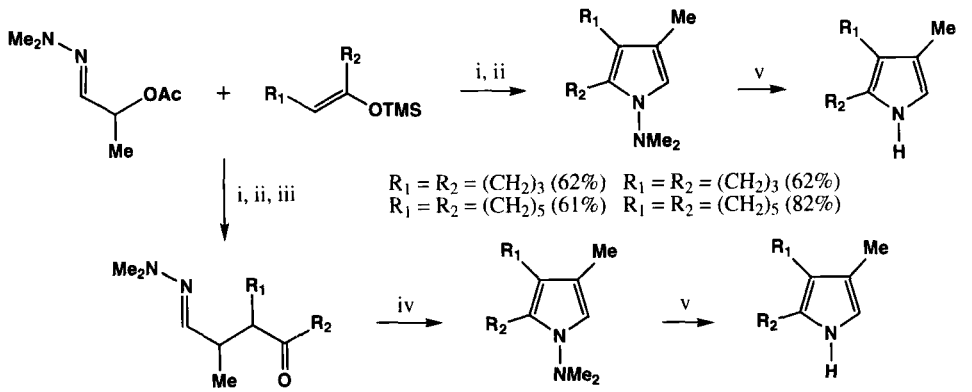
R = CH_3, R_1 = CH_3
R = C_6H_5, R_1 = CH_3

R = CH_3, R_1 = CH_3 (88%)
R = C_6H_5, R_1 = CH_3 (89%)

Preparation of Pyrroles by Addition of α-Nitroesters at α,β-Unsaturated Ketones

Scheme 10

Masked 1,4-dicarbonyl systems may also be acquired by the Lewis acid mediated reaction of 2-acetoxypropanal *N,N*-dimethylhydrazone with various acyclic and cyclic silyl enol ethers (*Scheme 11*). This reaction easily produces *N*-(dimethylamino)pyrroles in two steps from oxoaldehyde *N,N*-dimethylhydrazones. Reductive cleavage of N-N bond leads to di and trisubstituted pyrroles. This route represents a very efficient and flexible method for the preparation of various alkyl- and aryl-substituted 1H-pyrroles in good overall yields starting from easily available 2-acetoxy aldehyde *N,N*-dimethylhydrazones.[40]



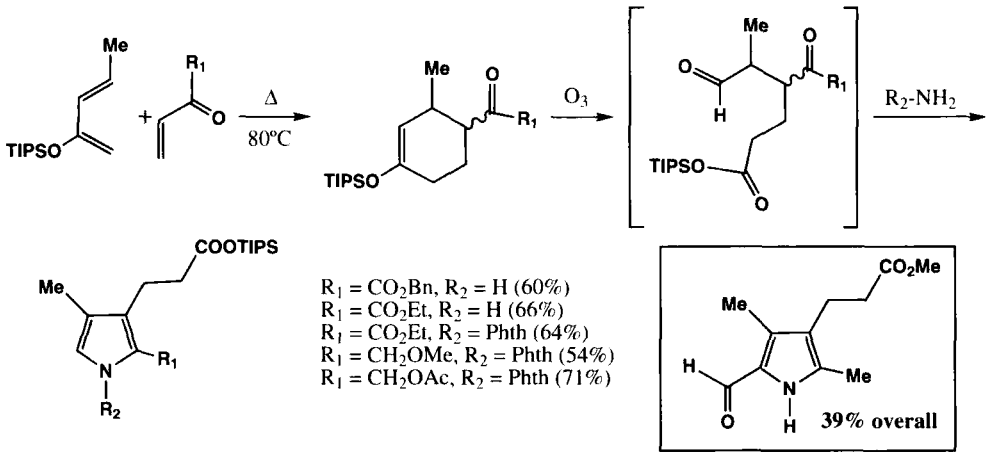
R_1 = Me, R_2 = *t*-Bu (86%) R_1 = Me, R_2 = t-Bu (78%) R_1 = Me, R_2 = *t*-Bu (30%)
R_1 = Me, R_2 = Ph (86%) R_1 = Me, R_2 = Ph (76%) R_1 = Me, R_2 = Ph (82%)

i) $TiCl_4$, CH_2Cl_2, -78 to -20°C; ii) Na_2CO_3 (aq.); iii) $TiCl_4$, CH_2Cl_2, -78°C to rt; iv) PTSA/toluene reflux; v) Na/NH_3, rt

Reaction of 2-Acetoxypropanal N,N-dimethylhydrazone with Silyl Enol Ethers

Scheme 11

1,4-Dicarbonyl compounds can be generated from several olefinic compounds by oxidative cleavage of the double bond. Oxidation of 2,5-dialkylfurans with *m*-chloroperbenzoic acid (MCPBA) produces *cis*-1,4-enediones which react *in situ* with primary amines to afford 2,3,5-trialkylpyrroles.[41] In 1997, Jacobi and coworkers extended their results on the synthesis of tetra-substituted pyrroles using a very interesting route to produce 1,4-dicarbonyl compounds (*Scheme 12*).[42] The method takes the advantage of a highly *ortho*-selective Diels-Alder reaction of 2-alkoxy-1,3-pentadienes with 2-oxo-3-butenoate esters to produce cyclohexenes, which upon ozonolysis and Paal-Knorr cyclization with N-aminophthalimide affords substituted pyrroles. Recently, Taber and Nakajima apllied this methodology for preparing tetrasubstituted pyrrole (see structure in the box).[43]

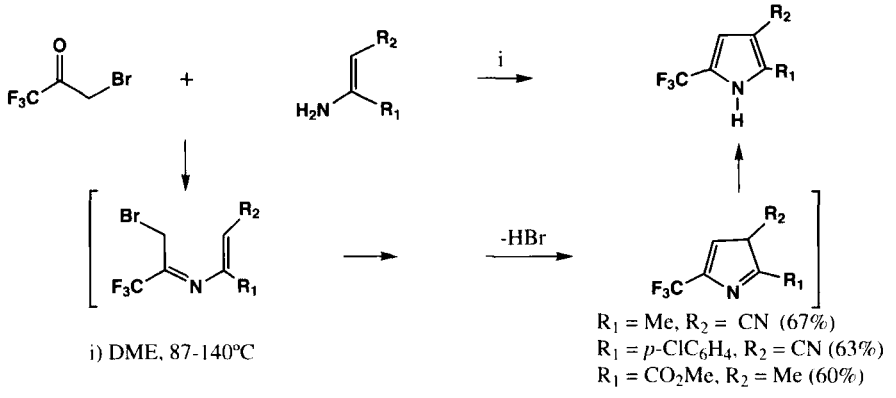


Methodology for Preparing 1,4-Dicarbonyl compounds by Ozonolysis of Diels-Alder Adducts then their Conversions to Pyrroles

Scheme 12

3. Hantzsch Pyrrole Synthesis and Related Reactions

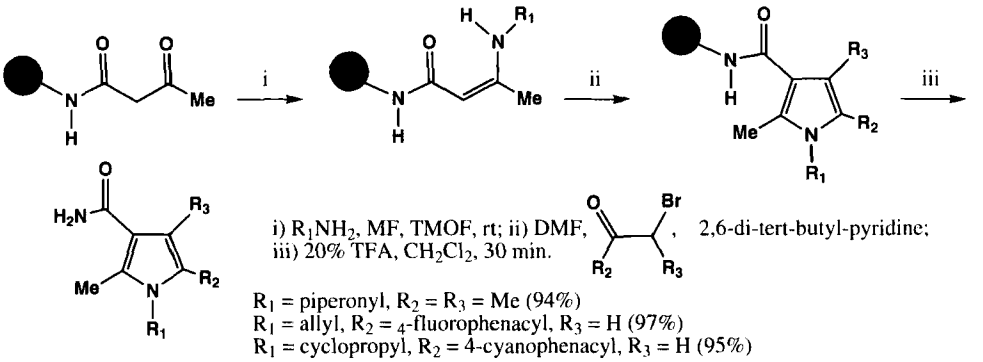
The Hantzsch reaction involves the condensation of α-haloketones or aldehydes with β-ketoesters (or β-diketones) in the presence of amines (enamines or ammonia).[44] Furans are by-products of these reactions and, in some cases, can become the main product. Despite this drawback, a great deal of effort has been devoted to improve the scope of this procedure. In a recent study directed towards the synthesis of pyrrole insecticides, Jiang and Kameswaran[45] reported the synthesis of 5-trifluoromethylpyrrole derivatives in good yields, by a modified Hantzsch methodology using 3-bromo-1,1,1-trifluoropropanone and enamines (*Scheme 13*).



Synthesis of 5-Trifluoromethylpyrrole Derivatives by Hantzsch Reaction

Scheme 13

Trautwein and coworkers recently described an efficient method for the solid-phase synthesis of pyrroles for applications in combinatorial chemistry (*Scheme 14*).[46] Polystyrene amide resin[47] is acetoacetylated and converted into polymer-bound enaminones by treatment with primary amines under acidic catalysis. These enaminones then undergo a Hantzsch reaction with α-bromoketones. After cleavage with 20% trifluoroacetic acid in dichloromethane, pyrrole-3-carboxamides are obtained in excellent yields and in high purity.



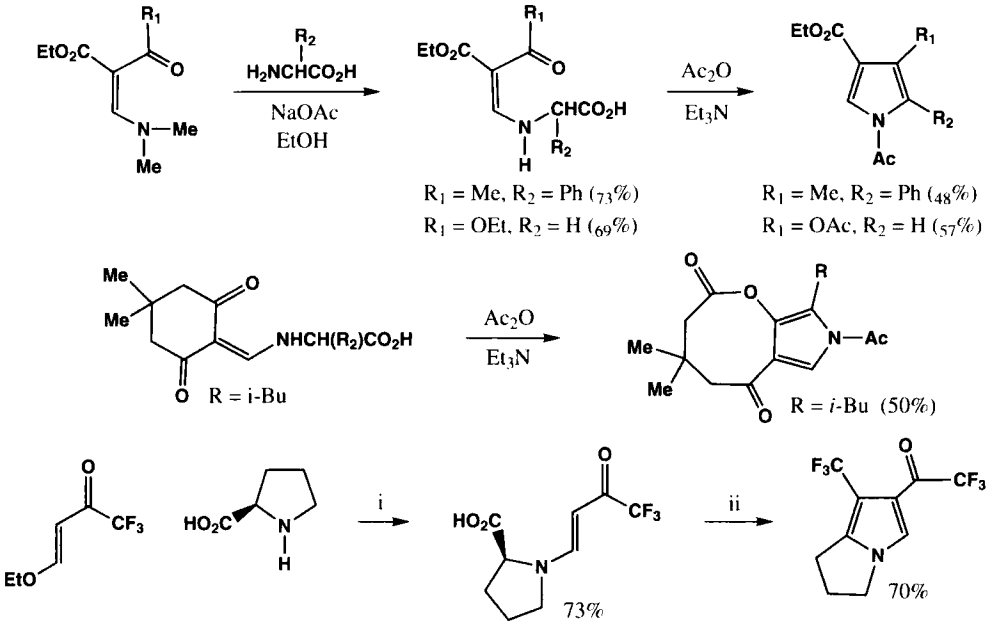
Hantzsch Solid-phase Synthesis of Pyrroles

Scheme 14

II- ZAV'YALOV PYRROLE SYNTHESIS

The Zav'yalov sequence for preparing pyrroles first described in 1973 involves the exchange of the β-dimethylamino moiety of β-dimethylaminomethylene ketones or acrylyl esters, or both, by an aminoacid, which in a second step cyclizes to the substituted pyrroles (*Scheme 15*).[48] By the original Zav'yalov chemistry, Heron and coworkers reported the synthesis of several substituted pyrroles and an unusual ring expansion reaction forming a new oxacino[2,3-c]pyrrole system also illustrated in Scheme 15.[49] Many variations of this methodology have been recently reported. For instance, Mellor and coworkers described that 4-ethoxy-1,1,1-trifluorobut-3-ene-2-one ($EtOCH{=}CHCOCF_3$) works as well as β-dimethylaminomethylene ketone for the synthesis of trifluoromethylpyrroles from several amino-acids (see example for proline in Scheme 15).[50]

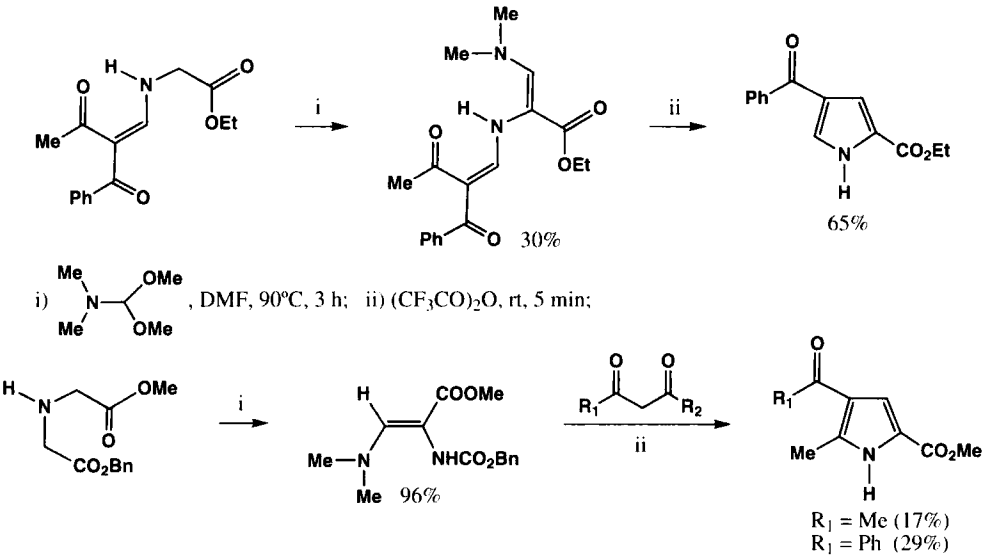
More recently, Stanovnik and coworkers developed a method for the synthesis of 2,3,4-trisubstituted pyrroles by using a similar protocol, but the cyclization is preceded by α-formylation reaction at the amino acid moiety. Thus, ethyl 2-(2-acetyl-2-benzoyl-1-ethenyl)amino-3-dimethylaminopropenoate[51] was transformed into 4-benzoyl-2-ethoxycarbonyl-3-methylpyrrole by treatment with trifluoroacetic anhydride. (*Scheme 16*).[52] Later on, the same group applied a slightly modified methodology for preparing pyrroles in low yield from active methylene compounds.[53] It seems that this reaction works well for preparing other heterocyclic compounds but needs to be explored further for use in pyrrole synthesis.



i) DMAP, CH_2Cl_2; ii) $(CF_3CO)_2$, CH_2Cl_2, 4 h

Zav'yalov Pyrrole Synthesis

Scheme 15

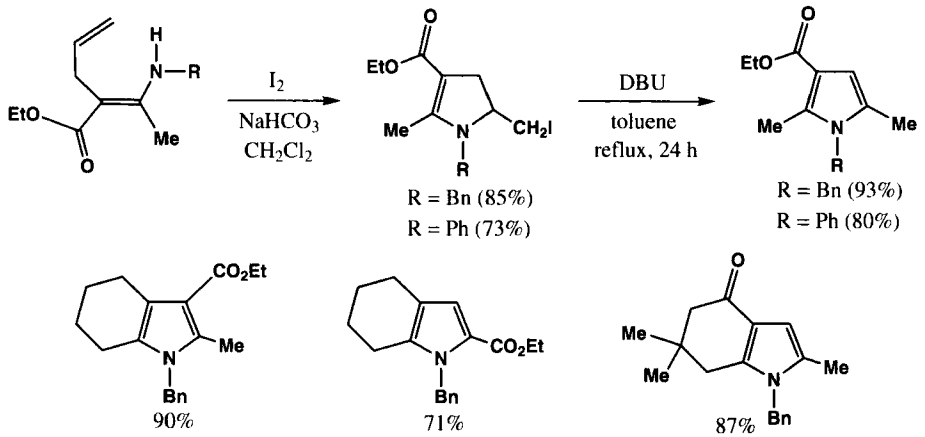


i) *t*-BuOCH$(NMe_2)_2$, toluene, reflux, 1 h; ii) AcOH, reflux.

Modified Zav'yalov Sequence by α-Formylation at the Amino Acid Moiety

Scheme 16

In a study to broaden the scope of iodine-promoted cyclization,[54] Ferraz and coworkers developed a process based on this chemistry, in which iodine-cyclization of β-enaminoesters and ketones bearing an α-allyl group leads to 1,2-dihydropyrroles. These substances were aromatized by a dehydrohalogenation elimination promoted by a strong base (*Scheme 17*). Several substituted pyrroles were synthesized by this methodology that can be considered a variation of the same protocol.[55]

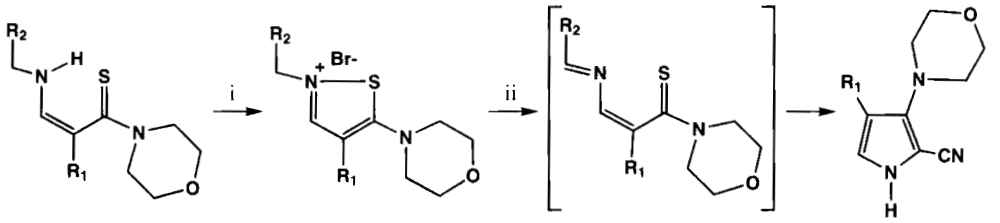


Synthesis of Pyrroles by Iodo-cyclization of α-Allyl β-Enaminones

Scheme 17

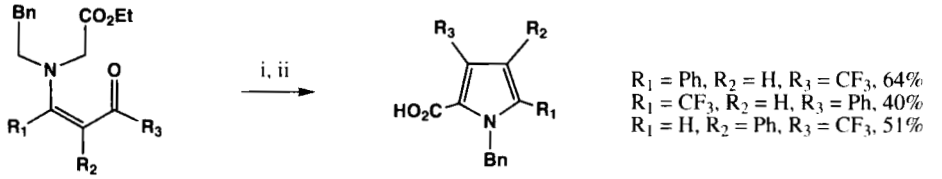
In a search for anticonvulsive compounds, Liebscher and coworkers developed a synthetic route for producing 3-aminopyrroles from 3-aminothioacrylamides, which is very similar to the original Zav'yalov pyrrole synthesis (*Scheme 18*).[56] The key step involves a base-catalyzed ring transformation-desulfurization of substituted 5-amino-2-methyl-1,2-thiazolium salts, which were generated by oxidative ring closure of 3-aminothioacrylamides. Further investigation on the mechanism of this transformation established the intermediacy of 3-alkylideneaminothioacrylamide in the formation of pyrroles.[57] In another similar ring closure process, highly substituted trifluoromethylpyrroles were obtained in moderate yields from β-enaminoketones upon cyclization under basic conditions.[58] However, the formation of other pyrrole by-products in this reaction limits the scope of this method.

Fottsch and coworkers recently investigated an interesting one-step approach for the synthesis of 3-aminopyrroles from diethyl aminomalonate and α-cyanoketone derivatives (*Scheme 19*). The authors speculated that an enamine intermediate is formed initially, which upon cyclization and decarboxylation produces 3-aminopyrroles with several substitution patterns, in poor to moderate yields.[59]



i) Br_2, $CHCl_3$-MeOH; ii) Et_3N, MeOH

$R_1 = p\text{-}ClC_6H_4$, $R_2 = CONH_2$, 44%

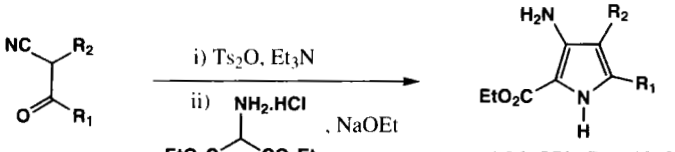


R_1 = Ph, R_2 = H, R_3 = CF_3, 64%
R_1 = CF_3, R_2 = H, R_3 = Ph, 40%
R_1 = H, R_2 = Ph, R_3 = CF_3, 51%

i) NaH/DMSO, benzene; ii) NaOH

Preparation of Pyrroles by Ring Closure of Alkylideneaminothioacrylamides and β-Enaminoketones

Scheme 18



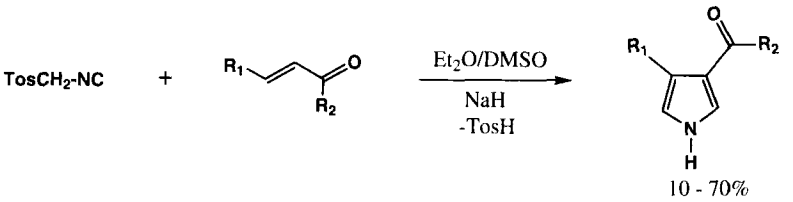
R_1 = 4-MeOPh, R_2 = H (30%)
R_1 = 2-furanyl, R_2 = H (61%)
R_1 = Me, R_2 = Ph (21%)

3-Aminopyrroles from Diethyl Aminomalonate and α-Cyanoketone Derivatives

Scheme 19

III. BARTON-ZARD PYRROLE SYNTHESIS AND RELATED REACTIONS

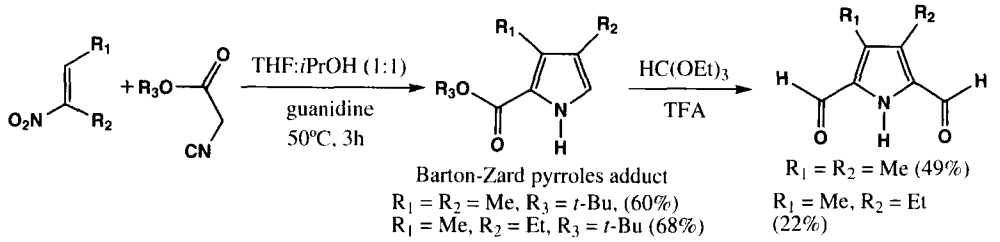
A large number of five-membered rings have been devised from carbanion addition to compounds containing activated double bonds. One general process based on this concept developed by van Leusen and coworkers, demonstrated that tosylmethylisocyanide (TosMIC) reacts with Michael acceptors in the presence of a non-nucleophilic base (*t*-BuOK and NaH) to produce pyrroles (*Scheme 20*).[60] The isocyanide anion generated by the base easily adds to the α,β-unsaturated ketones, esters or nitriles followed by a 5-*endo-dig* cyclization process and elimination of toluenesulfinate ion leading to pyrroles unsubstituted at the ring 1,2 and 5-positions (Scheme 20). TosMIC possesses the best leaving group for this reaction since the tosyl group is immediately lost during the aromatization step.



Preparation of Pyrroles by TosMIC Condensation with Michael Acceptors

Scheme 20

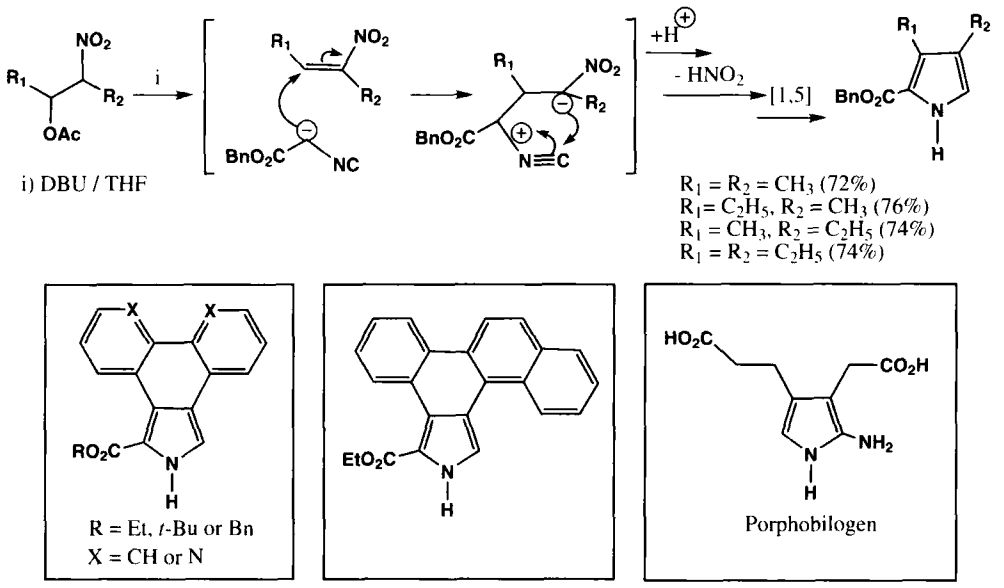
Somewhat later, Barton and Zard demonstrated that nitroolefins or β-acetoxynitro alkanes condensed with α-isocyanoacetate esters in the presence of a non-nucleophilic base (DBU or guanidine) to give polysubstituted pyrroles with ideal substituent patterns for the further synthesis of porphyrins and bile pigments.[61, 62] Basically, this method takes advantage of the ability of a nitro group to activate olefins towards Michael addition as well acting as a good leaving group (*Scheme 21*). The present approach is very important since the substituents at 3- and 4-positions arise from the nitroalkene precursors and the 2-carboxylate substituents from the α-isocyanoacetates. Since 3,4-disubstituted pyrrole-2,5-dicarbaldehydes are irreplaceable intermediates for the synthesis of porphyrins and homologs, Guilard and coworkers found a process to transform the Barton-Zard pyrrole adducts into pyrrole-2,5-dicarbaldehyde in one step.[63] The use of this methodology led to the synthesis of a number of antifungal pyrrole derivatives which were tested in vitro against *Mycobacterium tuberculosis*.[64, 65]



Nitroalkenes Condesation with Isocyanides in the Presence of Guanidine

Scheme 21

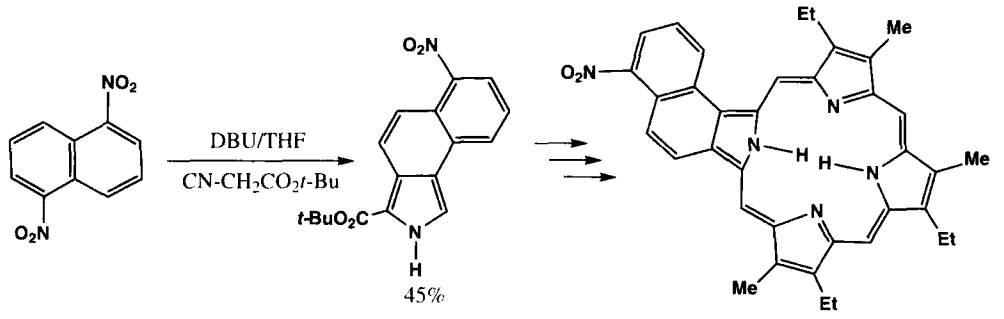
Lash and coworkers reexamined this chemistry using several nitroalkenes generated *in situ* by acetoxy group elimination (*Scheme 22*).[66] The same base (DBU) was also used to promote the addition of anion of benzylisocyanoacetate to nitroalkenes; a proton exchange followed by HNO_2 elimination and [1,5]-sigmatropic rearrangement furnished 2,3,4-trisubstituted pyrroles. It was shown by the same group that nitroarenes (*e. g.* 6-nitrochrysene, 1-nitroacenaphthylene, etc.) can be used in this reaction (DBU/THF). More recently, the same group found that unreactive nitroaromatic compounds condense with ethyl isocyanate using a more strong base.[67] Osuka and Nakajima[68] applied this protocol to produce 9-anthryl substituted pyrroles. Adamczyk[69] prepared porphobilogen for porphyrin syntheses (structures in the boxes, *Scheme 22*) and, Novi and coworkers also reported a useful synthesis of 4-ethynylpyrroles from 2,3-dinitrobutadienes and TosMIC catalyzed by several bases.[70]



Nitroalkenes Generated *in situ* in the Barton-Zard Reaction

Scheme 22

More recently, Lash and coworkers continued their work on the preparation of pyrroles by this chemistry and obtained fused aromatic *c*-pyrroles,[71] which were used in preparing modified porphyrins with potential application in molecular wires, as photosensitizers and in photodynamic therapy (*Scheme 23*).[72] In this study they found that 1,5- and 2,7-dinitronaphthalene condense with *t*-butyl isocyanoacetate more easily than nitronaphthalene, since it is more prone to nucleophilic attack by isocyanoacetate anion. It should be noted that further reaction to form dipyrrolic product was never observed.

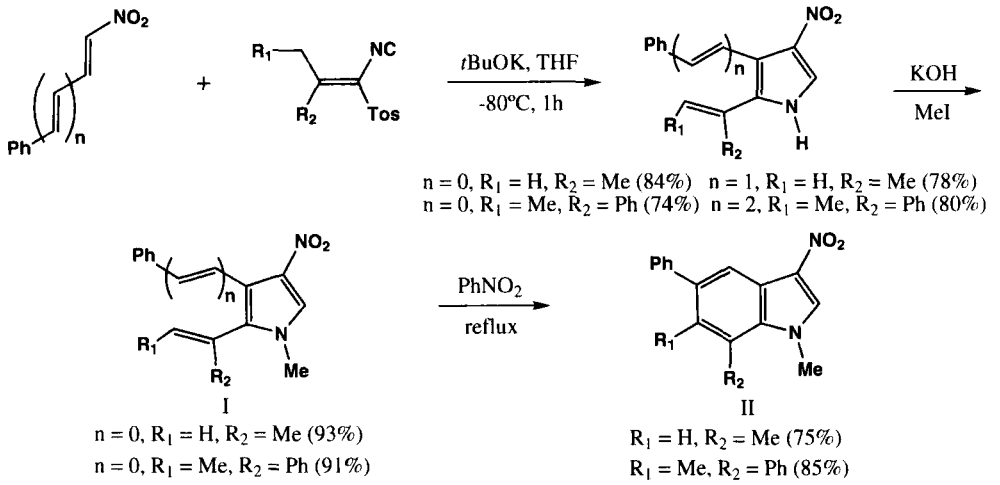


Preparation of fused aromatic *c*-pyrroles

Scheme 23

In a similar study exploiting the Barton-Zard pyrroles synthesis, van Leusen and coworkers prepared a series of 3(4)-nitropyrroles (structures type I in *Scheme 24*) with alkenyl substituents at the

2- and 3-positions (or 3-position only), efficiently, by a base-induced addition of tosylmethylisocyanide (TosMIC), or its unsaturated homologs (condensation products between TosMIC and ketones), to nitroalkenes.[73] The same group demonstrated in further work that these 4-nitropyrroles are ideal precursors for the synthesis of 3-nitroindoles[74] by thermal 6π-electrocyclization of 2,3-(dialkenyl)-4-nitropyrroles (structures type II in Scheme 24) in nitrobenzene, a solvent that promotes *in situ* aromatization of the initially formed dihydroindoles in good yields.



n = 0, R_1 = H, R_2 = Me (84%) n = 1, R_1 = H, R_2 = Me (78%)
n = 0, R_1 = Me, R_2 = Ph (74%) n = 2, R_1 = Me, R_2 = Ph (80%)

I

n = 0, R_1 = H, R_2 = Me (93%)
n = 0, R_1 = Me, R_2 = Ph (91%)

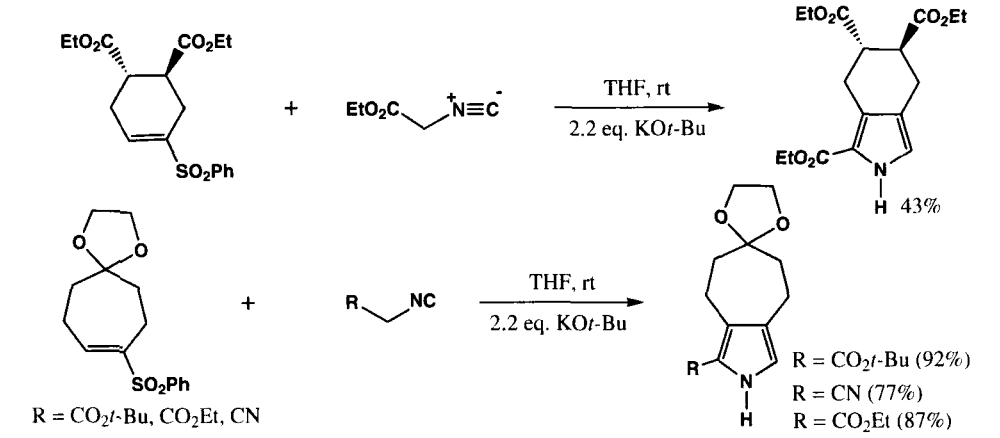
II

R_1 = H, R_2 = Me (75%)
R_1 = Me, R_2 = Ph (85%)

Synthesis and Thermal 6π-Electrocyclization of 2,3-(Dialkenyl)-4-nitropyrroles

Scheme 24

The addition of alkyl isocyanoacetates and isocyanoacetonitriles to α,β-unsaturated sulfones also produces pyrrole in a similar Barton-Zard process. This alternative protocol is a broad and very convenient one since α,β-unsaturated sulfones are easily obtained from readily available olefins (*Scheme 25*).[75]



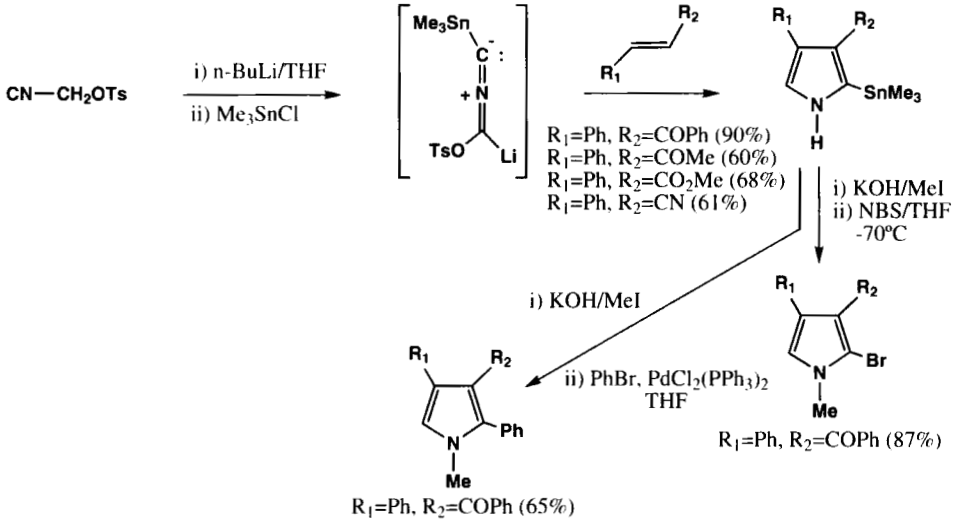
R = CO_2t-Bu, CO_2Et, CN

R = CO_2t-Bu (92%)
R = CN (77%)
R = CO_2Et (87%)

Use of a,b-Unsaturated Sulfones in a related Similar Barton-Zard Process

Scheme 25

An interesting achievement in this area was the preparation of stannylated tosylmethyl isocyanide and its use in the synthesis of a series of substituted 2-trimethylstannylpyrroles. The stannylated tosylmethyl isocyanide is efficiently prepared *in situ* from TosMIC by a base-induced reaction and then treated with Michael acceptors leading directly to the 2-stannylpyrroles. Further reaction on these stannylated pyrroles by Stille cross-coupling with bromobenzene has been performed successfully with the N-methyl derivative (*Scheme 26*).[76]



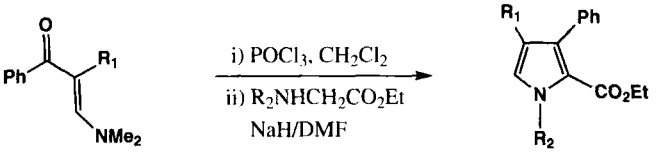
Stannylated TosMIC in the Preparation of 2-(Trimethylstannyl)pyrroles

Scheme 26

Since the Barton-Zard pyrrole synthesis is a flexible and efficient protocol, it has been used in several total syntheses. Very recently, Ono and coworkers showed that this methodology is very useful for preparing pyrrolostatin, a novel lipid peroxidation inhibitor, and its analogues.[77] Ley and coworkers developed a rapid and flexible method to generate libraries of tri-substituted pyrroles using this method in a multi-step reaction sequence based on polymer-supported reagents.[78]

IV. PYRROLES FROM 1,3-DICARBONYL DERIVATIVES

β-Dimethylamino ketones are useful intermediates for the synthesis of many heterocyclic compounds including pyrroles with a variety of substitution patterns. These ketones can be easily prepared from 1,3-dicarbonyl compounds.[79] Similarly to the Hanstzch reaction, the β-dimethylamino group can be exchanged by amino acids. In a skilful work devoted to accessing several heterocyclic compounds, Gupton and coworkers[80] extended the knowledge of this reaction by showing that ethyl glycinate adds regiochemically to disubstituted vinylogous iminium salts producing several 2,3,4-trisubstituted pyrroles (*Scheme 27*).

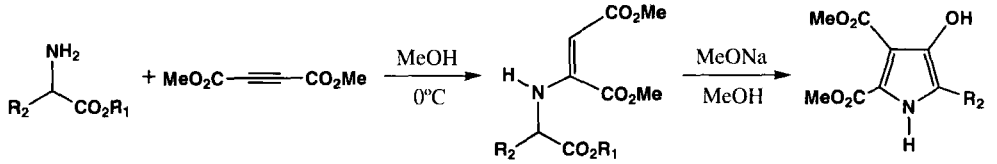


$R_1 = R_2 = Me$ (68%) $R_1 = Et$, $R_2 = Me$ (60%) $R_1 = Ph$, $R_2 = Me$ (60%)

Regiochemical Addition of Ethyl Glycinate in a Hanstzch Reaction

Scheme 27

Esters of alkyl, aryl, and heteroaryl substituted α-aminoacids have also been successfully used as synthons for the synthesis of the tetrasubstituted pyrroles (*Scheme 28*).[81] α-Aminoacids esters react easily with dimethyl acetylenedicarboxylate (DMAD) in methanol at 0-20°, forming mixtures of (E) and (Z)-enamines in quantitative yields, which are then transformed into tetrasubstituted pyrroles by a sodium methoxide-catalyzed Dieckmann-like condensation.

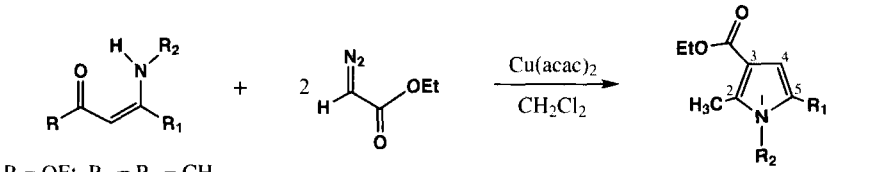


$R_1 = Me$, $R_2 = Bn$ (65%) $R_1 = Me$, $R_2 = (CH_3)_2CH{=}CH_2$ (68%) $R_1 = Me$, $R_2 = CH_3SCH{=}CH_2$ (54%)

Dieckmann-like Condensation for the Synthesis of Tetrasubstituted Pyrroles

Scheme 28

A further example exploiting the use of β-enaminones was developed by Kascheres and coworkers. The reaction of carbethoxycarbene with several acyclic enaminones ($RCOCH{=}CR_1NHR_2$) lead to substituted pyrroles. Structural variations of the enaminones show that the fragments C(3)-CO_2Et and C(2)-Me are derived from the diazo compound and that the fragment C(5)-R_1NHR_2 originated from the enaminones. The authors did not propose a mechanism to explain the formation of the pyrolles, but speculated that the RCO group of the enaminones is eliminated during the course of the reaction (*Scheme 29*).[82]



$R = OEt$, $R_1 = R_2 = CH_3$
$R = OEt$, $R_1 = CH_3$, $R_2 = H$
$R = R_1 = R_2 = CH_3$

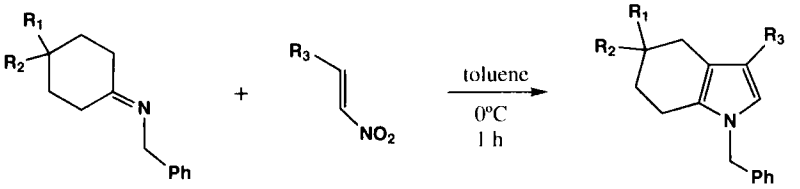
$R_1 = R_2 = CH_3$ (15%)
$R_1 = CH_3$, $R_2 = H$ (30%)
$R_1 = H$, $R_2 = CH_3$ (24%)

Preparation of Pyrroles by Carbenoid Insertion at Enaminones

Scheme 29

Very recently, Revial and coworkers found the optimal conditions for the reaction of imines with nitroalkenes to produce substituted pyrroles in one step.[83] This procedure is an improvement of the original work reported by Grob and coworkers in the early 50's,[84] which involves reaction

between secondary β-enaminoesters and 1-nitroalkenes followed by an intramolecular displacement of the nitro group by the amino group to yield pyrroles (*Scheme 30*). The efficiency and simplicity of the experimental conditions make this methodology very attractive but it is limited to symmetrical imines.

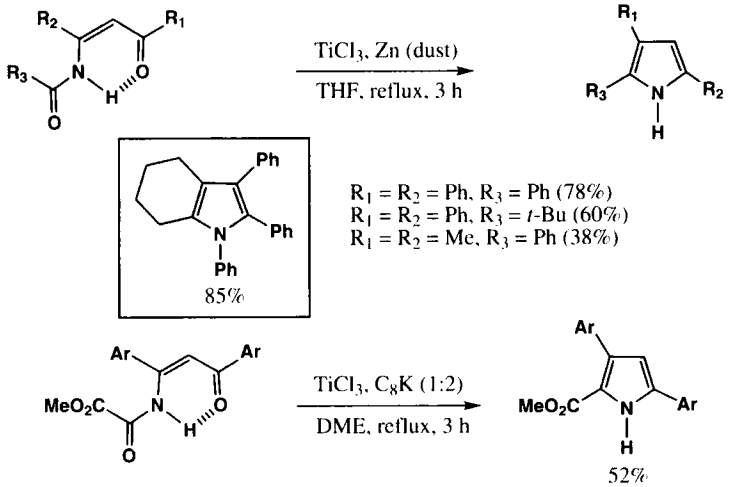


$R_1 = R_2 = H$, $R_3 = Ph$ (70%) $R_1 = R_2 = H$, $R_3 = Et$ (47%) $R_1 = R_2 = O(CH_2)_2O$, $R_3 = Ph$ (90%)

One Step Synthesis of Pyrroles from Imines and Nitro Vinyl Derivatives

Scheme 30

Low-valent transition metals have been known for long time to induce C-C bond formations in a catalytic process (McMurry reaction). Low-valent titanium based reagents efficiently perform reductive carbonyl couplings.[85] Continuous improvement of this reaction, since its discovery in the 1970s, led to impressive applications in the syntheses of natural products and pharmaceuticals. Fürstener and coworkers developed a new procedure to transform oxo-amides, acylated enaminones or masked 1,3-dicarbonyl compounds, into several substituted pyrroles by using a low valent titanium reagent (*Scheme 31*). This methodology was applied successfully to the synthesis of some important alkaloids. The exact mode of action of these reagents has been scrutinized and it was shown that the active titanium species responsible for the coupling is not generated during the reductive coupling of the carbonyl-containing substrate.[86]

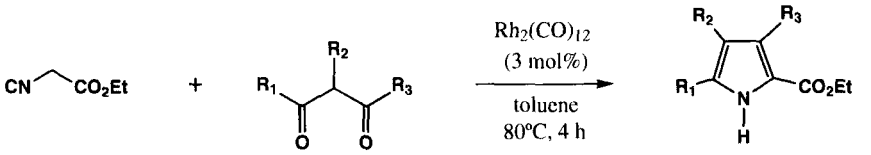


Transformation of Enaminones into Pyrroles by Low Valent Titanium Reagent

Scheme 31

Low-valent rhodium complexes are efficient catalysts for the activation of α-C-H bonds of isonitriles under neutral conditions. These metallated species easily add to electrophiles.[87] Very

recently, Murahashi and coworkers expanded this concept to prepare highly substituted pyrroles in one step by the $Rh_2(CO)_{12}$ catalyzed addition of isonitriles to 1,3-dicarbonyl compounds (*Scheme 32*).[88] It is worthy to note that the process produces tri- and tetrasubstituted pyrroles in moderate to good yields, and in highly regioselective fashion on the basis of either steric or electronic effects.



$R_1 = R_3 = Me$, $R_2 = H$ (84%) $R_1 = R_2 = R_3 = Me$ (68%) $R_1 = Me$, $R_2 = H$, $R_3 = CO_2Et$ (76%)
$R_1 = Ph$, $R_2 = H$, $R_3 = Me$ (52%) $R_1 = t$-Bu, $R_2 = H$, $R_3 = Me$ (65%)

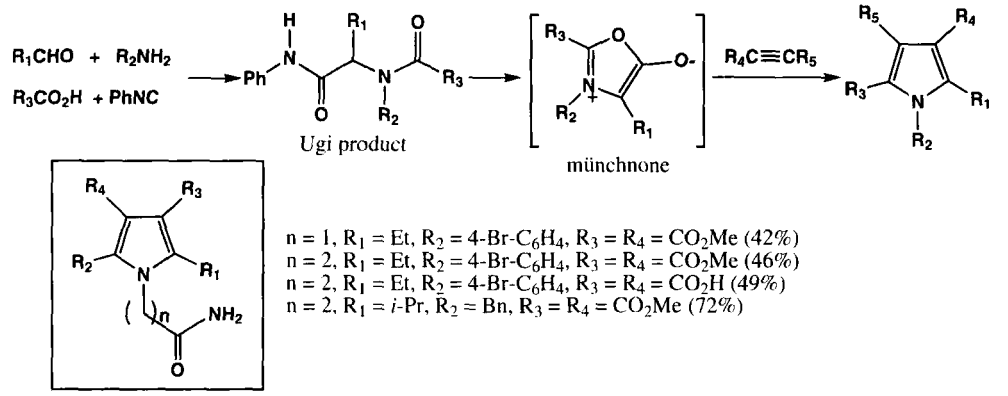
One-pot Pyrrole Synthesis by Rh2(CO)12 Catalyzed Addition of Isonitriles to 1,3-Dicarbonyl Compounds

Scheme 32

V. MULTIPLE-COMPONENT REACTIONS

Recent efforts have been directed towards to the development of multiple-component reactions (MCRs) since these processes are very attractive to produce drug-like small molecule libraries, mostly on solid supports, but also in solution.[89] MCRs have several advantages over conventional organic reactions, such as the preparation of new molecules from several small starting materials and a highly convergent methodology. Amongst known MCRs, the Ugi reaction is the far most versatile.

The Ugi four-component reaction (4-CC)[90] is a powerful multiple-component reaction[91, 92] that produces in a single step dipeptides or α-acylaminoamides (called Ugi product) from aldehyde, amine, carboxylic acid and isonitrile (*Scheme 32*). These Ugi products[93, 94] (see structure in Scheme 32) have been applied successfully to the synthesis of several heterocyclic compounds. For instance, when heated with alkynes containing either one or two electron-withdrawing substituents or with nitroalkenes, they lead to pyrroles in good yields through a 1,3-dipolar cycloaddition, of the münchnones (1,3-oxazolium-5-ones) class of mesoionic compounds *in situ* (*Scheme 33*).[95, 96]



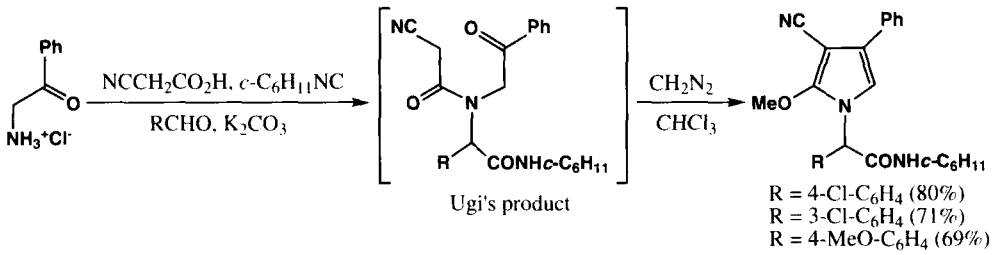
n = 1, R_1 = Et, R_2 = 4-Br-C_6H_4, $R_3 = R_4 = CO_2Me$ (42%)
n = 2, R_1 = Et, R_2 = 4-Br-C_6H_4, $R_3 = R_4 = CO_2Me$ (46%)
n = 2, R_1 = Et, R_2 = 4-Br-C_6H_4, $R_3 = R_4 = CO_2H$ (49%)
n = 2, R_1 = *i*-Pr, R_2 = Bn, $R_3 = R_4 = CO_2Me$ (72%)

1,3-Cycloaddition of Alkynes and Münchnones to Generate Pyrroles

Scheme 33

Other alkynyl compounds also have been used as other 1,3-dipoles in cycloaddition reactions to produce pyrroles.[97, 98] Since MCRs are superior to linear synthesis, their use in solid support reactions is quite adequate. Thus, Mjalli and Baiga used a solid supported reagent to obtain the Ugi product and its conversion into several pyrroles (see box in the Scheme 33).[99]

In a recent study, Bossio and coworkers reported a simple one-pot synthesis of densely functionalized pyrroles by a four-component condensation (4-CC) protocol (*Scheme 34*).[100] The initial step consists of a condensation between phenacylamine hydrochloride, cyanoacetic acid, cyclohexyl isocyanide, and aldehydes in the presence of potassium carbonate. The 4-CC product generated *in situ* was immediately treated with diazomethane to produce pyrroles in good yields (Scheme 34).

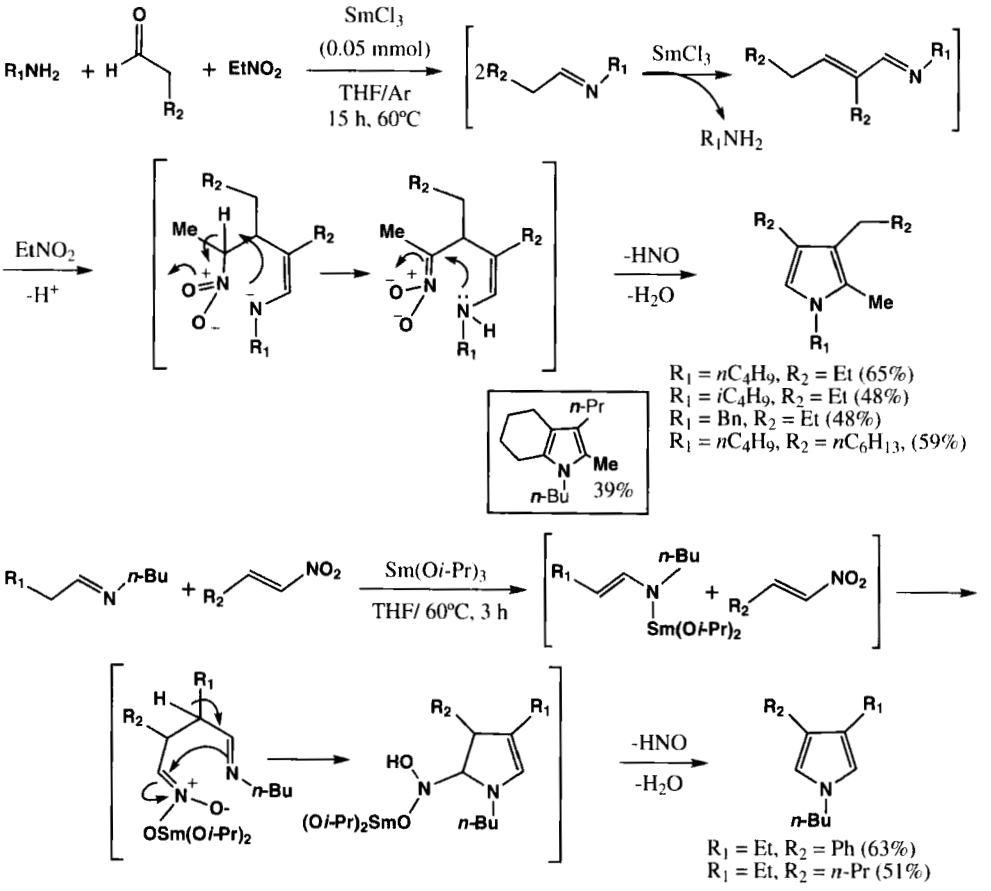


Densely Functionalized Pyrroles from Ugi 4-CC Intermediate

Scheme 34

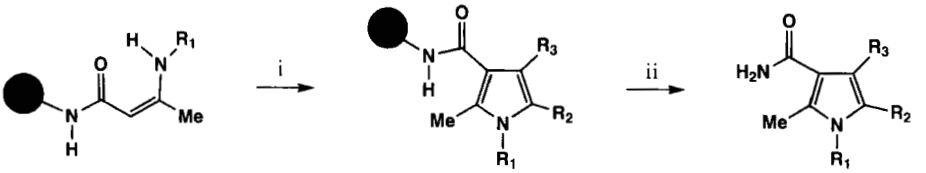
In another study, pyrroles were synthesized by a three-component (3-CC) reaction of aldehydes, amines, and nitroalkanes in the presence of samarium halide under mild conditions.[101] The reaction involves the coupling of α,β-unsaturated imines with nitroalkanes. The imines are formed *in situ* by the samarium-catalyzed condensation generated from the amines and the aldehydes, which then react with nitroalkanes to produces pyrroles (*Scheme 35*). This process can also be carried out in absence of any catalyst. For instance, when a mixture of n-butylamine, 2-butylidenecyclohexanone and nitroethane reacts at 60° for 15 hours produces an isoindole is produced in 39% yield (see box in Scheme 35), which is difficult to prepare by other conventional methods. Later on, the same group reported a short variation of the above method, in which imines couple with nitroalkenes under catalysis by lanthanide compounds.[102] Amongst all lanthanide compounds tested they found that samarium tri-O-isopropoxide was the better catalyst for this kind of coupling. Very recently, an improved procedure for this methodology has been developed in an one-pot reaction of α,β-unsaturated aldehydes/ketones, amines and nitroalkanes on the surface of silica gel, without any solvent, under microwave irradiation, to produce pyrroles in good yields.[103]

Combinatorial chemistry has become an important tool for the discovery of new biological active compounds and solid phase is by far the technique most utilized for preparing small organic molecule libraries. Three-component reactions are also very suitable for combinatorial synthesis in the solid phase method. Jung and Trautwein[104] applied a similar methodology for the synthesis of pyrrole libraries. The reactions were performed with aromatic aldehydes, nitroalkanes, enaminones supported on a solid resin, and piperidine as the base in DMF leading to pyrrole 3-carboxamides in reasonable yields (*Scheme 36*).



Synthesis of Pyrroles by a 3-Component Coupling Reaction

Scheme 35

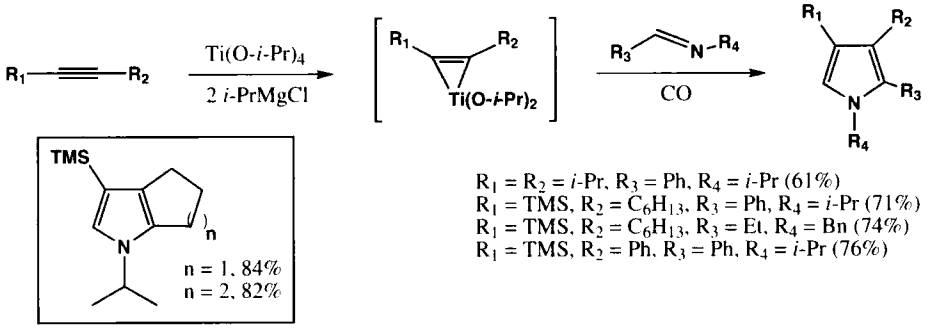


i) $R_2CH_2NO_2$, R_3CHO, DMF/EtOH (1:1), 70°C, 5 h, ii) 20% TFA, CH_2Cl_2, 30 min.

3-CC Synthesis of Pyrroles in Solid Phase

Scheme 36

In another study, a very straight favored 3-CC process for preparing pyrroles in good yields from alkynes, imines and carbon monoxide *via* organotitanium intermediate was developed by Sato and coworkers.[105, 106] The one-pot process involves the facile formation of (η^2-propene)Ti(O*i*Pr)$_2$ generated *in situ* from acetylenes, Ti(O*i*Pr)$_4$ and 2 equivalents of *i*-PrMgCl. Its reaction with imines affords azatitanacyclopentene complexes. Finally, CO insertion into the Ti-C bond leads to substituted pyrroles.[107] This sequence uses nontoxic and commercially available reagents and also tolerates a variety of functional groups in the acetylenic reagent (*Scheme 37*).

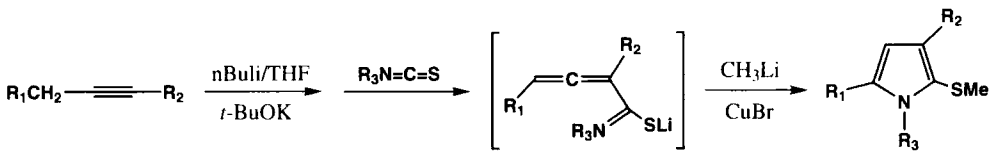


$R_1 = R_2 = i$-Pr, R_3 = Ph, $R_4 = i$-Pr (61%)
R_1 = TMS, $R_2 = C_6H_{13}$, R_3 = Ph, $R_4 = i$-Pr (71%)
R_1 = TMS, $R_2 = C_6H_{13}$, R_3 = Et, R_4 = Bn (74%)
R_1 = TMS, R_2 = Ph, R_3 = Ph, $R_4 = i$-Pr (76%)

Synthesis of Substituted Pyrroles by CO Insertion into Azatitanacyclopentene Complexes

Scheme 37

Very recently, a new 3-CC approach for the construction of pyrrole rings was developed from alkynes, isothiocyanates and alkyl lithiums. The utility of this process was demonstrated by the synthesis of 1,2,3,5-tetrasubstituted pyrroles starting from alkyl isothiocyanates and alkynylamines or alkynyl ethers. The key step of this process is the regiospecific functionalization of lithiated 2-alkynylamines, or the analogous ethers, with alkyl isothiocyanates. Despite the fact that only two examples of pyrroles were reported from this approach, it can be anticipated to be a useful method for preparing pyrrole derivatives (*Scheme 38*).[108]



$R_1 = NEt_2$, $R_2 = NEt_2$, R_3 = Et (87%) R_1 = OMe, R_2 = 2-furyl, R_3 = Me (63%)

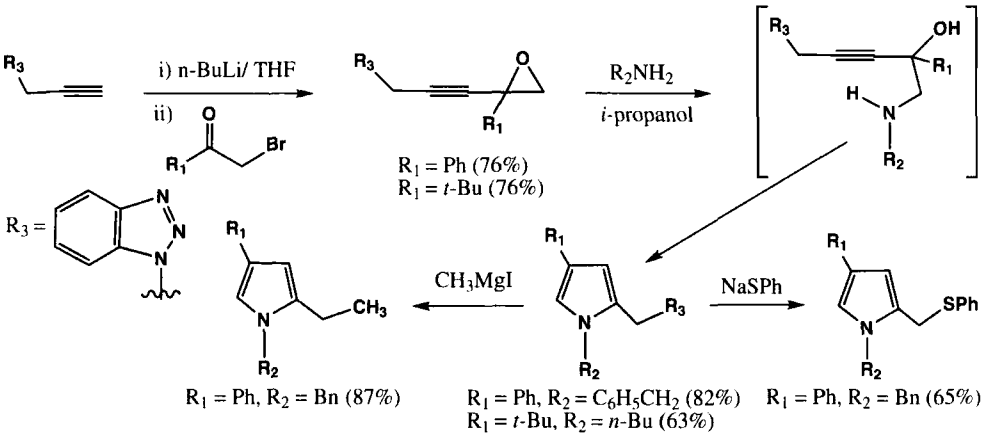
3-CC Approach for the Construction of Pyrrole Rings

Scheme 38

VI - SYNTHESES OF PYRROLES FROM ALKYNYL COMPOUNDS

Alkynes are important building blocks in material science and organic synthesis. The utilization of these substances in the synthesis of pyrroles represents one of the most versatile and efficient tools for the preparation of this class of compounds. A number of processes, which allow for the construction of properly functionalized pyrroles from acetylenic building blocks, have been developed lately, providing an important new dimension in the design of synthetic strategies.

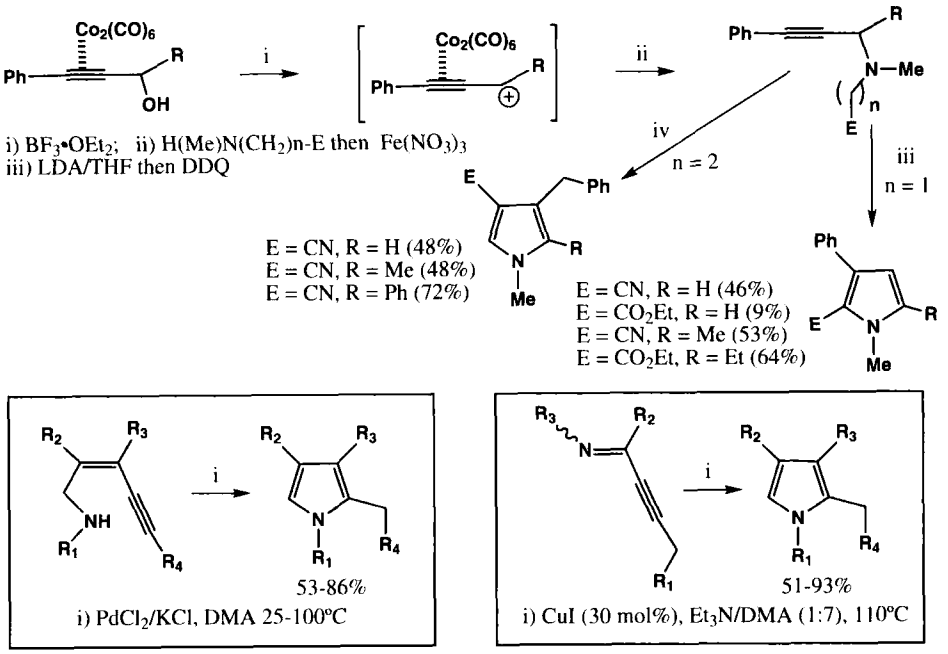
In this regards, Katrizky and Li[109] reported an extended method[110] for the synthesis of polysubstituted pyrroles having a CH_2-benzotriazole substituent (*Scheme 39*). Thus, benzotriazole-pyrroles were easily prepared by 5-*endo*-cyclization from an aminoalcohol intermediate generated from the reaction of 5-(benzotriazol-1-yl)-1,2-epoxy-3-pentynes with primary amines in *i*-PrOH. The 2-(benzotriazol-1-yl)methyl side chains were elaborated by nucleophilic substitution followed by replacement or elimination of the benzotriazolyl moiety[111] to afford a variety of polysubstituted pyrroles. The Scheme 39 illustrates some selected examples of pyrroles prepared by using this methodology.



Use of 5-(Benzotriazole-1-yl)-1,2-epoxy-3-pentynes for Pyrrole Synthesis

Scheme 39

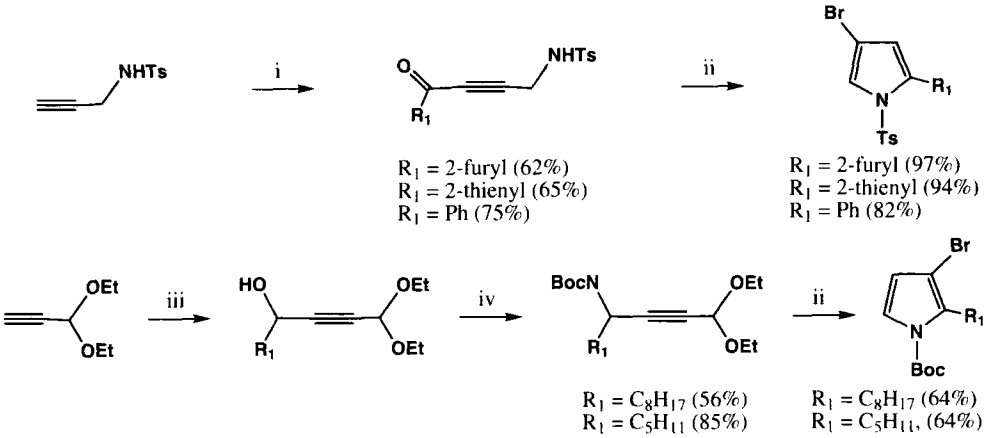
Yeh and coworkers showed the preparation of substituted pyrroles by 5-*endo-dig* and 5-*exo-dig* cyclizations. Treatment of cobalt-stabilized propargylium complexes with $BF_3.Et_2O$ and the appropriate amine give the propargyl amines, which are deprotonated with LDA and then converted to dihydropyrroles in one-step intramolecular cyclization reaction. These dihydropyrroles can be further transformed into pyrroles by oxidation with DDQ (*Scheme 40*). Salermo and coworkers recently reported another similar ring closure, presumably initiated by nitrogen attack on Pd-complex triple bond.[112] They obtained tetrasubstituted pyrroles in one-step Pd-catalyzed cycloisomerization of (Z)-(2en-4-ynyl)amines. Also, Gevorgyan and coworkers reported a novel and general method for the construction of a variety of substituted pyrroles *via* Cu-assisted cycloisomerization of alkynyl imines[113] (see boxes in Scheme 40).



Carbanion Addition to Carbon-carbon Triple Bond by 5-*endo-dig* and 5-*exo-dig* Cyclization

Scheme 40

Obrecht and coworkers have studied a general route for the synthesis of N-protected-3-halopyrroles[114, 115] in good yields from acid catalyzed cyclization of the corresponding acetylenic ketones or acetylenic acetals (*Scheme 41*).

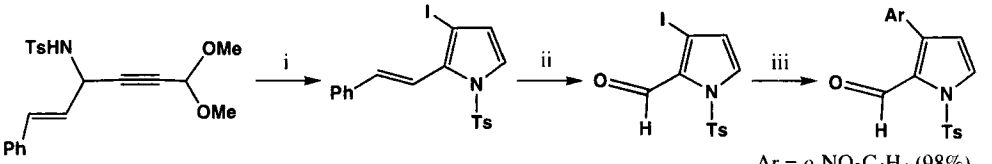


i) LDA, THF, -78°C; HMPT/R_1CHO; MnO_2, CH_2Cl_2; ii) HBr/AcOH, 33%; iii) nBuLi, THF, -78°C; R_1CHO; iv) MsCl, BocNH.

Pyrrole Synthesis from Propynaldehyde Diethylacetal or N-protected Propynylamine

Scheme 41

In a recent paper, Ghosez and coworkers expanded the above method applying the Suzuki reaction for the coupling of 3-halopyrroles with arylboronic acids catalyzed by $Pd(PPh_3)_4$.[116] For instance, the coupling of halopyrroles with *o*-nitrophenylboronic acid took place in 5 minutes at 80° in 98% yield with this catalyst (*Scheme 42*). Guéritte and coworkers recently described the preparation of di-*nor*-secorhazinilam, an analogue of (-)-rhazinilam, by a similar methodology using $PdBnCl(PPh_3)_2$ as the catalyst for the Suzuki cross-coupling reaction[117, 118]



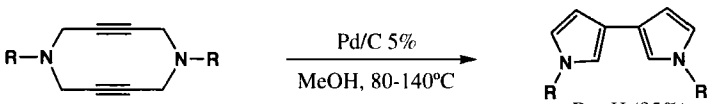
i) HI aq., -10°C, 71%; ii) $KMnO_4$ aq., 4 h, 48%;
iii) $ArB(OH)_2$/DMF-H_2O, $Pd(PPh_3)_4$

Ar = *o*-$NO_2C_6H_4$ (98%)
Ar = *m*-$NO_2C_6H_4$ (88%)
Ar = *o*-$MeOC_6H_4$ (88%)
Ar = C_6H_5 (92%)

Coupling of 3-Halopyrroles with Arylboronic Acids by Suzuki Protocol

Scheme 42

Another route which employs alkynyl compounds in the synthesis of pyrroles was reported by Gleiter who found an interesting rearrangement of 1,6-diisopropyl-1,6-diazacyclodecadiyne in an one-pot Pd/C catalyzed reaction leading to 3,3'-bispyrroles (*Scheme 43*).[119]

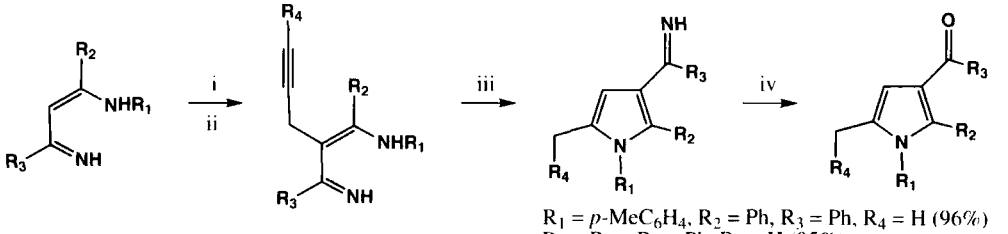


R = H (95%)
R = *i*-Pr (95%)
R = Ph (53%)

3,3'-Bispyrroles Obtained from Alkynyl Compounds

Scheme 43

Barluenga and coworkers developed an efficient two-step synthesis of polysubstituted pyrroles by metallation of 1-azabutadiene forming propargylic-substituted 4-amino-1-azabutadiene followed by a 5-*exo-dig* type thermal cycloamination (*Scheme 44*).[120] Several points are worthy of note here. The starting azadienes and their alkylated derivatives are easily prepared in multigram quantities. The cycloamination takes place chemoselectively at the substituted nitrogen since it is nearly coplanar with the triple bond. In very recent works, Arcadi and coworkers also studied several routes for producing substituted and fused pyrroles by 5-*exo-dig* cyclization of γ-ketoalkyne derivatives (4-pentynones) in the presence of primary amines.[121]

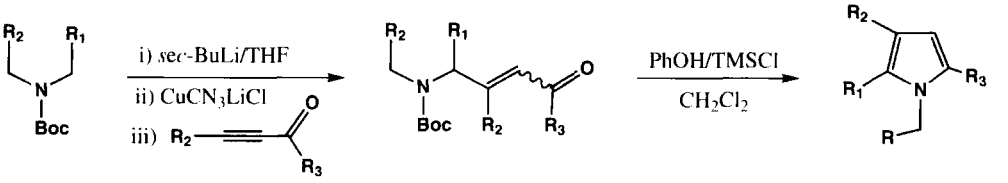


R_1 = *p*-MeC_6H_4, R_2 = Ph, R_3 = Ph, R_4 = H (96%)
R_1 = R_2 = R_3 = Ph, R_4 = H (95%)
R_1 = *n*-Bu, R_2 = Ph, R_3 = Ph, R_4 = H (91%)
R_1 = R_3 = *p*-MeC_6H_4, R_2 = Ph, R_4 = H (96%)

Chemoselective Cycloamination of Propargylic-azabutadiene

Scheme 44

Very recently, Dieter expanded his early work on 1,4-conjugate addition of α-aminoalkyl-cuprates[122] to α,β-allenyl esters and developed one broad strategy employing the same type of addition to α,β-alkynyl ketones catalyzed by copper in order to construct the carbon skeleton of the pyrrole ring.[123] This protocol is divided in two steps: conjugate addition of α-aminoalkylcuprates to alkynyl ketones generating γ-amino-α,β-enones; in a second step, treatment with PhOH/TMSCl in CH_2Cl_2 effected deprotection of the amine and subsequent cyclization afforded polysubstituted pyrroles (*Scheme 45*). It is worth noting that this synthetic strategy provides an efficient and rapid entry to the synthesis of several highly substituted pyrroles using readily available starting materials. Also, addition of ketoxime to propyne or allene in strongly basic medium produces in one step 2,5-di and 2,3,5-trisubstituted pyrroles in good yields.[124]



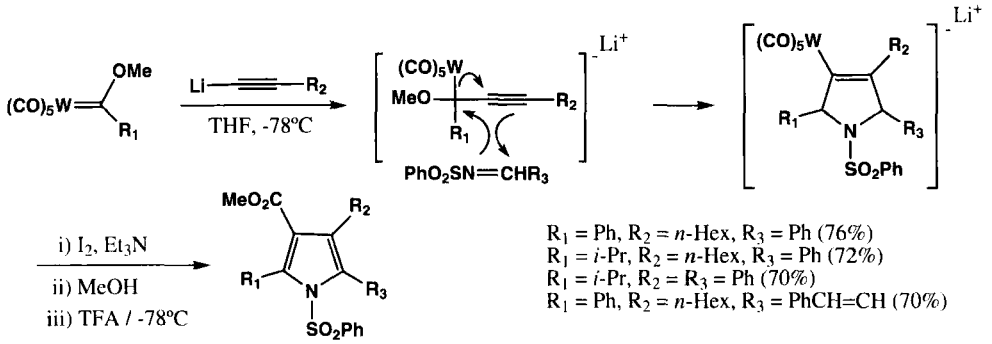
R = R_1 = H, R_2 = Bu, R_3 = Me (79%) R = R_1 = H, R_2 = Ph, R_3 = Me (66%)
R = R_1 = H, R_2 = Bu, R_3 = *t*-Bu (66%) R = R_3 = H, R_1 = Ph, R_2 = Bu (41%)

Pyrrole Synthesis by α-Aminoalkylcuprate Addition to Alkynyl Ketones

Scheme 45

Fully substituted pyrroles are obtained from alkynyl compounds using a reported method by Iwasawa and coworkers,[125, 126] who explored a special migration pattern of the Fischer carbene complexes.[127] Thus, addition of alkynyllithium to Fischer-type carbene tungsten complexes forms an intermediate that reacts with several electrophiles[128, 129] leading to butenolides or dihydropyrroles. Upon oxidation with iodine, the compounds produce furans or pyrroles, respectively (*Scheme 46*).

The most special feature of this methodology is the synchronized heterocycloaddition to a Fischer-type carbene followed by [1,2]-metallopentacarbonyl migration of the metal group. Other types of heterocyclizations such as [4 + 3] and [3 + 3] involving metallopentacarbonyl complexes have been used to prepare pyrroles.[130]



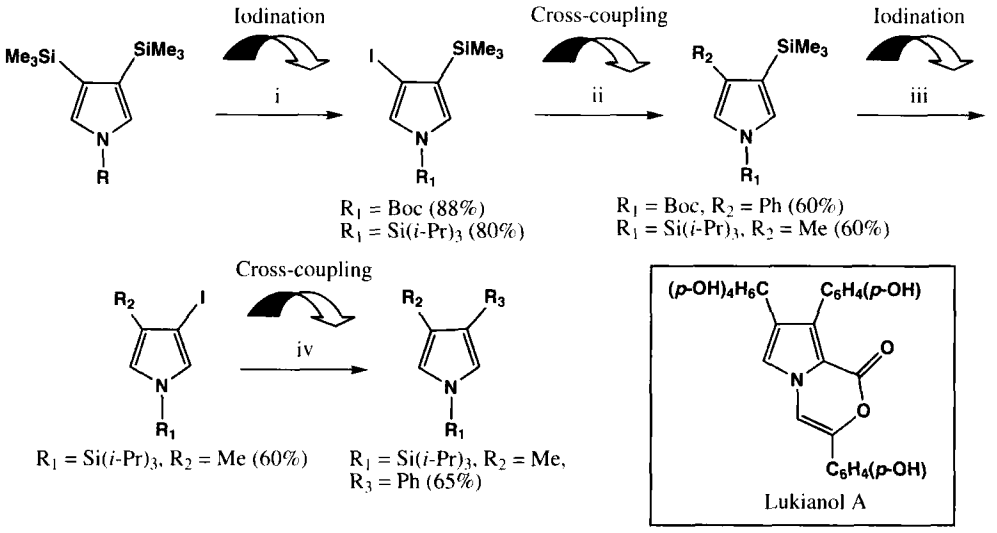
Use of Fischer-type Carbene Complexes for the Synthesis of Pyrroles

Scheme 46

VII- OTHER REACTIONS

Wong and coworkers developed a versatile method for the synthesis of 3,4-disubstituted pyrroles. The starting material in this method was 3,4-*bis*(trimethylsilyl)-1H-pyrrole. Through a highly regioselective monoiodination reaction only one trimethylsilyl group was substituted. Subsequent palladium-catalyzed cross-coupling reactions led to alkyl or aryl substitution of the iodine on the resulting pyrrole, which again underwent further iodination replacement of the remaining trimethylsilyl group; finally then another palladium-catalyzed cross-coupling reactions led to symmetrical or unsymmetrical 1-protected-3,4-disubstituted 1H-pyrroles (*Scheme 47*). This protocol represents a rapid and efficient method for obtaining regioselectively 3,4-disubstituted-pyrroles.[131, 132] The scope of this methodology was broadened by a combination of α-lithiation and nucleophilic substitutions of 3,4-*bis*(trimethylsilyl)-pyrrole derivatives leading to several 2-substituted 3,4-bis(trimethylsilyl)-1H-pyrrole-1-sulfonamides.[133] Taking the advantage of the β-effect of the trimethylsilyl group, a highly regioselective synthesis of 2,3,4-trisubstituted 1H-pyrroles was accomplished in good yields. By using this methodology, the marine natural product lukianol A was prepared in few steps (see box in Scheme 47).

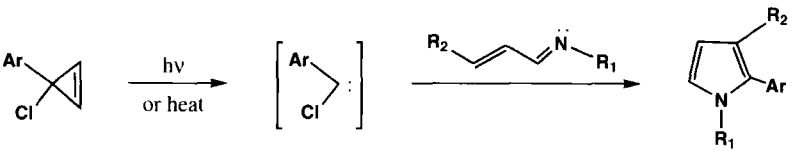
Carbene and metal carbenoids are very useful reactive intermediates in the syntheses of several heterocycle rings. Liu and coworkers prepared 1,2,3-trisubstituted pyrroles in good yields from the reaction of chlorocarbenes with 1-azabuta-1,3-diene in one step (*Scheme 48*).[134] Although only moderate yields were obtained in thermal catalyzed reactions, the process is still valuable for the synthesis of pyrroles due to the fact that arylchlorodiazirines and 1-azabuta-1,3-diene are easily prepared from commercially available reagents.



i) I_2/CF_3CO_2Ag, THF, -78°C, 1h; ii) $PhB(OH)_2$, $Pd(PPh_3)_2$, CuI, Et_2NH, 22-24 h;
iii) I_2/CF_3CO_2Ag, THF, 1 h; iv) $PhB(OH)_2$, $Pd(PPh_3)_2$, Na_2CO_3, MeOH-PhMe, 80°C.

Preparation of Pyrroles by Substitutions of TMS Groups at the Pyrrole Ring

Scheme 47

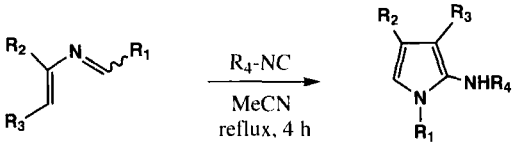


Ar = Ph, R_1 = Me, R_2 = Ph (54%) Ar = *p*-MeC_6H_4, R_1 = Me, R_2 = Ph (65%)
Ar = *p*-MeC_6H_4, R_1 = Bn, R_2 = Ph (58%)

One-step Cyclization of Chlorocarbenes with 1-Azabuta-1,3-dienes

Scheme 48

Among many reports concerning the use of isocyanides in pyrrole synthesis, the formal [1 + 4] cycloaddition of aldimines (or protonated aldimines) and isocyanides represents a new route to access to 2-aminopyrroles in one-pot reaction. The starting aldimines are readily prepared from the corresponding aldehydes and appropriate primary amines. The main feature of this method is the construction of the ring by simultaneous formation of N(1)-C(2) and C(2)-C(3) bonds, which can be classified as a C3 + C1 reaction in terms of the number of carbon atoms supplied to the heterocycle (*Scheme 49*).

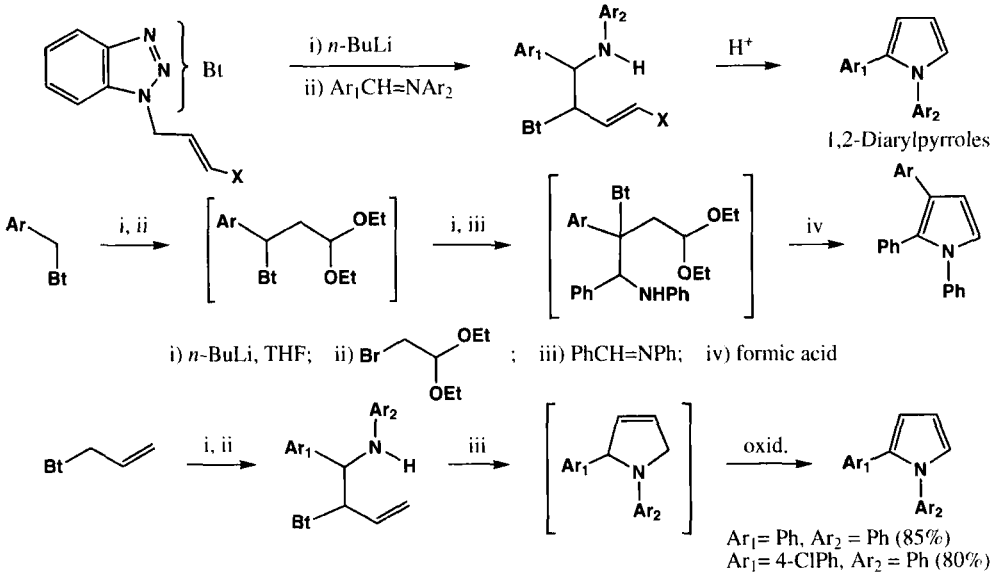


R_1 = Ts, R_2 = Me, R_3 = Ph, R_4 = *t*-Bu (71%)
R_1 = Ts, R_2 = Ph, R_3 = Me, R_4 = *t*-Bu (63%)

One-pot [1 + 4] Cycloaddition of Aldimines and Isocyanides

Scheme 49

Continuing his extensive work on the synthesis of heterocyclic compounds exploring the strong electron withdrawing and nucleofugicity of the benzotriazolyl group Katritzky and coworkers have developed several new routes to 1,2-diarylpyrroles (*Scheme 50*)[135] and recently reported the extension of this methodology to construct trisubstituted pyrroles in good yields in one-step synthesis. The key step of this approach was a double alkylation of N-benzylbenzotriazole derivatives ($BtCH_2Ar$) leading to an intermediate which cyclizes in acid medium producing pyrroles (Scheme 50).[136] The same group showed also that N-allylbenzotriazolyl derivatives is also suitable for alkylation with diarylimines leading to benzotriazolyl-anilines. The process involves Pd (II)-catalyzed intramolecular γ-amination-cyclization by generating *in situ* dihydropyrroles, which then by an oxidation step led to 1,2-diarylpyrroles in moderate to high yields.[137] Goré and coworkers found that dihydropyrroles can be oxidized also to pyrroles by MCPBA in CH_2Cl_2.[138]

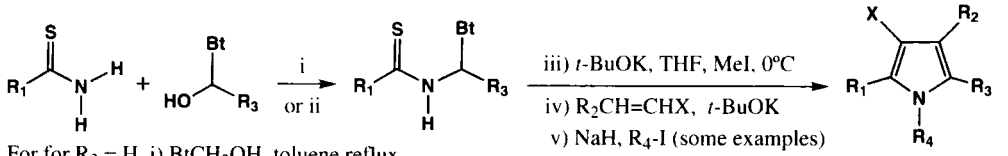


i) *n*-BuLi, THF; $Ar_1CH{=}NAr_2$; iii) $Pd(OAc)_2/PPh_3/CuCl_2/K_2CO_3$/THF

Use of Benzotriazol Methodology for the Synthesis of Substituted Pyrroles

Scheme 50

A more versatile one-pot synthesis to obtain highly substituted pyrroles by benzotriazole methodology was recently reported by Katritzky and coworkers (*Scheme 51*).[139] Thioamides react easily with hydroxymethyltriazole to produce benzotriazole-tioamides in high yields. The treatment of these amides with t-BuOK and MeI forms *in situ* S-methylhioamidates that react with several Michael acceptors producing tri- and tetrasubstituted pyrroles in good yields. This method provides at least four points of diversification. It allows obtaining a variety of highly substituted pyrroles containing ester, amide, sulfone, and various aryl, and heterocyclic groups.



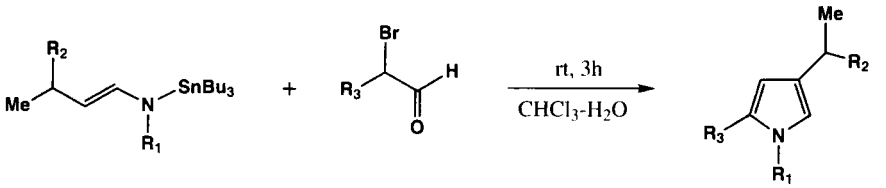
For for R_3 = H i) $BtCH_2OH$, toluene reflux
For R_3 = alkyl or aryl ii) $BtCH_2OH$, R_3CHO, PTSA

X = CN, R_1 = R_2 = Ph, R_3 = R_4 = H (99%)
X = SO_2Ph, R_1 = R_2 = Ph, R_3 = R_4 = H (90%)
X = CO_2Et, R_1 = Ph, R_2 = CF_3, R_3 = H, R_4 = Me (67%)
X = CO_2Et, R_1 = R_2 = Ph, R_3 = H, R_4 = Me (89%)

Use of Benzotriazole-tioamides in the Synthesis of Highly Substituted Pyrroles

Scheme 51

A very interesting approach for preparing trisubstituted pyrroles was developed by Baba and coworkers, in which the coupling of organotin enamines with α-haloaldehyde compounds was performed in one-step reaction in high yields (*Scheme 52*).[140]

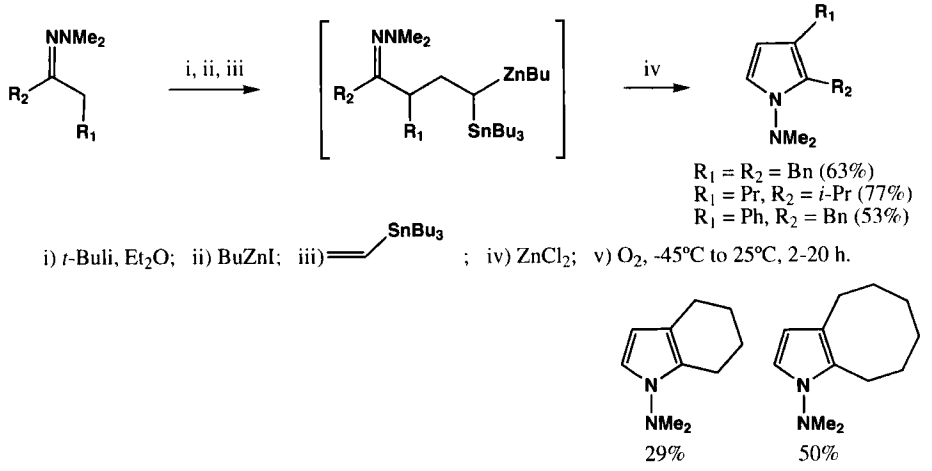


R_1 = *i*-Bu, R_2 = H, R_3 = C_5H_{11} (>99%)
R_1 = *t*-Bu, R_2 = H, R_3 = C_5H_{11} (>99%)
R_1 = *i*-Pr, R_2 = Me, R_3 = C_5H_{11} (74%)
R_1 = *i*-Pr, R_2 = H, R_3 = Ph (94%)

Synthesis of Substituted Pyrroles from Tin Enamines

Scheme 52

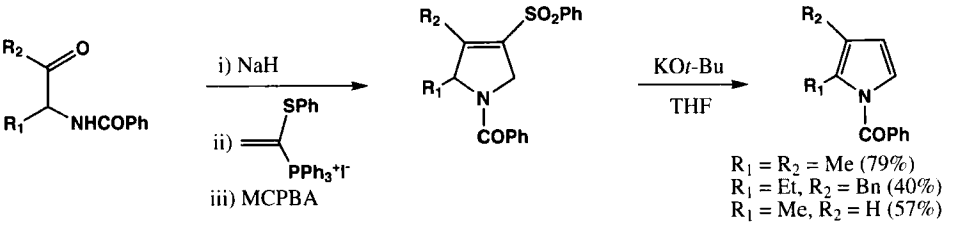
Very recently, Nakamura and coworkers reported a completely new strategy to prepare 1-(dimethylamino)-1H-pyrroles through [3 + 2] coupling of ketone hydrazones and a vinylstannane in one-pot reaction (*Scheme 53*).[141] The key step of this process is the carbometalation reaction of zincate hydrazones with a vinylstannane producing *gem*-Zn/Sn dimetallic species. Oxidative work-up with oxygen and $ZnCl_2$ decomposes the stanne-zincate intermediate producing dimethylamino-1H-pyrroles in moderate yield.



One-pot Synthesis of Pyrroles via Carbonzincation Reaction of Hydrazones

Scheme 53

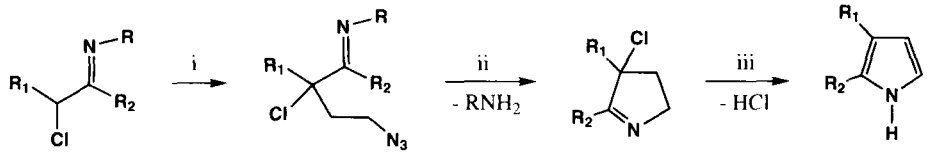
In 1995, Hewson and coworkers described a new route to prepare 2,3-dialkyl pyrroles by an intramolecular Wittig reaction as the key step (*Scheme 54*).[142] More recently, the same group optimized the last step of this sequence making this protocol more useful.[143] Thus, treatment of α-amidoketone with a α-phenylmercapto-α-triphenylphosphonium iodide under basic conditions, followed by oxidation with MCPBA, led to sulfonyl dihydropyrroles. Further treatment of this intermediate with KO*t*-Bu produced substituted pyrroles by deconjugation of the vinyl sulfone followed by elimination of benzenesulfinic acid.



Preparation of 2,3-Dialkylpyrroles by an Intramolecular Wittig Reaction

Scheme 54

De Kimpe and coworkers disclosed a totally new entry into 2,3-disubstituted pyrroles, in which the key step is an α-alkylation of carbonyl compounds with β-haloazides. These azides upon reduction furnish pyrroles in good overall yields (*Scheme 55*). This methodology can also be applied to prepare other nitrogen containing heterocyclic compounds depending upon the length of the carbon chain of haloazides.[144]

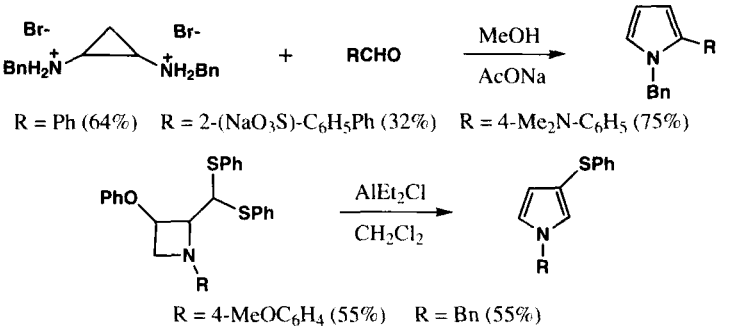


i) LDA/HMPA, THF -78°C then I-$(CH_2)_2N_3$ to 0°C; ii) $SnCl_2$, MeOH, 4-5 h; iii) NaOMe/MeOH.

Preparation of Pyrroles by Alkylation of Carbonyl Compounds with Haloazides

Scheme 55

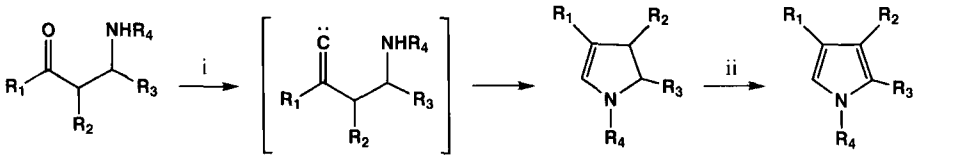
Several small ring opening and cyclization reactions have been explored in the synthesis of pyrroles. An unusual approach for preparing di- or tri-substituted pyrroles was reported by Quast and coworkers.[145] Reaction of cyclopropane-1,2-diammonium salts with aromatic aldehydes produes pyrroles in moderate to good yields. This method provides other points of diversification by using substituted cyclopropane-diamines (*Scheme 56*). Also azetidine ring can be rearranged to pyrroles by catalysis with diethylaluminum chloride.[146]



Preparation of Substituted Pyrroles from Cyclopropane and Azetidine Rings

Scheme 56

A very unusual approach for preparing substituted pyrroles in two-step reaction was reported by Shioiri and coworkers, which explored the addition of lithium trimethylsilyldiazomethane ($TMSC(Li)N_2$) to β-aminoketones. The reaction involves an attack of $TMSC(Li)N_2$ to the carbonyl forming an alkylidene carbene intermediate, which upon an intramolecular N-H insertion produces pyrrolines. Oxidation of the later compounds with MnO_2 produces pyrroles in high to moderate yields (*Scheme 57*).[147]



i) $Me_3SiC(Li)N_2$, THF; ii) MnO_2, CH_2Cl_2, 12 h

Pyrrolines and Pyrroles from Alkylidene Carbene Intramolecular N-H Insertion

Scheme 57

VIII. SUMMARY

Recent advances in the synthesis of highly substituted pyrroles have been reviewed. Although the first synthesis of pyrrole was described more than 100 years ago, and pyrrole synthesis have been extensively studied during these years, novel methodologies concerning the preparation of pyrroles continue to be reported. Many versatile, and in several cases unique heterocyclizations were reported, which may provide an important new dimension in the design of synthetic strategies for the construction of the pyrrole ring. A few of the more notable highlights reported within the last five years include mainly organometallic mediated heterocyclizations such as Pd-catalyzed oxidation of the enamine-intermediate of Knorr synthesis, the preparation of 2-(trimethylstannyl)pyrroles from stannylated TosMIC, pyrrole syntheses by three-component coupling reaction catalyzed by samarium, enaminone (enamines) transformation into pyrroles by low valent titanium (or tin) and, carbonzincation reaction of hydrazones. Processes using alkynyl compounds are also still valuable since the acetylenic derivatives are readily available. Also noteworthy: α-aminoalkylcuprate addition to alkynyl ketones, CO insertion into azatitaniumcyclopentenes and chromium Fischer-type carbene complexes. In the past five years, some advances in the field of the classical methods has continued under investigation mainly towards their improvement by the introduction of solid phase synthesis, *e. g.* MCRs in solid-phase. Other approaches should be noted: Knorr pyrrole synthesis based on Weinreb α-aminoamides and iodo-cyclization of β-enaminone vinylogous 1,4-dicarbonyl compounds, including 3-carbonyldihydrofuran. It is important to mention that considerable work has been devoted to improve the Barton-Zard reaction, 1,3-cycloadditions involving münchnone intermediates, and the use of benzotriazol group in the synthesis of pyrroles.

REFERENCES

1. a) I. F. Gimenez and O. L. Alves, *J. Braz. Chem. Soc.* **10**, 167 (1999), this full paper can be obtained in http://www.scielo.br; b) J. R. Reynolds, P. A. Poropatic and R. L. Toyooka, *Macromolecules*, **20**, 958 (1987)

2. a) R. E. Nizurski-Mann and M. P. Cava, *Heterocycles*, **34**, 2003 (1992); b) S.-S. P. Chou and Y.-H. Yeh, *Tetrahedron Lett.*, **42**, 1309 (2001).

3. C. D'Silva and D. A. Walker, *J. Org. Chem.*, **63**, 6715 (1998).

4. P. Evans, B. P.J. de Lacy, N. Guernion, N. M. Ratcliffe, P. S. Sivanand, G. C. Teare, *Synthetic Metals*, **114**, 181 (2000).

5. For recent review on synthesis of pyrrolizidines and indolizidines alkaloids, see: a) G. Casiraghi, F. Zanardi, G. Rassu and L. Pinna, *Org. Prep. Proced. Int.*, **28**, 641 (1996); b) H. Takohata and T. Momose, The Alkaloids, G.A. Cordell (ed.) Academic Press, San Diego (1993).

6. a) A. C Spivey, C. S. Frampton, and A. R. Battersby, *J. Chem. Soc. Perkin Trans. 1*, 2103 (**1996**); b) P. A. Jacobi and S. C Buddhu, D. Fry, and S. Rajeswari, *J. Org. Chem.*, **62**, 2894 (1997); c) Leung, S. H.; Nguyen, L. T. and K. M. Smith, *Heterocycl. Commun.*, **2**, 9 (1996).

7. A. Furstner, H. Weintritt, and A. Hupperts, *J. Org. Chem.*, **60**, 6637 (1995).

8. G. T. Gupton, K. E. Krumpe, B. S. Burnham, K. A. Dwornik, *Tetrahedron*, **54**, 5075 (1998).

9. I. K. Khanna, R.M. Weier, Y. Yu, P.W. Collins, J. M. Miyashiro, C. M. Koboldt, A.W. Veenhuizen, J. L. Currie, K. Seibert, P. C. Isakson, *J. Med. Chem.*, **40**, 1619 (1997).

10. A. Thurkauf, J. Yuan, X. Chen, J. W. Wasley, R. Meade, K. H. Woodruff, K. Huston, P. C. Ross, *J. Med. Chem.*, **38**, 4950 (1995).

11. J. R. Carson, R. J. Carmosin, P. M. Pitis, J. L. Vaught, H. R. Alamond, J. P. Stables, H. H. Wolf, E. A. Swinyard and H. S. White, *J. Med. Chem.*, **40**, 1578 (1997).

12. H. Pudleiner and H. Laatsch, *Liebigs Ann. Chem.*, 423 (**1990**).

13. D. G. Davies and P. Hodge, *Tetrahedron Lett.*, 1673 (1970).

14. a) P. Lue and J.V. Greenhill, *Adv. Heterocycl. Chem.*, **67**, 207 (1996); b) R. A. Jones (ed.) *Chem Heterocycl. Compds.*, **38**, 1 (1990); b) T. L. Gilchrist, *J. Chem. Soc. Perkin Trans. 1*, 615 (**1998**) and 2849 (1999); c) T. L. Gilchrist, *Contemp. Org. Synth.*, **2**, 337 (1995); d) R. J. Sundberg, *Prog. Heterocycl. Chem.*, **4**, 81 (1992); e) R. J. Sundberg and P. V. Nguyen, *Prog. Heterocycl. Chem.*, **6**, 110 (1994); f) M. Tiçler, P. Kolar, *Adv. Heterocycl. Chem.*, **64**, 1 (1995), f) J. M. Patterson, *Synthesis*, 281 (1976); f) S. Marcaccini and T. Torroba, *Org. Prep. Proc. Int.*, **25**,143 (1993); I. Collins, *J. Chem. Soc. Perkin Trans. 1*, 2845 (2000).

15. a) R. A. Jones and G. P. Been, The Chemistry of Pyrroles; Academic Press, NY, 1977; b) C. W. Bird and C. W. H. Cheeseman, "*Comprehensive Heterocyclic Chemistry*", Ed. A. R. Katritzky and C.W. Rees, Pergamon Press, Oxford, p.89, 1984; c) R.J. Sundberg, "*Comprehensive Heterocyclic Chemistry II*", ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford vol.2, p.119, 1996; d) R. J. Sundberg, "*Progress in Heterocyclic Chemistry*", Ed. H. Suschitzky and G. W. Griibble, Pergamon, Oxford, vol.8, p.103, 1996; e) T. L. Gilchrist, "*Heterocyclic Chemistry*", 2nd ed., Longman Scientific & Technical, Harlow, UK, p.189, 1994.

16. a) L. Knorr, *Chem. Ber.*, **17**, 546 (1884); b) L. Knorr, *Justus Liebigs Ann. Chem.*, **236**, 290 (1886); b) D. T. Davies, *"Aromatic Heterocyclic Chemistry"*, p. 10, Oxford, New York, N.Y., 1992.

17. T. L. Gilchrist, *"Heterocyclic Chemistry"*, 2nd ed., p. 188, John Wiley & Sons, New York, N.Y., 1992.

18. A. J. Moreno-Vargas, I. Robina, J. G. Fernández-Bolaños and J. Fuentes, *Tetrahedron Lett.*, **39**, 9271 (1998).

19. H. Fujii, T. Yoshimura and H. Kamada, *Tetrahedron Lett.*, **38**, 1427 (1997).

20. S. Nahm and S. Weinreb, *Tetrahedron Lett.*, **22**, 3851 (1981).

21. P. Nagafuji and M. Cushman, *J. Org. Chem.*, **61**, 4999 (1996).

22. A. Alberola, A. G. Ortega, M. L. Sábada and C. Sañudo, *Tetrahedron*, **55**, 6555 (1999).

23. P. Nagafuji and M. Cushman, *J. Org. Chem.*, **61**, 4999 (1996).

24. Y. Aoyagi, T. Mizusaki and A. Ohta, *Tetrahedron Lett.*, **37**, 9203 (1996).

25. A. R. Katrizky, *Handbook of Heterocyclic Chemistry"*, 1st Ed., Pergamon Press, New York, N.Y., 1985.

26. S. E. de Laszlo, D. Visco, L. Agarwal, L. Chang, J. Chin, G. Croft, A. Forsyth, D. Fletcher, B. Frantz, C. Hacker, W. Hanlon, C. Harper, M. Kostura, B. Li, S. Luell, M. MacCoss, N. Mantlo, E. A. O'Neill, C. Orevillo, M. Pang, J. Parsons, A. Rolando, Y. Sahly, K. Sidler, S. J. O'Keefe, *Bioorg. Med. Chem. Lett.*, **8**, 2689 (1998).

27. S. Demirayak, A. Ç. Karaburum and N. Kiraz, *Eur. J. Med. Chem.*, **34**, 275 (1999).

28. J. Soloducho, *Synthetic Metals*, **99**, 181 (1999).

29. T. N. Danks, *Tetrahedron Lett.*, **40**, 3957 (1999).

30. S. -X. Yu and P. W. Le Quesne, *Tetrahedron Lett.*, **36**, 6205 (1995).

31. K. Ogura, H. Yanai, M. Miokawa and M. Akazome, *Tetrahedron Lett.*, **40**, 8887 (1999).

32. A. Ramila, J. Plumet and E. Camacho, *Heterocycles*, **45**, 2425 (1997).

33. C. W. Ong, C. M. Chen, L.H. Wang, J. J. Jan and P. C. Shieh, *J. Org. Chem.*, **63**, 9131 (1998).

34. I. Baussanne and J. Royer, *Tetrahedron Lett.*, **37**, 1213 (1996).

35. Y. Fang, D. Leysend and H. C. J. Ottenheijm, *Synth. Commun.*, **25**, 1857 (1995).

36. A. C. Cunha, V. F. Ferreira, M. C. V. B. de Souza and L. O. R. Pereira, *Synth. Commun.*, **40**, 3215 (2000).

37. V. F. Ferreira, L. O. R. Pereira, M. C. B. V. de Souza and A. C. Cunha, *Quím. Nova*, **24**, In press (2001).

38. B. Quiclet-Sire, I. Thévenot and S. Z. Zard, *Tetrahedron Lett.*, **35**, 9469 (1995).

39. D. S. Black, M. C. Bowyer and N. Kumar, *Tetrahedron*, **53**, 8565 (1997).

40. a) D. Enders, S.-H. Han and R. Maaben, *Tetrahedron Lett.*, **36,** 8007 (1995); b) D. Enders, S.-H. Han and R. Maaben, *Liebigs Ann. Org. Bioorg. Chem.*, **10**, 1565 (1996).

41. R. Ballini, L. Barboni, G. Bosica, and B. Petrini, *Synlett*, 391 (2000).

42. a) P. A. Jacobi and G. Cai, *Tetrahedron Lett.*, **32**, 1765 (1991); b) P. A. Jacobi, S. C. Buddhu, D. Fry and S. Rajeswari, *J. Org. Chem.*, **62**, 2894 (1997).

43. D. F. Taber and K. Nakajima, *J. Org. Chem.*, **66**, 2515 (2001).

44. A. Hantzsch, *Chem. Ber.*, **23**, 1474 (1890).

45. V. Kameswaran and B. Jiang, *Synthesis*, 530 (1997).

46. A. W. Trautwein, R. D. Süssmuth and G. Jung, *Bioorg. Med. Chem. Lett.*, **8**, 2381 (1998).

47. Rink amide AM PS (1% DVD) is a common solid-supported reagent used in combinatorial chemistry. H. Rink, *Tetrahedron Lett.*, **28**, 3787 (1987). For a recent review, see: D. H. Drewry, D. M. Coe and S. Poon, *Med. Res. Rev.*, **19**, 97 (1999).

48. S. I. Zav'yalov, I. F. Mustafaeva, N. I. Aranova and N. N. Makhova, *Izv. Akad. Nauk. SSSR, Ser. Khim.* (Engl. Transl.), 2505 (1973).

49. C. D. Gabbutt, J. D. Hepworth, B.M. Heron, M. R. J. Elsegood, W. Clegg, *Chem. Commun.*, 289 (1999).

50. R. J. Andrew and J. M. Mellor, *Tetrahedron*, **56**, 7267 (2000).

51. For a recent review about transformation 3-dimethylpropenoates in heterocyclic compounds, see: B. Stanovnik and J. Svete, *Synlett*, 1077 (2000).

52. M. Malesic, A. Krbavcic, A. Golobit, L. Golic and B. Stanovnik, *J. Heterocycl. Chem.*, **34**, 1757 (1997).

53. R. Toplak, J. Svete, S. G. Golic and B. Stanovinik, *J. Heterocycl. Chem.*, **36**, 225 (1999).

54. H. M. C. Ferraz, E. O. de Oliveira, M. E. Payret-Arrua and C. A. Brandt, *J. Org. Chem.*, **60**, 7357 (1995).

55. H. M. C. Ferraz, F. L. C. Pereira, F. S. Leite, M. R. S. Nunes and M. E. Payret-Arrúa, *Tetrahedron*, **55**, 10915 (1999).

56. A. Rolfs, H. Bosig and J. Liebscher, *J. Prakt. Chem.*, **337**, 310 (1995).

57. A. Rolfs, P.G. Jones and J. Liebscher, *J. Chem. Soc. Perkin Trans. 1*, 2339 (1996).

58. R. Bartnik, A. Bensadat, D. Cal, R. Faure, N. Khatimi, A. Laurent, E. Laurent, C. Rizzon, *Bull. Soc. Chim. Fr.*, **134**, 725 (1997).

59. N. Chen, Y. Lu, K. Gadamasetti, C. R. Hurt, M. H. Norman and C. Fottsch, *J. Org. Chem.*, **65**, 2603 (2000).

60. A. M. van Leusen, H. Siderius and D. van Leusen, *Tetrathedron Lett.*, 5337 (1972).

61. D. H. R. Barton and S. Z. Zard, *J. Chem Soc. Chem. Commun.* 1098 (1985).

62. a) D. H. R. Barton, J. Kervagoret, and S. Z. Zard, *Tetrahedron*, **46**, 7587 (1990); D. H. Burns, C. S. Jabara and M. W. Burden, *Synth. Commun.*, **25**, 379 (1995).

63. C. Tardieux, F. Bolze, C. P. Gros and R. Guilard, *Synthesis*, 267 (1998).

64. R. Di Santo, R. Costi, M. Artico, S. Massa, G. Lampis, D. Deidda and R. Pompei, *Bioorg. Med. Chem. Lett.*, **8**, 2931 (1998).

65. R. Ragno, G. R. Marshall, R. Di Santo, R. Costi, S. Massa, R. Rompei and M. Artico, *Bioorg. Med. Chem.*, **8**, 1423 (2000).

66. T. D. Lash, J. R. Bellettini, J. A. Bastian and K. B. Couch, *Synthesis*, 170 (1994).

67. T. D. Lash, M. L. Thompson, T. M. Werner and J. D. Spence, *Synlett*, 213 (2000).

68. S. Nakajima and A. Osuka, *Tetrahedron Lett.*, **36**, 8457 (1995).

69. M. Adamczk and R. E. Reddy *Tetrahedron Lett.* **37**, 2325 (1996).

70. C. Dell'Erba, A. Giglio, A. Mugnoli, M. Novi, G. Petrillo and P. Stagnaro, *Tetrahedron*, **51**, 5181 (1995).

71. T. D. Lash, C. Wijesinghe and J. R. Patel, *Tetrahedron Lett.*, **38**, 2031 (1997).

72. C. H. Sibata, V. C. Colussi, N. L. Oleinick and T. J. Kinsella, *Braz. J. Med. Biol. Res.*, **33**, 869 (2000).

73. R.-T. Have, F. R. Leusink and A. M. van Leusen, *Synthesis*, 871 (1996).

74. R. ten Have and A. M. van Leusen, *Tetrahedron*, **54**, 1913 (1998).

75. Y. Abel, E. Haake, G. Haake, W. Schmidt, D. Struve, A. Walter and F.-P. Montforts, *Helv. Chim. Acta*, **81**, 1978 (1998).

76. H. P. Dijkstra, R. ten Have and A. M. van Leusen, *J. Org. Chem.*, **63**, 5332 (1998).

77. Y. Fumoto, T. Eguchi, H. Uno and N. Ono, *J. Org. Chem.* **64**, 6518 (1999).

78. M. Calderalli, J. Habermann and S. V. Ley, *J. Chem. Soc. Perkin Trans. 1*, 107 (1999).

79. H. K. Hombreccher and G. Horter, *Synthesis*, 389 (1990) and references citated therein.

80. J. T. Gupton, *Tetrahedron*, **52**, 6879 (1996).

81. a) P. Kolar and M. Tisler, *J. Chem. Educ.*, **73**, 986 (1996); b) P. Kolar and M. Tisler, *Synth. Commun.*, **24**, 1887 (1994).

82. R. Augusti, M. N. Eberli and C. Kascheres, *J. Heterocycl. Chem.*, **32**, 1355 (1995).

83. S. Lim, I. Jabin, and G. Revial, *Tetrahedron Lett.*, **40**, 4177 (1999).

84. C. A. Grob and K. Camenisch, *Helv. Chim. Acta*, **36**, 49 (1953).

85. A. Furstner, A. Hupperts and E. Janssen, *J. Org. Chem.*, **46**, 6695 (1991).

86. A. Fürstner and B. Bogdanovic, *Angew. Chem. Int. Ed. Engl.*, **35**, 2442 (1996).

87. S.-I. Murahashi, H. Takaya and S. Kojima, *Acc. Chem. Res.*, **33**, 225 (2000).

88. S.-I. Murahashi, H. Takaya and S. Kojima, *Org. Lett.*, **3**, 421 (2001).

89. A. Dömling, *Curr. Opinion Chem. Biol.*, **4**, 318 (2000).

90. I. Ugi, A. Dömling and W. Hörl, *Endeavour*, **18**, 115 (1994).

91. A. Dömling, *Comb. Chem. High Throughput Screen*, **1**, 1 (1999).

92. T. Lindhorst, H. Bock and I. Ugi, *Tetrahedron*, **55**, 7411 (1999).

93. A. M. Strocker, T. A. Keating, P. A. Tempest and R. W, Armstrong, *Tetrahedron Lett.*, **37**, 1149 (1996).

94. A. M. Strocker, T. A. Keating, P. A. Tempest and R. W, Armstrong, *J. Org. Chem.*, **61**, 8935 (1996).

95. M. Avalos, R. Babiano, A. Cabanillas, P. Cintra, J. L. Jiménez, J. C. Palacios, M. A. Aguilar, J. C. Corchado and J. Espinosa-García, *J. Org. Chem.*, **61**, 7291 (1996)

96. F. Berrée and G. Morel, *Tetrahedron*, **51**, 7019 (1995).

97. J. J. Tufariello, "1,3-Dipolar Cycloaddition Chemistry", Ed. A. Padwa, John Wiley and Sons, Inc., New York, vol. 2, p. 83, 1989.

98. a) B.-X. Zhao, Y. Yu and S. Eguchi, *Tetrahedron*, **52**, 12049 (1996); b) G. W. Gribble, E. T. Pelkey and F. L. Switzer, *Synlett*, 1061 (1998).

99. A. M. M. Mjalli, S. Sarshar and T. J. Baiga, *Tetrahedron Lett.*, **37**, 2943 (1996).

100. R. Bossio, S. Marcaccini, R. Pepino and T. Torroba, *Heterocycles*, **50**, 463 (1999).

101. H. Shiraishi, T. Nishitani, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, **63**, 6234 (1998).

102. H. Shiraishi, T. Nishitani, T. Nishihara, S. Sakaguchi and Y. Ishii, *Tetrahedron*, **55**, 13957 (1999).

103. B. C. Ranu, A. Hajra and U. Jana, *Synlett*, 75 (2000).

104. A. W. Trautwein and G. Jung, *Tetrahedron Lett.*, **39**, 8263 (1998).

105. Y. Gao, M. Shirai and F. Sato, *Tetrahedron Lett.*, **37**, 7787 (1996).

106. Y. Gao, Y. Yoshida and F. Sato, *Synlett*, 1353 (1997).

107. For one-pot synthesis of dihydropyrroles using carbon dioxide, see: Y. Gao, M. Shirai and F. Sato, *Tetrahedron Lett.*, **38**, 6849 (1997).

108. L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Eur. J. Org. Chem.*, **10**, 2663 (1999).

109. A. R. Katritzky and J. Li, *J. Org. Chem.*, **61**, 1624 (1996).

110. H. Kinoshita, S. Tanaka, and K. Inomata, *Chem. Lett.*, 1107 (1989).

111. A. R. Katritzky, H. Chang and S. V. Verin, *Tetrahedron Lett.*, **37**, 5641 (1996).

112. a) J.-L. Wang, C.-H. Ueng, M.-C. P. Yeh, *Tetrahedron Lett.*, **36**, 2823 (1995); b) B. Gabriele, G. Salermo, A. Fazio and M. R. Bossio, *Tetrahedron Lett.*, **42**, 1319 (2001).

113. A. V. Kel'in, A. W. Sromek and V. Gevorgyan, *J. Am. Chem. Soc.*, **123**, 2074 (2001)

114. D. Obrecht, *Helv. Chim. Acta*, **72**, 447 (1989).

115. D. Obrecht and T. Masquelin, *Synthesis*, 276 (1995).

116. C. Franc, F. Denonne, C. Cuisinier and L. Ghosez, *Tetrahedron Lett.*, **40**, 4555 (1999).

117. For a recent review on Suzuki's reaction, see: N. Miyaura and A. Suzuki, *Chem. Rev.*, **95**, 2457 (1995).

118. C. Dupont, D. Guénard, C. Thal, S. Thoret and F. Guéritte, *Tetrahedron Lett.*, **41**, 5853 (2000).

119. R. Gleiter and J. Ritter, *Tetrahedron*, **52**, 10383 (1996).

120. J. Barluenga, M. Tomáz, E. Rubio, V. Kouznetsov and A. Suárez-Sobrino, *J. Org. Chem.*, **61**, 2185 (1996).

121. a) A. Arcadi and E. Rossi, *Tetrahedron*, **54**, 15253 (1998); A. Arcadi, R. Anacardio, G. D'Annibale and M. Gentile, *Synlett*, 1315 (1997); c) A. Arcadi and E. Rossi, *Synlett*, 667 (1997).

122. a) R. K. Dieter and K. Lu, *Tetrahedron Lett.*, **40**, 4041 (1999); b) R. K. Dieter, C. W. Alexander and L. E. Nice, *Tetrahedron*, **56**, 2776 (2000).

123. R. K. Dieter and H. Yu, *Org. Lett.*, **2**, 2283 (2000).

124. B. A. Trofimov, O. A. Tarasova, A. I. Mikhaleva, N. A. Kalinina, L. M. Sinegovskaya and J. Henkelmann, *Synthesis*, 1585 (2000).

125. N. Iwasawa, K. Maeyama and M. Saitou, *J. Am.Chem. Soc.*, **119**, 1486 (1997).

126. N. Iwasawa, T. Ochiai and K. Maeyama, *Organometallics,* **16**, 5137 (1997).

127. K. H. Döts, C. Christoffers, P. Knochel, *J. Organomet. Chem.*, **489**, C84 (1995).

128. J. Barluenga, A. A. Trabanco, J. Floréz, S. Garcia-Granda and M.-A. Llorca, *J. Am. Chem. Soc.*, *120*, 12129 (1998).

129. N. Iwasawa, T. Ochiai and K. Maeyama, *Organometallics*, **16**, 5137 (1997).

130. J. Barluenga, M. Tomáz, E. Rubio, J. A. López-Pelegrin, S. García-Granda and M. P. Priede, *J. Am. Chem. Soc.*, **121**, 3065 (1999).

131. H. W. Chan, P. C. Chan, J. H. Liu and H. N. C. Wong, *Chem. Commun.*, 1515 (1997).

132. J. H. Liu, H. W. Chan and H. N. C. Wong, *J. Org. Chem.,* **65**, 3274 (2000).

133. J. H. Liu, Q. C. Yang, T. C. Mak and H. N. Wong, *J. Org. Chem.*, **65**, 3587 (2000).

134. Y. N. Romashin, M. T. H. Liu and R. Bonneau, *Chem. Commun.*, 447 (1999).

135. a) A. R. Katritzky, H. Wu, L. Xie, S. Rachwal, B. Rachwal, J. Jiang, G. Zhang and H. Lang, *Synthesis*, 1315 (1995); b) A. R. Katritzky, D. Cheng and R. P. Musgrave, *Heterocycles*, **44**, 67 (1997); c) A. R. Katritzky, L. Zhu, H. Lang, O. Denisko and Z. Wang, *Tetrahedron*, **51**, 13271 (1995); d) A. R. Katritzky, J. Yao and M. Qi, *J. Org. Chem.*, **63**, 5232 (1998); e) A. R. . Katritzky, H.-X. Chang and S. V. Veria, *Tetrahedron Lett.*, **36**, 343 (1995).

136. A. R. Katritzky, Z. Q. Wang, J. Q. Li and J. R. Levell, *J. Heterocycl. Chem.,* **34**, 1379 (1997).

137. A. R. Katritzky, L. Zhang, J. Yao and O. Denisko, *J. Org. Chem.*, **65**, 8074 (2000).

138. V. Breuil-Desvergnes, P. Compain, J.-.M. Vatèle and J. Goré, *Tetrahedron Lett.*, **40**, 8789 (1999).

139. A. R. Katritzky, T.-B. Huang, M. V. Voronkov, M. Wang and H. Kolb, *J. Org. Chem.*, **65**, 8819 (2000).

140. M. Yasuda, J. Morimoto, I. Shibata and A. Baba, *Tetrahedron Lett.*, **38**, 3265 (1997).

141. M. Nakamura, K. Hara, G. Sakata and E. Nakamura, *Org. Lett.*, **1**, 1505 (1999).

142. I. Burley and A. T. Hewson, *Synthesis*, 1151 (1995).

143. I. Burley, B. Bilic, A. T. Hewson and J. R. A. Newton, *Tetrahedron Lett.*, **41**, 8969 (2000).

144. W. Aelterman, N. De Kimpe, V. Tyvorskii and O. Kulinkovich, *J. Org. Chem.*, **66**, 53 (2001).

145. W. von der Saal, R. Reinhardt, J. Stawitz and H. Quast, *Eur. J. Org. Chem.*, 1645 (1998).

146. B. Alcaide, P. Almendros, C. Aragoncillo and N. R. Salgado, *J. Org. Chem.*, **64**, 9596 (1999).

147. T. Yagi, T. Aoyama and T. Shioiri, *Synlett*, 1063 (1997).

(Received March 3, 2001; in final form May 30 2001)