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REVIEW

4,4-Dialkoxybutan-2-ones as Synthons

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Abstract—The review considers the synthetic potential of 4,4-dialkoxybutan-2-ones which are promising synthons available from diacetylene-containing industrial gases. The reactivity of 4,4-dialkoxybutan-2-ones toward mono- and difunctional reagents, as well as in cycloaddition processes, is discussed.

1. INTRODUCTION

The chemistry of diacetylene has started to rapidly develop in 1950s since polyynes have been found in some naturally occurring substances and among products of electrocracking and oxidative pyrolysis of methane [1, 2]. A way of utilizing diacetylene in large-scale organic synthesis is processing of diacetylene-containing gases formed in the manufacture of acetylene to obtain 4,4-diethoxy(or dimethoxy)butan-2-one [3–13]. This way was implemented in the manufacture of acetylene by electrocracking of natural gas and was tested in the synthesis of acetylene by oxidative pyrolysis of methane [3, 5]. 4,4-Dialkoxybutan-2-ones are the most valuable intermediate products in large-scale organic synthesis, as follows from the data of a number of reviews [1, 2, 6, 14–23]. The synthesis of 4,4-dimethoxy-2-butanone from acetone and sodium methoxide was covered by patent [24]. Acetals derived from acetoacetaldehyde are used as modifiers for silicon dioxide surface [25], components of reagents for development of photographic materials [26], and resistors (in combination with other materials) [27, 28].

Taking into account that no dicaceylene-based products were available by Russian chemical industry [23], it seemed important to consider methods of preparation of 4,4-dialkoxybutan-2-ones and syntheses on their base. Transformations of the terminal methyl group (C^1), reactions of the ketone (C^2) and acetal (C^4) moieties, and cyclizations involving both these are described.

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2. METHODS OF SYNTHESIS OF 4,4-DIALKOXYBUTAN-2-ONES FROM DIACETYLENE

Scheme 1 illustrates the formation of 1-alkoxy-1-buten-3-ynes **2** from diacetylene **1** and their transformations under conditions of base and acid catalysis [14, 23].

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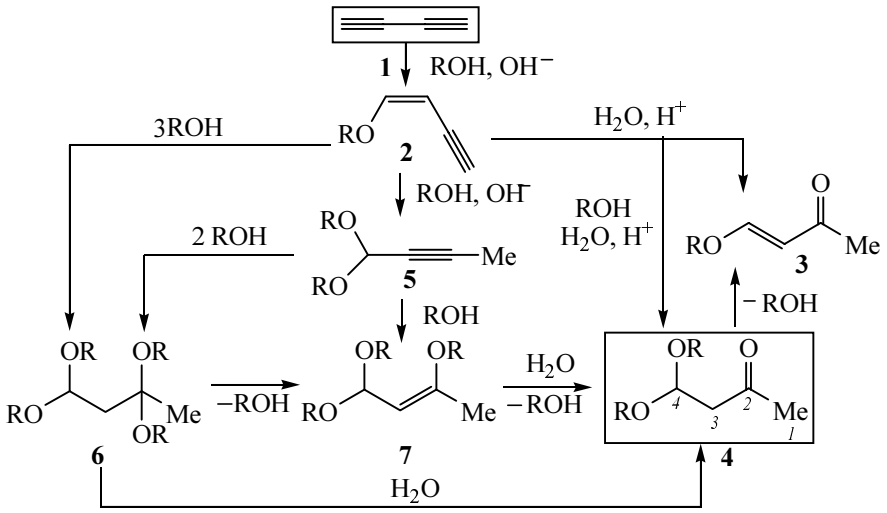
Scheme 1.



3, **4**, R = Me (**a**), Et (**b**).

Addition of the second methanol molecule in the presence of alkali gives 4,4-dimethoxy-2-butyne (**5**, R = Me). Hydration of the triple bond in **5** in boiling aqueous methanol, catalyzed by mercury salt in acid medium, leads to formation of 80% of 4,4-dimethoxybutan-2-one (**4a**, R = Me) [14, 23]. 4,4-Diethoxybutan-2-one (**4b**, R = Et) was obtained on a large scale in ~70% yield by reaction of a dilute solution of ethoxybutenyne (3–9 wt %) with ethanol in a flow reactor (112–115°C, 0.4 MPa, reactant supply rate 3–5 l/h, concentration of sulfuric acid as catalyst 7–9 mmol/l) [3, 5, 6]. The stage of formation of 4,4-dialkoxy-2-butynes (**5**) may be by-passed by combining the hydration and alkoxylation in the presence of acid catalyst in a one-pot process [14]. Under the same conditions, but with the use of anhydrous methanol (3 equiv), 1,1,3,3-tetramethoxybutane (**6**, R = Me) can be obtained together with a small amount of 1,1,3-trimethoxy-2-butene (**7**, R = Me). Mild hydrolysis of this mixture yields acetal **4** [14]. Thus the most stable compounds available from diacetylene are acetals **4** [2, 14, 23]. Thermal or catalytic elimination of methanol from the corresponding acetal **4** gives 4-methoxy-3-buten-2-one (**3a**, R = Me) [5, 6, 23], while in the presence of a catalytic amount of an acid or alkali a mixture of compounds **4a** and **3a** is formed at a ratio of 7 : 3 [3–6]. From diethyl acetal **4b**, an equilibrium mixture of **4b** and **3b** (R = Et) was obtained (ratio 7.5 : 2.5) [5] (Scheme 1).

3. REACTIONS AT THE METHYL GROUP

γ-Pyrone **8** was obtained by reaction of dimethoxybutanone **4a** with formic acid esters **9** (10°C, MeONa/C_6H_6, 1.5 h) [17, 22]. Presumably, intermediate **10** undergoes [3,3]-sigmatropic rearrangement to methoxydihydropyranone **11** which loses methanol molecule to afford compound **8** (Scheme 2).

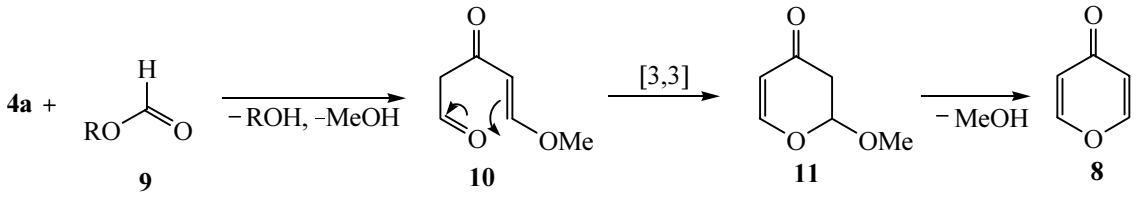
Condensations of dialkoxybutanones **4** with esters were used to prepare other oxygen-containing heterocycles. Adduct **12** was formed by reaction of **4a** with diethyl oxalate via condensation at the methyl group in **4** [17, 22]. Aldol condensation of **12** with formaldehyde gave hydroxymethyl derivative **13**, and cyclization of the latter in acid medium afforded furandione **14** and then furopyranone **15**. Reactions of **15** with amines and thiols are accompanied by opening of the pyranone ring with formation of dihydrofuranone derivatives **16** [22] (Scheme 3).

The condensation of acetal **4a** with cytral **17** was reported to afford isophytol (**18**, 7,11-dimethyl-1,1-dimethoxy-4,6,10-dodecatrien-3-one) which is an intermediate product in the syntheses of vitamins E and K_1 [15, 23] (Scheme 4). Franke and Kuther [16] described a procedure for the synthesis of 5-hydroxy-1,1-dimethoxy-5-phenylpentan-3-one (**19**) from acetal **4a** and benzaldehyde through organomagnesium intermediates (Scheme 5).

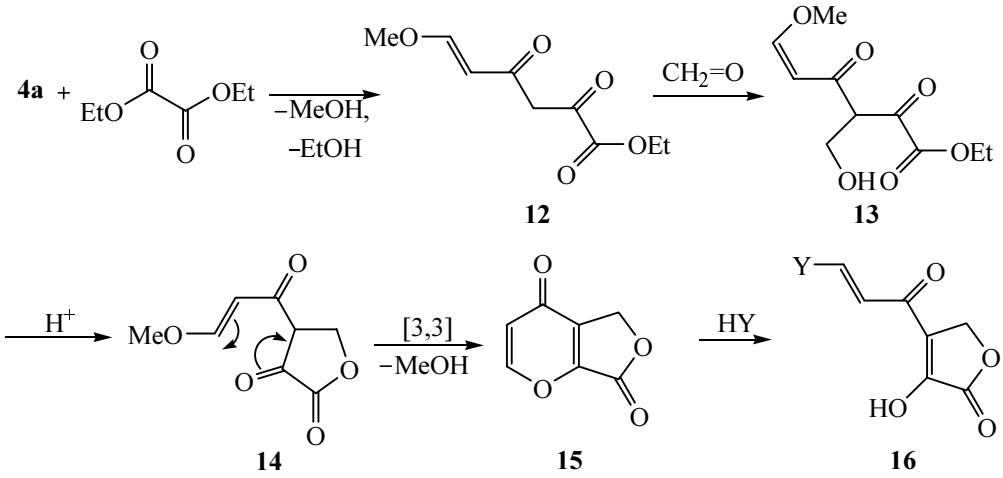
4. TRANSFORMATIONS OF THE CARBONYL GROUP

The reduction of the carbonyl group in acetal **4a** with sodium tetrahydridoborate or trialkylaluminum gives 4,4-dimethoxybutan-2-ol (**20**) [6, 17] (Scheme 6). The transformation of dialkoxybutanones **4** into optically

Scheme 2.

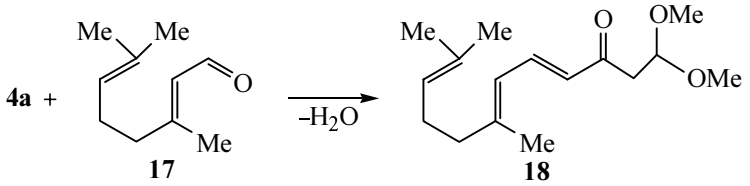


Scheme 3.

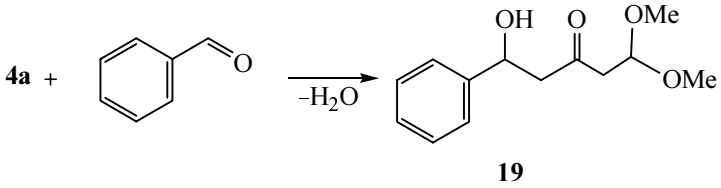


Y = R_2N, S, R.

Scheme 4.



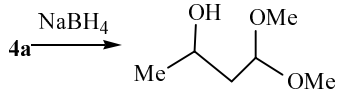
Scheme 5.



active butenols as intermediate products in the synthesis of antibiotics was described in patent [29]. Addition of hydrogen cyanide to acetal **4a** afforded 2-hydroxy-4,4-dimethoxy-2-methylbutanenitrile, alkylation of the hydroxy group therein gave trimethoxy nitrile **21**, the cyano group in the latter was reduced to obtain amine **22**, and the subsequent acetylation and ring closure led to formation of 3-methylpyrrole (**23**, X = H) or 1-acetyl-3-methylpyrrole (**23**, X = Ac) [15] (Scheme 7).

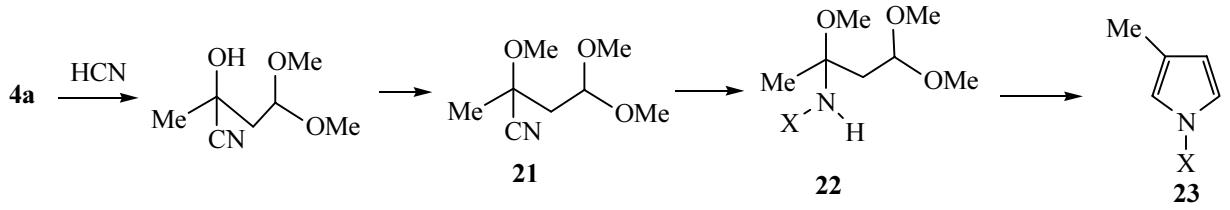
Kawai *et al*. [30] patented a procedure for the synthesis of pyrrole derivatives as leucosis and tremor

Scheme 6.

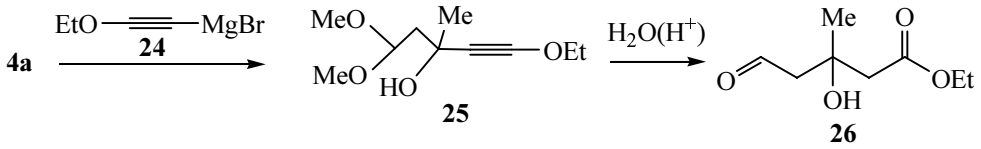


antagonists (inhibitors of TNF biosynthesis) using dialkoxybutanones **4** as starting compounds. A number of publications described the synthesis of structures related to 3,4-dihydroxy-3-methylpentanoic (mevalonic) acid [31]. For example, the reaction of acetal **4a** with

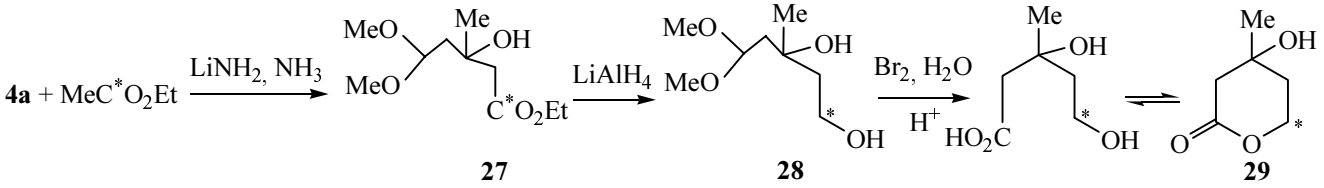
Scheme 7.



Scheme 8.



Scheme 9.



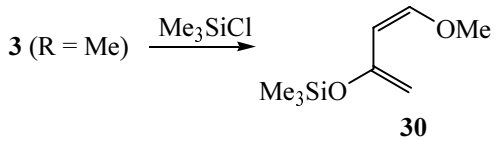
ethoxyethynylmagnesium bromide (**24**), followed by hydrolysis of the acetal group and hydration of the triple C≡C bond in **25**, afforded unsaturated aldehydoester **26** which is structurally related to mevalonic acid [17, 23] (Scheme 8).

D,L-5-[^{13}C]-Mevalonolactone was obtained by reaction sequence including condensation of acetal **4a** with ethyl acetate in liquid ammonia in the presence of lithium amide to ethyl 1-[^{13}C]-3-hydroxy-5,5-dimethoxy-3-methylpentanoate (**27**), reduction of the ester group in **27** to hydroxy with lithium tetrahydridoaluminate, removal of the acetal protection from diol **28**, oxidation of the aldehyde group to carboxylic with bromine in water, and lactonization of the resulting hydroxy acid [17, 23] (Scheme 9).

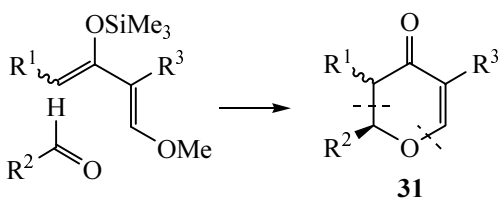
Dialkoxybutanone **4a** was converted into methoxybutenone **3a** which was treated with chlorotrimethylsilane to obtain 1-methoxy-3-trimethylsiloxy-1,3-butadiene (**30**; Danishefsky's diene; Scheme 10) [23] which is a synthon in Diels–Alder reactions [32, 33] and in the preparation of pyridinones and pyranones [32]. Compound **30** is also used in Mannich–Michael reactions for the synthesis of piperidinones and enamino ketones [17, 32–35]. Diene **30** ensures effective synthetic routes to aromatic and cyclohexanone systems, enantioselective syntheses of cyclopentenones [36–38], and diastereoselective syntheses of dihydropyranones which are then converted into substituted tetrahydropyrans **31** [39] (Scheme 11).

Treatment of **4a** with dimethylamine in methanol gives enaminoketone **33** which reacts with trialkylchlorosilanes to afford a new class of highly reactive hetero-dienes, 1-amino-3-trialkylsiloxy-1,3-butadienes **32** [40, 41] (Scheme 12). Methods for the synthesis of dienes containing different hetero and amino groups were reported [35, 40–43]. α,β-Unsaturated aldehydes and ketones were obtained by reduction of the carbonyl group in dimethoxybutanone **4a** with lithium tetrahydridoaluminate, followed by dehydration of alcohol **20** to butenal **34** [6, 17] (Scheme 13).

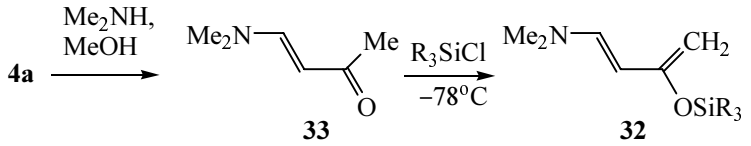
Scheme 10.



Scheme 11.

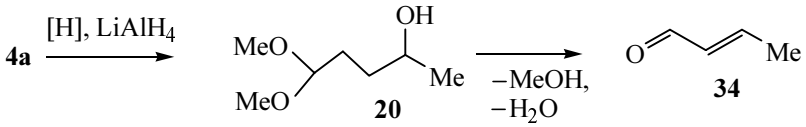


Scheme 12.

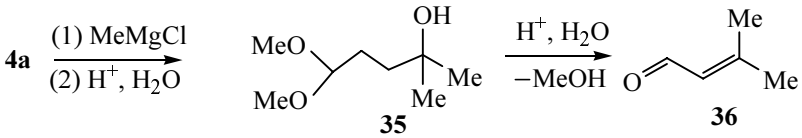


R = Me, Et.

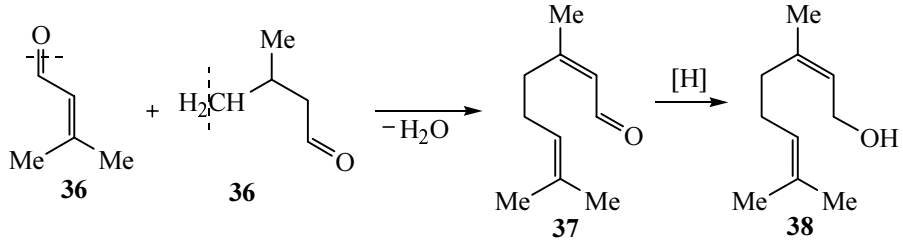
Scheme 13.



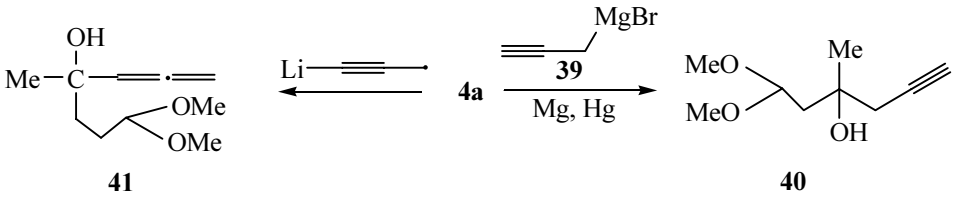
Scheme 14.



Scheme 15.



Scheme 16.

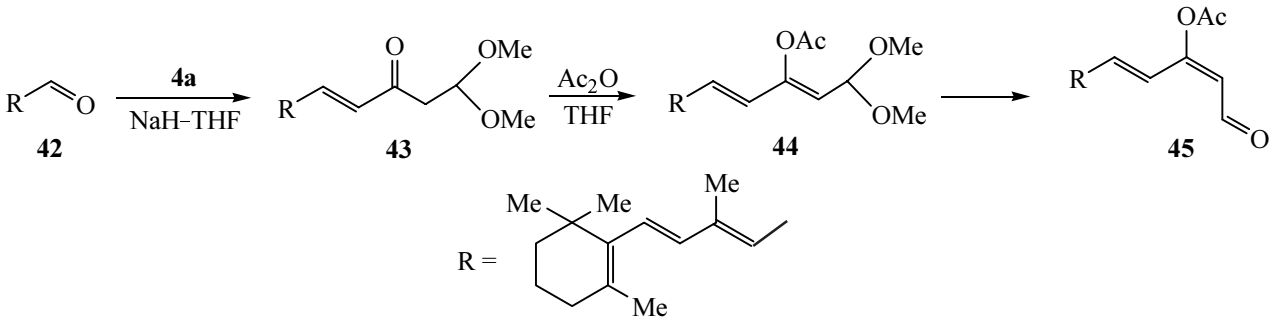


Organomagnesium compounds readily react with acetals **4** normally at the carbonyl group. For example, 3-methyl-2-butenal (**36**) was synthesized from **4** through alcohol **35** [6] (Scheme 14). Crotonization of aldehyde **36**, which accompanies the synthesis of alcohol **35**, leads to formation of 2,7-dimethyl-2,6-octadienal (**37**, dihydrocytral), and reduction of the latter gives 2,7-dimethyl-2,6-octadien-1-ol (**38**, geraniol) [6, 23] (Scheme 15). Berger *et al*. [44] described the synthesis of stable "push–pull" acetylenes from alkoxy ketones **3** (R = Me, Et) via bromination–dehydrobromination, followed by ready solid-phase rearrangement.

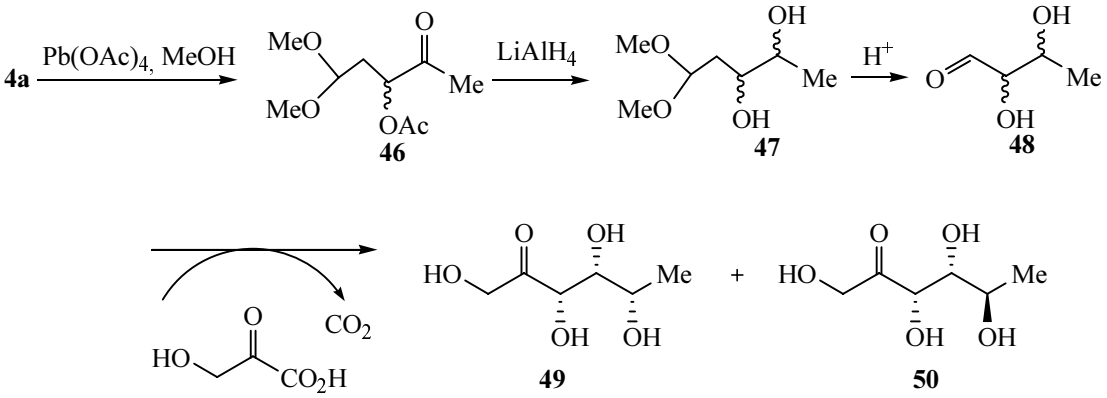
Another approach to intermediate products in the synthesis of carotinoids is also possible. The reaction of dimethoxybutanone **4a** with 2-propynyl bromide (**39**) in the presence of magnesium activated by mercury gives rise to structural fragments intrinsic to geraniol and phytol **40** [6, 17] (Scheme 16). Phytol (3,7,11,15-tetramethyl-2-hexadecen-1-ol) and isophytol (7,11-dimethyl-1,1-dimethoxy-4,6,10-dodecatrien-3-one) are intermediate products in the synthesis of vitamins E and K_1 [23, 45]. Regioselective allenylation of dialkoxybutanone **4a** was effected using 1-propynyllithium; hydroxyallene **41** was thus obtained [46]. Kii and Maruoka [47] used bidentate Ti(IV) complexes with dialkoxybutanones **4**, which coordinated the carbonyl group in the allylation.

A general method for the preparation of unsaturated ketones may be based on the reduction of methoxy-

Scheme 17.

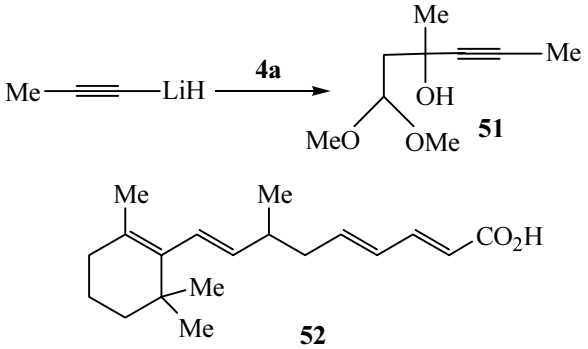


Scheme 18.



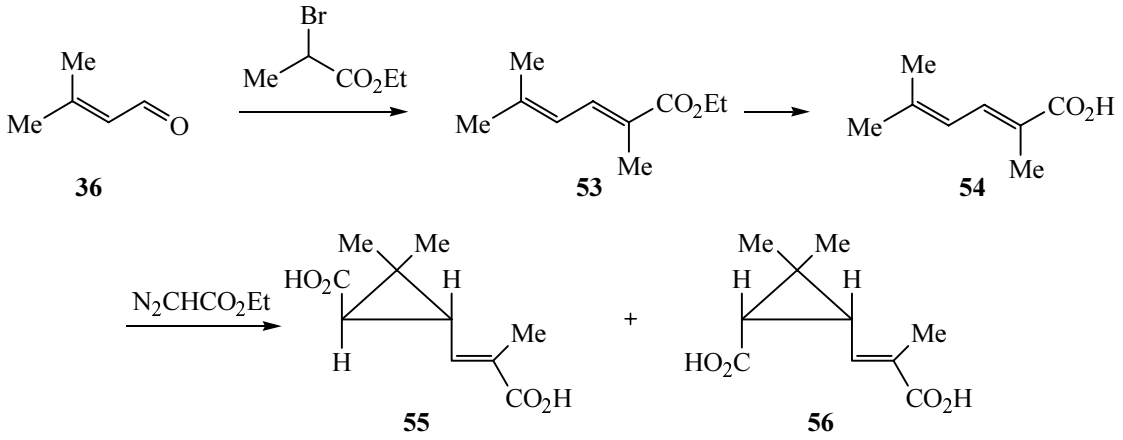
butenone **3a** with triethylaluminum. In this way, 3-hexen-2-one was obtained [17, 23]. The condensation of aldehyde **42** with acetal **4a** in THF leads to formation of (4*E*,6*E*,8*E*)-1,1-dimethoxy-7-methyl-9-(2,6,6-trimethyl-1-cyclohexenyl)nona-4,6,8-trien-3-one (**43**). Successive treatment of **43** with sodium hydride in THF and with acetic anhydride gives enol acetate **44**, and acid hydrolysis of the latter in acetone under Bio–Rad irradiation yields 13-acetoxy-13-demethylretinal **45** [48] (Scheme 17). D,L-2-Deoxyrybose was synthesized from 1-alkoxy-1-buten-3-ynes (**2**) [23, 49]. Enzymatic syntheses of L-6-deoxysorbose (**49**) and D-6-deoxy-fructose (**50**) in the presence of *trans*-ketolase were described in [50, 51]. 3-Acetoxy-4,4-dimethoxybutan-2-one (**46**) was obtained as a mixture of two racemates from acetal **4a**. The mixture was separated by chromatography and reduced to 2,3-dihydroxy-1,1-dimethoxybutane (**47**). Hydrolysis of the latter gave 2,3-dihydroxybutanal (**48**). Selective reactions of the (*R*,*R*) and (*R*,*S*) isomers afforded deoxyhexoses **49** and **50** (Scheme 18). The synthesis of intermediate products for the preparation of carotinoids on the basis of dialkoxybutanones **4** was covered by patents [52, 53].

Scheme 19.

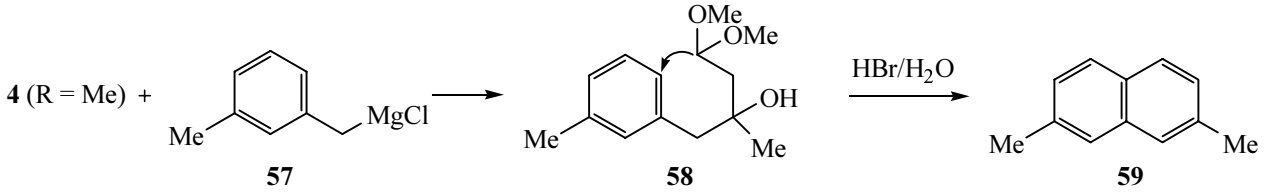


Reactions of acetals **4** with unsaturated organomagnesium compounds underlie procedures for the preparation of polyunsaturated compounds which are used in the synthesis of vitamin A [6, 15, 54]. A new synthetic approach to 3-hydroxy-1,1-dimethoxy-3-methyl-4-hexyne (**51**) with the use of 2-propynyllithium was proposed by Arens [54] (Scheme 19); here, methylacetylene–allene mixture can also be used. Polyunsaturated intermediate products for the synthesis of vitamin A can also be obtained from acetals **4**, β-ionone and 2-propynyl bromide [3, 6, 15, 23]. The preparation of newest intermediates like **52** for retinoid syntheses on the basis of dialkoxy-

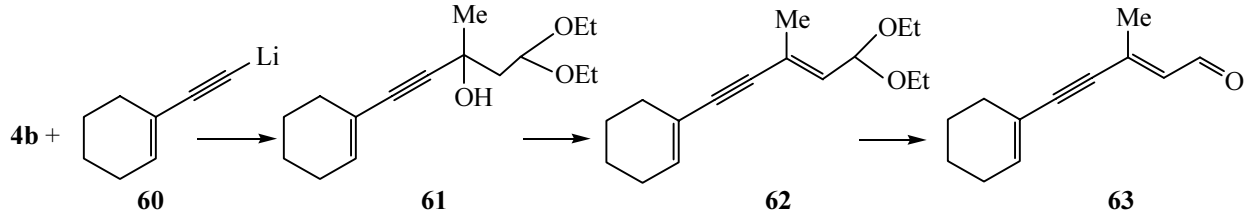
Scheme 20.



Scheme 21.



Scheme 22.



butanones **4** was patented [55]. Complexes of polyethylene imines with retinol acids, their synthesis from dialkoxybutanones, structure, and scope of application were described [56]. General synthetic approaches to a number of natural compounds were developed on the basis of dialkoxybutanones **4** [57].

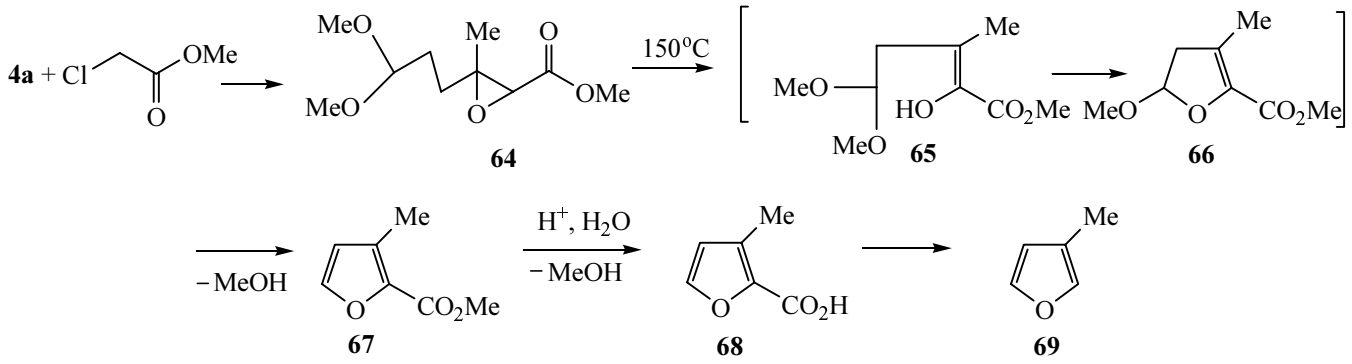
3-Methyl-2-butenal (**36**) obtained from acetal **4** reacts with ethyl 2-bromopropionate to give ethyl 2,5-dimethyl-2,4-hexadienoate (**53**). Hydrolysis of **53** to acid **54**, followed by treatment with ethyl diazoacetate, leads to a mixture of (α)-*trans*(*cis*)-3-(2-carboxy-1-propenyl)-2,2-dimethylcyclopropane-1-carboxylic acids **55** and **56** which are used in the synthesis of complex natural acids of the cyclopropane series [15, 58] (Scheme 20).

Ito *et al*. [59] patented a procedure for the preparation of 3-oxo-α-ionone derivatives starting from dialkoxybutanones **4** through intermediate *endo*-7-*exo*-8-bicyclooctenes. Schulz *et al*. [60] described the synthesis of a synthetic analog of natural monoterpene on the basis of acetal **4a**. The reaction of **4a** with Grignard compound **57** gave 3-hydroxy-3-methyl-4-(3-methylphenyl)butanal dimethyl acetal (**58**) whose cyclization by the action of HBr/H_2O afforded 2,7-dimethylnaphthalene **59** [6, 15, 17, 23] (Scheme 21).

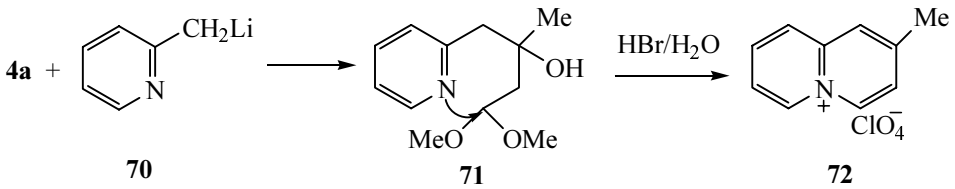
Syntheses of acetylenes from acetals **4** were also accomplished in the alicyclic series. Condensation of lithium 1-cyclohexenylacetylenide **60** at the carbonyl group of acetal **4b** leads to 5-(1-cyclohexenyl)-1,1-diethoxy-3-methyl-2-penten-4-yne (**61**); dehydration of **61** gives acetal **62** whose hydrolysis results in formation of aldehyde **63** [17, 61] (Scheme 22).

Darzens reaction of halogenated carboxylic acid esters with acetal **4a** occurs at the carbonyl group of the latter to give ester **64** which undergoes intramolecular cyclization to furan derivative **66** through intermediate **65**; the subsequent hydrolysis of ester **67** and decarb-

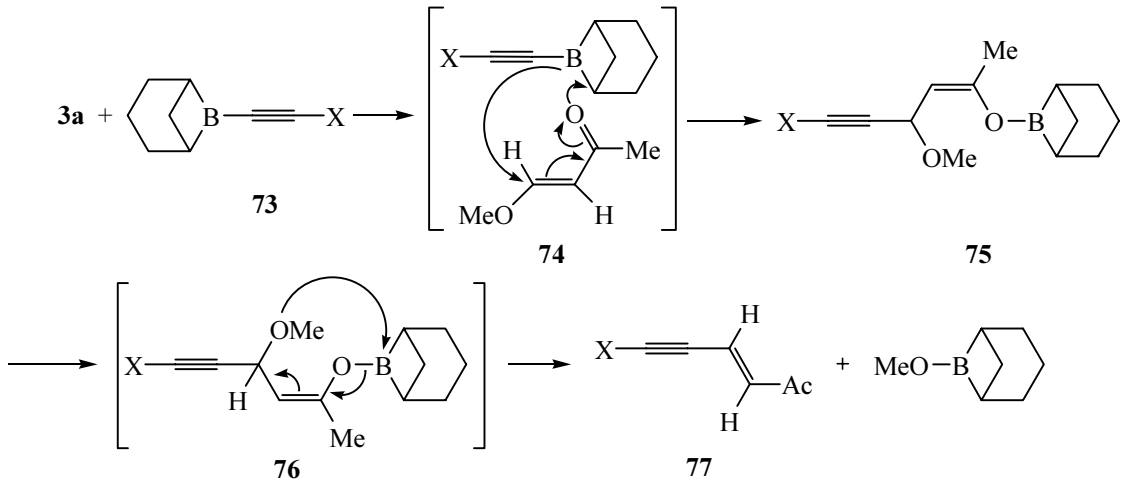
Scheme 23.



Scheme 24.



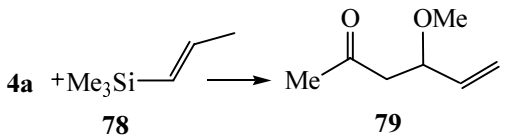
Scheme 25.



X = Et, Bu.

oxylation of acid **68** yield 3-methylfuran (**69**) [6, 15, 23] (Scheme 23). Acetal **4a** reacts with 2-pyridylmethyllithium (**70**) to give alcohol **71** whose cyclization leads to 3-methylquinolizinium salt **72** [6, 17].

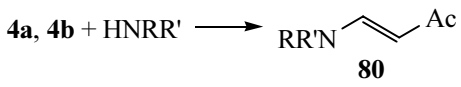
Scheme 26.



5. REACTIONS AT THE ACETAL GROUP

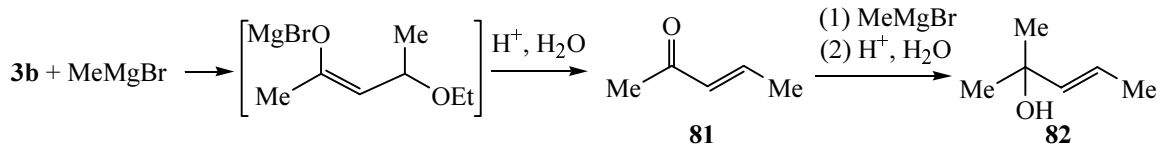
Compounds **4** are involved in reactions typical of acetals. For example, their hydrolysis gives acetoacetaldehyde which undergoes trimerization to triacetylbenzene [14, 15]. The reactions of 7-(1-alkynyl)-6-borabi-

Scheme 27.

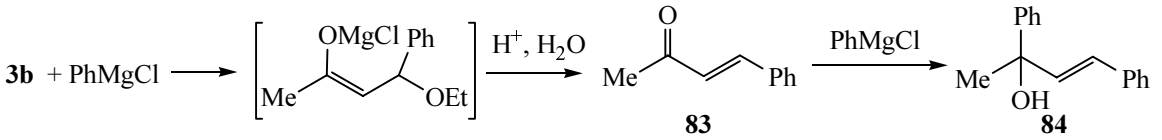


R, R' = Alk.

Scheme 28.



Scheme 29.



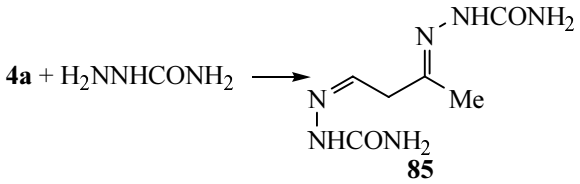
cyclo[3.1.1]heptanes **73** with methoxybutenones **3** (R = Me, Et) lead to formation of (*E*)-3-alken-5-yn-2-ones **77** through intermediates **75** and **76** [17] (Scheme 25). Chemoselective replacement of the methoxy group in **4a** by vinyl was effected by the action of trimethylvinylsilane (**78**) to obtain 4-methoxy-5-hexen-2-one (**79**) [17] (Scheme 26).

In the presence of alkaline catalysts, acetals **4** lose alcohol molecule to give β-alkoxyvinyl ketones **3** (R = Me, Et) [6, 14, 22]. The reaction occurs quantitatively in the presence of iron (4 h, 150°C) or at 300°C in the presence of 20% BaO + 80% SiO_2 [22]. Acetals **4** (R = Me, Et) readily react with primary and secondary amines to afford 4-dialkylamino-3-buten-2-ones **80** [16, 22, 23, 62– 64] (Scheme 27). The alkoxy group in alkoxy ketones is readily replaced by amino or sulfanyl group [16, 17]. The kinetics of nucleophilic substitution of the methoxy group in **3a** by diethylamino group were studied in [22, 65–67]. Bleaching of a support by treatment with dialkoxybutanones **4** (R = Me, Et) in the presence of quaternary ammonium salts was covered by patent [68]. Gerus *et al*. [69] and Campos *et al*. [70] described halogenation of dialkoxybutanones **4** (R = Me, Et) as a synthetic route to polyhalogenated α-chloro-β-alkoxyvinyl ketones. Dialkoxybutanone **4a** was used to obtain methyl β-(1-benzotriazolyl)vinyl ketone in which the benzotriazolyl group is readily replaced by morpholine, 2-nitropropane, and phenylbutyronitrile [71].

6. REACTIONS INVOLVING BOTH CARBONYL AND ACETAL MOIETIES

Ethoxybutenone **3b** reacts with methylmagnesium bromide at positions *1*, *4* of the conjugated system, yielding

Scheme 30.

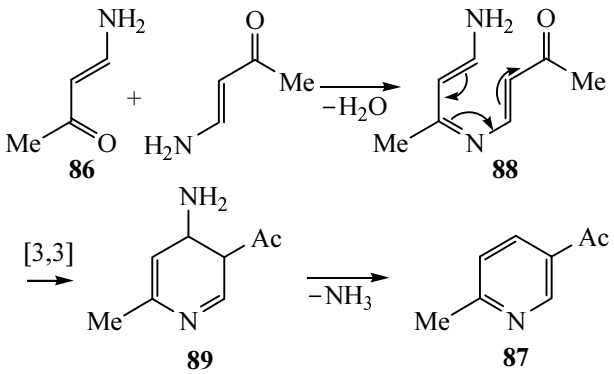


3-penten-2-one (**81**) [23] which takes up the second reagent molecule to form 2-methyl-3-penten-2-ol (**82**) [6, 15] (Scheme 28). Phenylmagnesium bromide also adds to compound **3b** at positions *1*, *4*; benzylideneacetone (**83**) thus formed reacts with the second phenylmagnesium bromide molecule to give 2,4-diphenyl-3-buten-2-ol (**84**) [6, 17] (Scheme 29). The reaction of acetal **4a** with semicarbazide involves both functional groups and leads to formation of bis-semicarbazide **85** [15, 17] (Scheme 30).

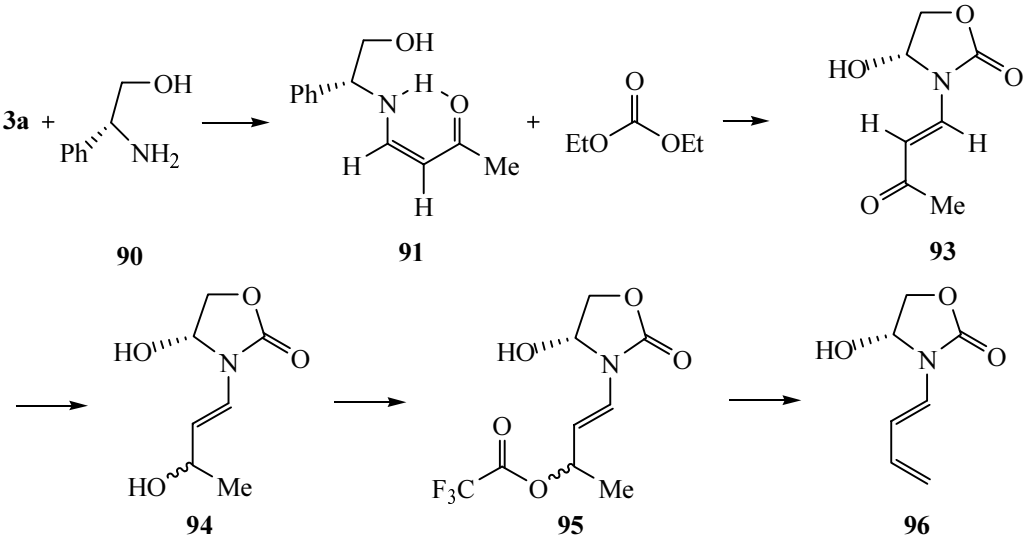
7. CYCLIZATIONS

7.1. Reactions with ammonia and amines. Dialkoxybutanones **4a** and **4b**, as well as (*E*)-4-ethoxy-3-

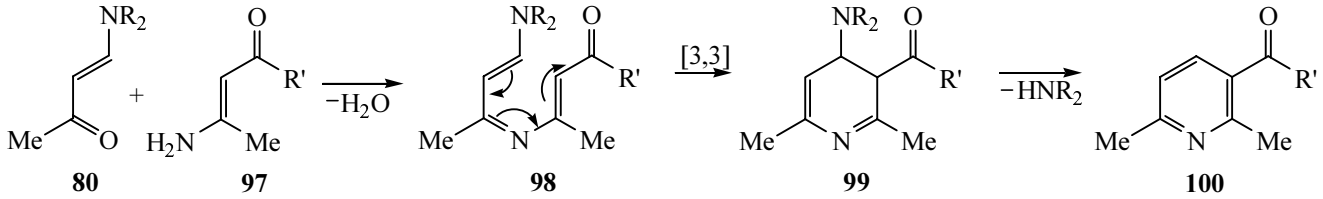
Scheme 31.



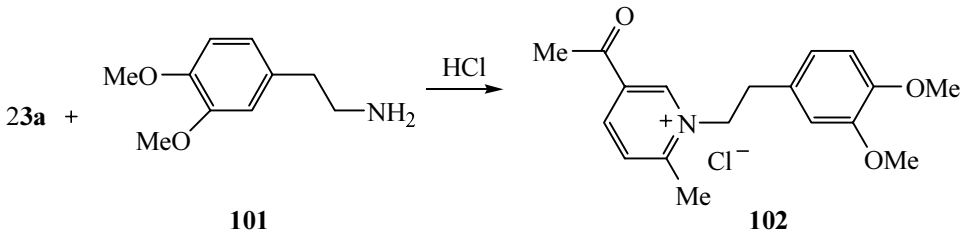
Scheme 32.



Scheme 33.



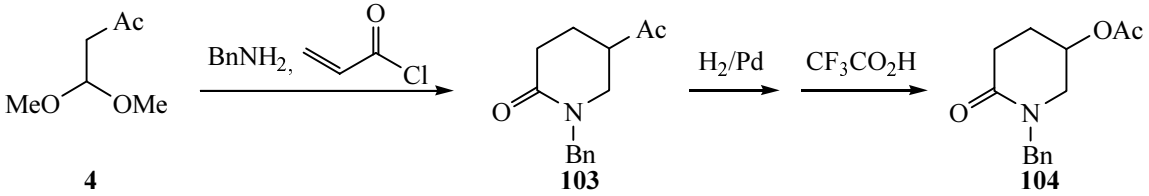
Scheme 34.



buten-2-one (**3b**), react with gaseous ammonia (–30°C, EtOH or without a solvent) to afford 4-amino-3-buten-2-one (**86**) [16, 17, 22, 63, 64]. Presumably, aminobutenone **86** undergoes intermolecular self-condensation involving the carbonyl group in one molecule and the amino group in the other. [3,3]-Sigmatropic rearrangement in condensation product **88** gives dihydropyridine **89** which loses ammonia molecule, thus being converted into a mixture of 5-acetyl-2-methylpyridine (**87**) and 3-acetyl-4-methylpyridine [22] (Scheme 31). Pyridine **87** was also obtained by heating of aminobutenone **86** [17, 22, 63, 64]. 5-Acetyl-2-methylpyridine (**87**) is used in the synthesis of nicotinic acid via oxidation of the acetyl group with 20% nitric acid to 2-methylpyridine-5-carboxylic acid. Oxidation of the latter with ozone gives cinchomeronic acid (pyridine-2,5-dicarboxylic acid) [3, 6, 14, 23] which is converted into nicotinic acid by decarboxylation [6,14,72].

The reaction of (*R*)-(–)-2-amino-2-phenylethanol (**90**) with (*E*)-methoxybutenone **3a** gave (*Z*)-aminovinyl ketone **91** which was identified by ^{1}H NMR spectroscopy. Ketone **91** reacted with diethyl carbonate (**92**) to form oxazolidinone **93** which was reduced with sodium tetrahydridoborate to obtain a mixture of stereoisomeric alcohols **94** [73]. The latter were converted into the corresponding trifluoroacetates **95**, and the subsequent elimination of trifluoroacetic acid by the action of triethylamine in acetonitrile afforded diene **96** [73] (Scheme 32). The above synthesis of 4-substituted oxazolidin-2-ones has no analogies in the literature.

Scheme 35.



4 **103** **104**

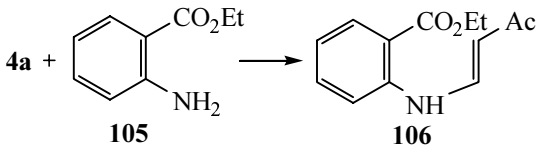
Reactions of 4-dialkylamino-3-buten-2-ones **80** with aminovinyl ketones **97** are likely to involve formation of intermediate **98** and its [3,3]-sigmatropic rearrangement to dihydropyridines **99** [22]; as a result, only 3-acyl-2,6-dimethylpyridines **100** are formed (40–50°C, AcONa, AcOH, 5 h; Scheme 33). Analogous reactions of dialkoxybutanones **4a** and **4b** give rise to mixtures of 3-substituted 2,4- and 2,6-dimethylpyridines [15]. Methoxybutenone **3a** reacts with primary amine **101** to give pyridinium salt **102** (Scheme 34); the reaction requires two molecules of **3a** per amine molecule [22].

Cook *et al*. [74] synthesized pyridine alkaloid **104** by condensation of benzylamine with acetal **4a** and acryloyl chloride through intermediate piperidinone **103** (Scheme 35). Compound **104** acts as blocking agent toward α-L-mannosidase (diabetes, cancer, arthritis).

The reaction of acetal **4a** with ethyl 2-aminobenzoate (**105**) was reported to give ethyl 2-(3-oxo-1-butenylamino)benzoate **106** [22] (Scheme 36). Acetals **4** react with potassium 2-(2-aminophenyl)-2-oxoacetate (**107**) (0°C, 35% KOH, 10 min) to afford analogous product **108** which undergoes acid-catalyzed intramolecular dehydration with formation of 3-acetylquinoline-4-carboxylic acid (**109**) [17, 22] (Scheme 37). The latter exhibits antipyretic and analgetic properties.

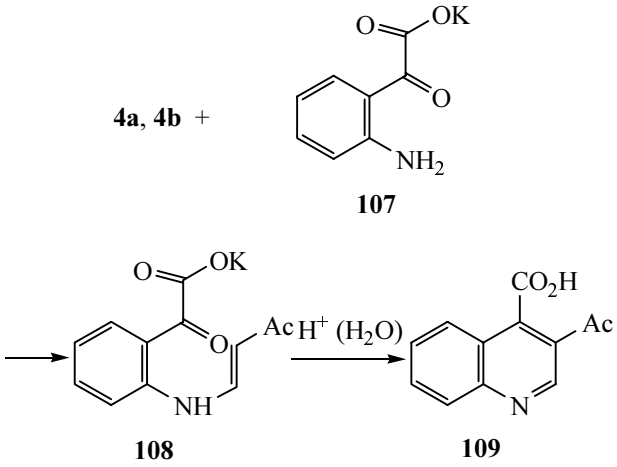
Analogous schemes are typical of reactions of acetal **4a** and methoxybutenone **3a** with primary aromatic amines and diamines of the aromatic and heterocyclic series. Functionalized amines, such as *m*-aminophenol, 3-amino-2-chlorophenol, and 3-amino-4-chlorophenol, react with acetal **4a** (concentrated sulfuric acid) to give functionalized derivatives of 4-methylquinoline [22]. *o*-Aminobenzaldehyde **110** reacts with acetal **4a** in methanolic potassium hydroxide to afford 2-methylquinoline-3-carbaldehyde dimethyl acetal (**111**) [17, 22] (Scheme 38). The reaction of [2-(3,4-dihydroxyphenyl)-ethyl]amine hydrobromide (**112**, Dopamine) with dimethoxybutanone **4a** leads to pyridinium salt **113**; its oxidation with potassium permanganate gives 2-pyridinone, while in aqueous medium quinolinium salt **114** is formed [17, 22, 75] (Scheme 39). Acetal **4a** reacts with

Scheme 36.



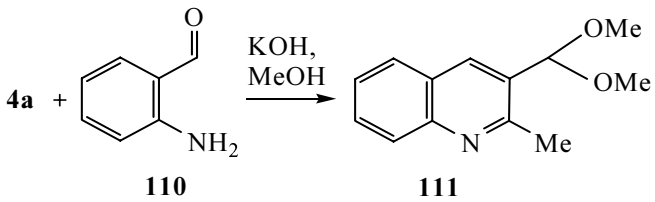
105 **106**

Scheme 37.



107 **108** **109**

Scheme 38.

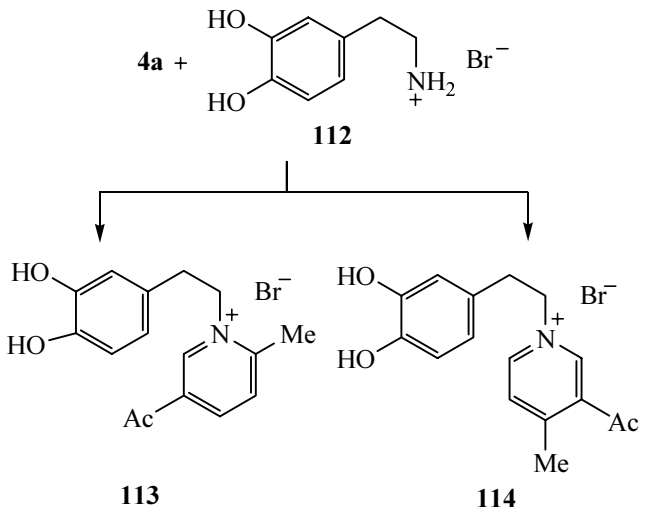


110 **111**

3-(2-aminoethyl)indole (**115**, tryptamine) both at the primary amino group and at the endocyclic NH moiety [17, 22, 75, 76–79]. Direct ketovinylation of the α-position in the indole ring of **115** can be effected with methoxybutenone **3a** or acetal **4** in alkaline medium. 3-Amino-2-2-chlorophenol and 3-amino-4-chlorophenol react with acetal **4a** to give 2-ketovinyl derivative **116** whose condensation with ethyl cyanoacetate (**118**) leads to formation of macrocyclic product **117** [80] (Scheme 40).

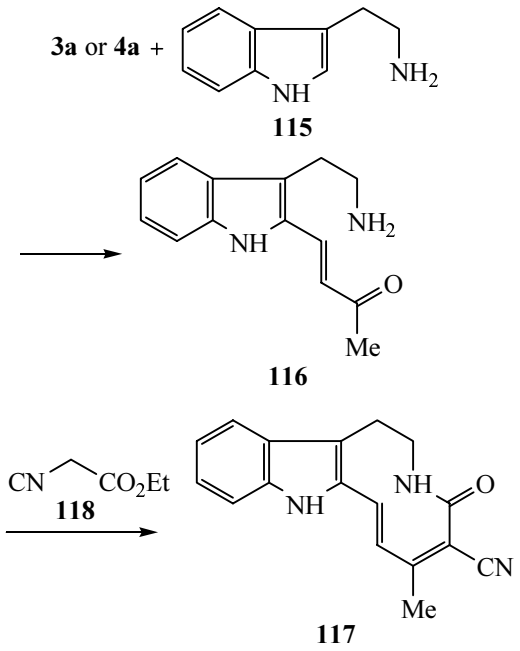
2-Methylindole (**119**) reacts with methoxybutenone **3a** or acetal **4a** at the β-position of the indole ring rather

Scheme 39.



112 **113** **114**

Scheme 40.



115 **116** **117**

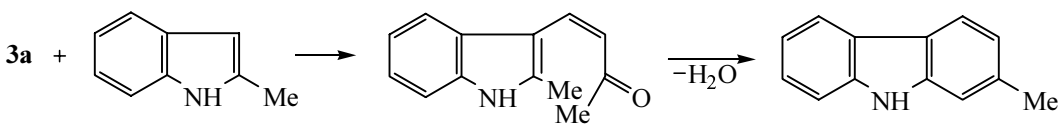
than at the NH group, and the product is 3-(3-oxo-1-butenyl)-2-methylindole (**120**) which undergoes intramolecular cyclization to 2-methylcarbazole (**121**) [22] (Scheme 41). The condensation of **4a** with 3-aminopyrazole (**122**) follows pathway *a* which includes formation of intermediate **123** and closure of pyrimidine ring to afford 5-methylpyrazolo[1,5-*a*]pyrimidine (**124**). According to alternative pathway *b*, the primary reaction involves the acetal moiety of substrate **4a** with formation of condensation product **125** whose cyclization yields 7-methylpyrazolo[1,5-*a*]pyrimidine (**126**) [17, 81, 82] (Scheme 42).

Bamaung *et al*. [83] described a synthesis of azole Cytokine (Interleukine) inhibitors from 1,2,4-triazole and acetal **4a**. The latter was also used to obtain triazole derivatives which exhibit anticonvulsant properties and block sodium channels [84, 85]. Biological properties of a new class of potential selective peripheral benzodiazepine receptors (prepared on the basis of acetal **4a**), *N*,*N*-diethyl(2-arylpyrazolo[1,5-*a*]pyrimidin-3-yl)acetamides, were described [86]. Bunnage *et al*. [87] patented a synthesis of pyrazolopyrimidine derivatives which inhibit physiological disfunctions [87] and exhibit antihypertensive activity [88]. Acetal **4a** was used in the synthesis of new unsaturated amino acids containing a pyrazolo[1,5-*a*]pyrimidine fragment [89]. Acetal **4a** reacts with 2-aminoimidazole (**127**) to give 7-methylimidazo[1,5-*a*]pyrimidine (**128**) as the major product [17, 90] (Scheme 43). Imidazolopyrimidine derivatives obtained from acetal **4a** are used as ligands for GABA receptors in pharmaceutical compositions [91–93]. Kleschick *et al*. [94] synthesized a series of new 2,5-difluoro(trifluoromethyl)- and 6-substituted anilines like **129**, which contain an imidazo[1,5-*a*]pyrimidine fragment and are potential herbicides.

The condensation of acetal **4a** with 3-amino-1,2,4-triazole (**130**) follows both pathway *a* (see Scheme 42; 45%) to give 5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (**131**) and *b* (15%), the latter leading to 7-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (**132**) and a small amount of triacetylbenzene (**133**) (Scheme 44). The formation of compound **133** indicates that some amount of acetoacetaldehyde is present in the reaction mixture [22, 84].

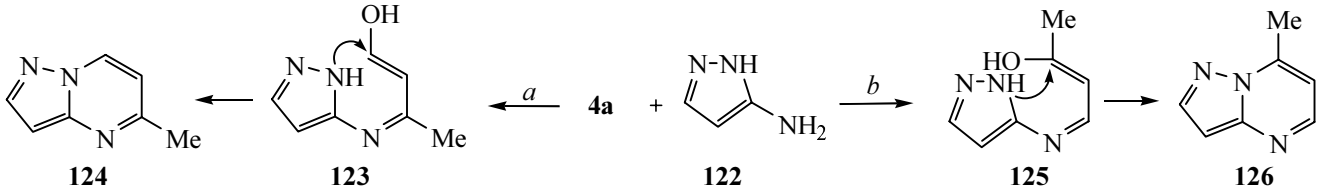
In the condensation of acetal **4a** with 4-amino-1,2,4-triazole (**134**), the contributions of pathways *a* and *b* are 58% and 20%, respectively, and the corresponding

Scheme 41.

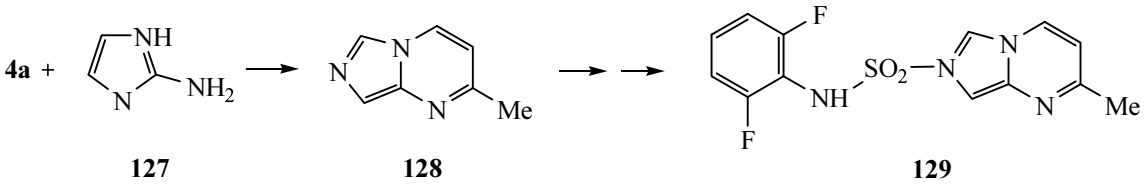


119 **120** **121**

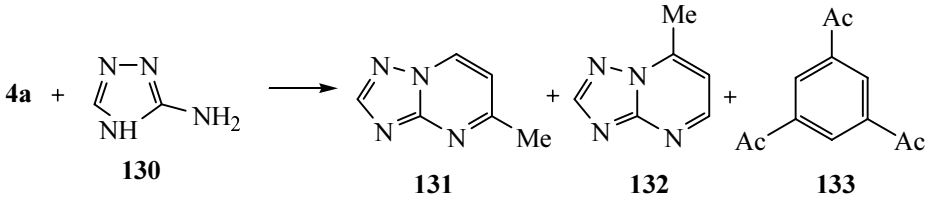
Scheme 42.



Scheme 43.



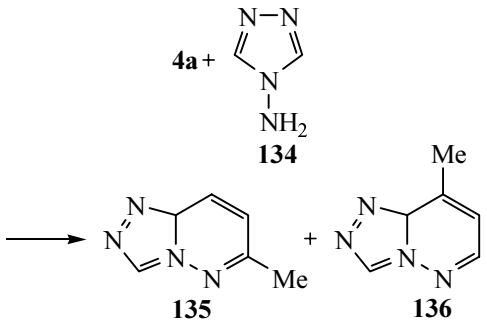
Scheme 44.



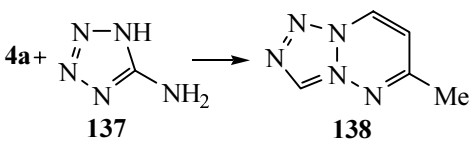
products are 6-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine (**135**) and 8-methyl[1,2,4]triazolo[4,3-*b*]pyridazine (**136**) [22, 84, 95] (Scheme 45). Acetal **4a** reacts with 5-aminotetrazole (**137**) exclusively at the acetal moiety to form 7-methyltetrazolo[1,5-*a*]pyrimidine (**138**) [22, 84, 85] (Scheme 46). The reaction of 2-amino-5-methylpyridine (**139**) with acetal **4a** in acid medium gives 2,6-dimethylpyrido[1,2-*a*]pyrimidin-5-ium perchlorate (**140**), while 2,5-diaminopyridine (**141**) reacts with **4a** in neutral and alkaline media first at the ketone group with formation of 7-amino-2-methyl-1,8-naphthyridine (**142**) [17] (Scheme 47). The latter pathway is also typical of reactions of acetal **4a** with 2-aminobenzimidazole (**143**) and 2-amino-1-phenylpyrazole-4-carbonitrile (**145**): the products are, respectively, 2-methylpyrido[1,2-*a*]benzimid-azole (**144**) and 6-methyl-1-phenylpyrrolo[2,3-*b*]pyridine-3-carbonitrile (**146**) which are potential antimalarial agents [17, 22] (Scheme 48).

5-Methyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione (**147**) was synthesized by reaction of acetal **4a** with 6-amino-1,2,3,4-tetrahydropyrimidine-2,4-dione

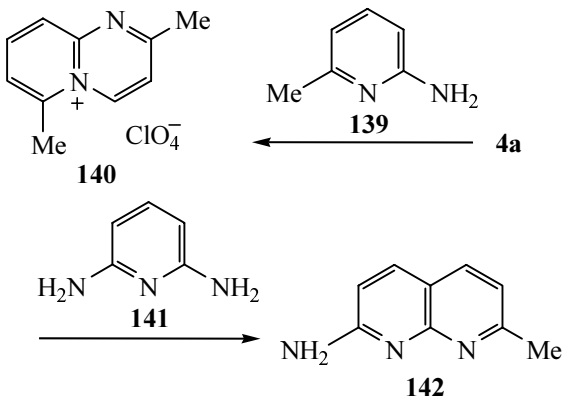
Scheme 45.



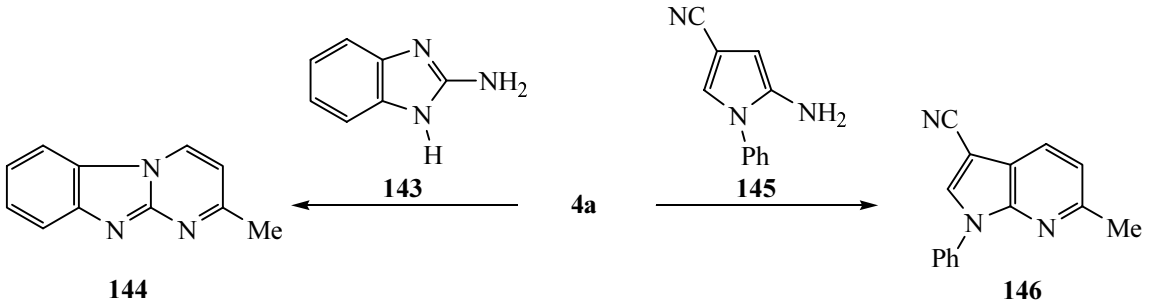
Scheme 46.



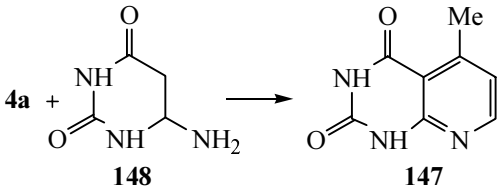
Scheme 47.



Scheme 48.



Scheme 49.

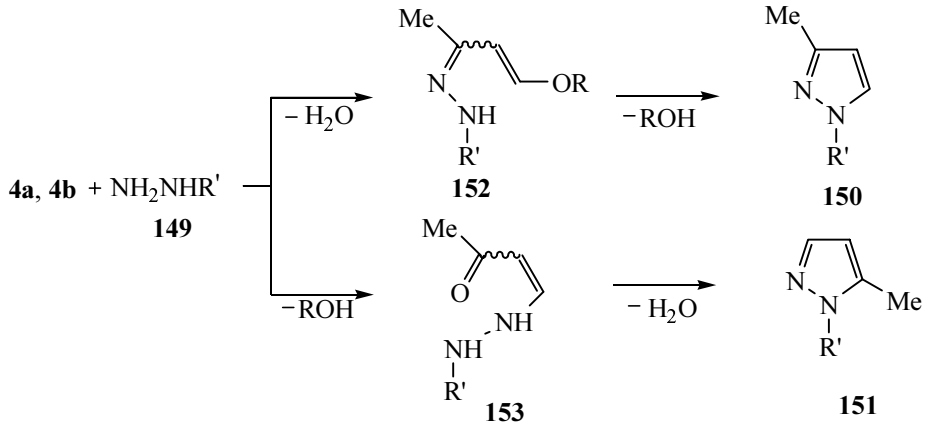


(1**48**), which involved the acetal moiety in the former and the primary amino group in the latter (Scheme 49); compound **147** has found application in pharmaceutics and agrochemistry [22, 96–98].

7.2. Reactions with hydrazines and hydroxylamine. Compounds **4a** and **4b** react with monosubstituted hydrazines (95°C, H^+, MeOH/H_2O, 2–10 h) to give mixtures of pyrazoles **150** and **151** [23] (Scheme 50), their ratio depending on the acidity of the medium. In acid medium, isomers **152** are formed as the major products [17, 22]. Reactions of aminobutenones **80** with hydrazine give only 5-methylpyrazoles [14, 21]. Presumably, enehydrazones **152** and **153** are formed as intermediates. The reaction of acetal **4a** with 2-(4-methoxyphenyl)ethylhydrazine (**154**) was reported to afford a mixture of isomeric 1-[2-(4-methoxyphenyl)ethyl]-3-methylpyrazole (**155**) and 1-[2-(4-methoxyphenyl)ethyl]-5-methylpyrazole (**156**) which act as thrombosis inhibitors [99] (Scheme 51).

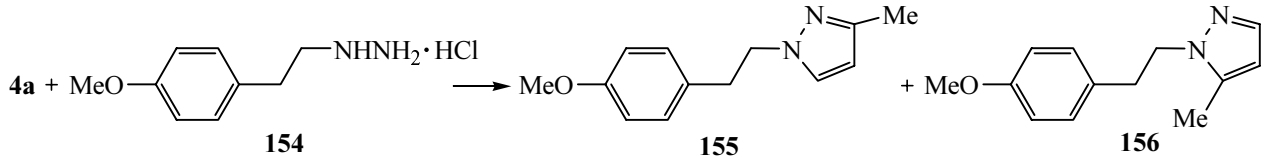
A synthesis of pyrazolopyrimidines from methoxybutenone **3a** was described in patents [100, 101]; syntheses of these monomers and their homo- and heteropolymerizations were also developed. Biological additives to polymeric materials were synthesized on the basis of pyrazoles derived from diacetylene (**1**) [14]. *C*-Vinylpyrazoles were obtained from pyrazoles **150** which were prepared from commercial diacetylene (**1**) [14, 102]. The

Scheme 50.

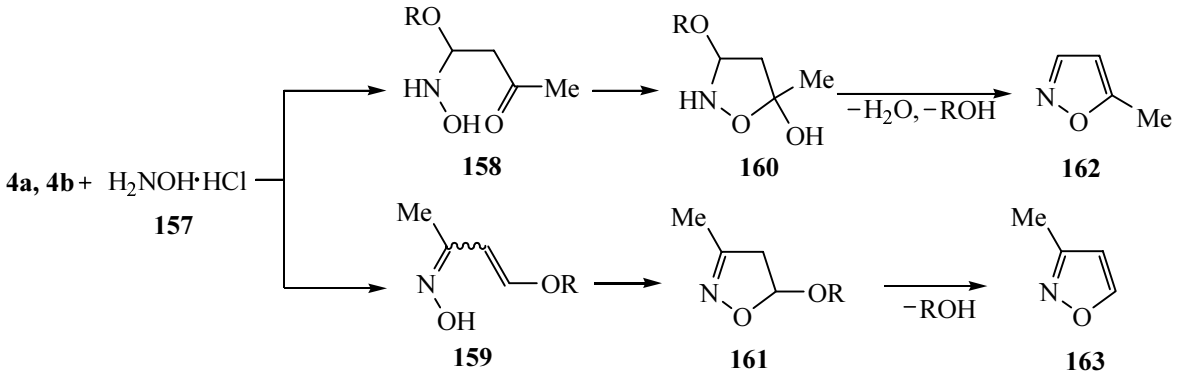


R' = H, Me, Ph.

Scheme 51.



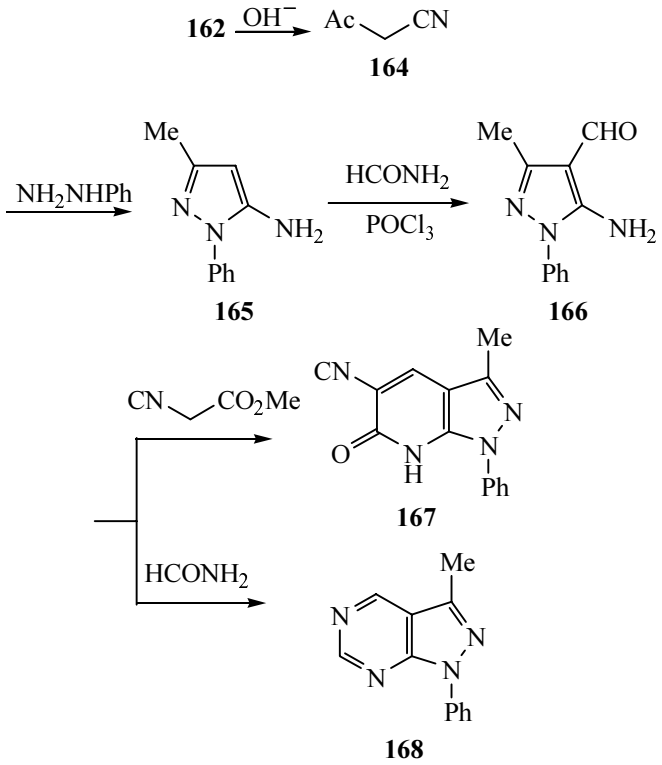
Scheme 52.



use of vinyl derivatives of some azoles, including pyrazole, in various fields of technics, manufacture of plastics and fibers, radio engineering, and medicine was also noted [14]. New herbicides [14, 103–105], pesticides [106, 107], antidiabetic agents [108], immune adjuvants [109], and perfume compositions [110] were developed on the basis of pyrazoles **150** and **151**. Preparation of polychelates of the pyrazole series for curing of epoxy resins was described [14]. The possibility for extraction of noble metals (Pd, Au, Ag) with the aid of pyrazoles **150** and **151** hydrochlorides was demonstrated [111, 112]. Pyrazole derivatives were also used to prepare complexing ion exchangers [113], absorbing agents for concentration of platinum metals [114], and catalysts for nitration [115] and disproportionation in the synthesis of monoalkyl- and monoarylhalosilanes [116]. 1-Guanyl-3-methylpyrazole was synthesized from pyrazole **150** [14]. Derivatives of pyrazole-1-carboxylic acid exhibit pesticide and insecticide properties [14].

Acetals **4a** and **4b** react with hydroxylamine hydrochloride (**157**), presumably through intermediates **158**–**161**, yielding a mixture of 5-methylisoxazole (**162**) and 3-methylisoxazole (**163**) [14, 22, 117] (Scheme 52). The reactions of acetonitrile with ketone (*E*)-**3a** and 3-buten-2-one regioselectively give 5-acetyl-3-methyl- and 3-acetyl-4-methylisoxazoles, respectively [118]. Alkaline cleavage of 5-methylisoxazole (**162**) gives cyanoacetone (**164**) [6, 14, 119] which reacts with phenylhydrazine to form 5-amino-3-methyl-1-phenylpyrazole (**165**) [6, 14, 22, 119, 120]. Formylation of the latter according to Vilsmeier–Haak leads to 5-amino-3-methyl-1-phenylpyrazole-4-carbaldehyde (**166**) [6, 121] which is used to build up fused pyrazolopyridine and pyrazolopyrimidine systems **167** and **168** [6, 14, 122] (Scheme 53). Aminopyrazole **166** is an important product in the synthesis of pharmacologically active compounds (antidepressants,

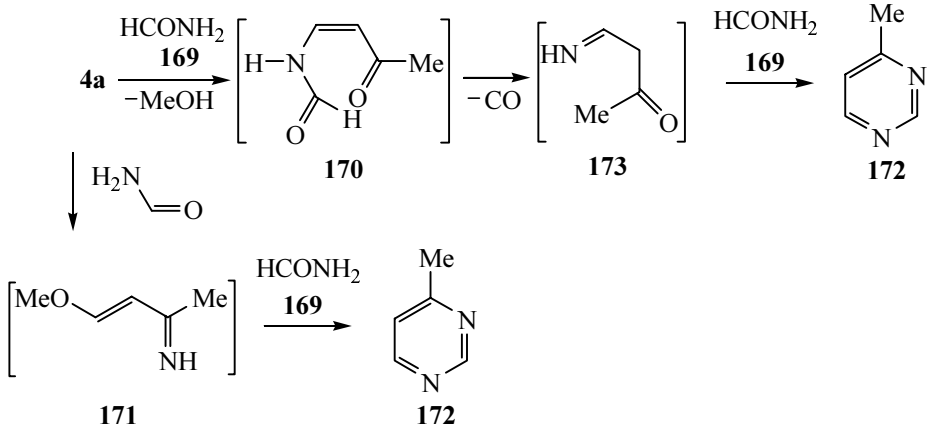
Scheme 53.



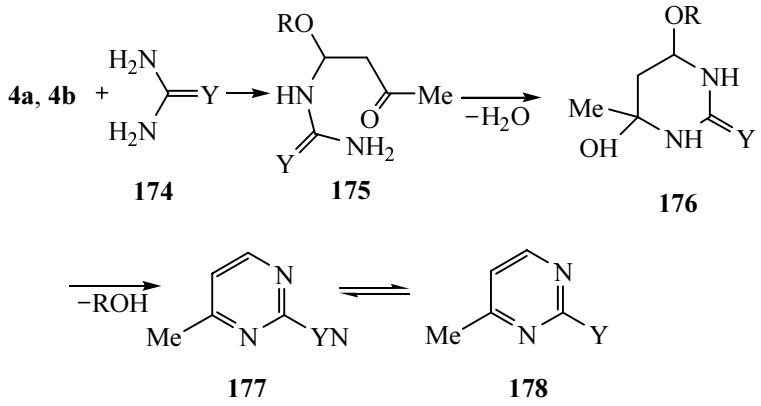
anticonvulsants, analgetics) [121], biologically active reagents [122], and diazo dyes for color printing on paper [123].

7.3. Reactions with carboxylic acid amides and nitriles. Acetal **4a** reacts with formamide (**169**) (180°C, H_2O, 7 h). The process is accompanied by transamination of formamide. The cyclization scheme proposed in [22] includes nucleophilic replacement of the alkoxy group by amino with formation of formamide **170** or imine **171**; as a result, 4-methylpyrimidines **172** are formed [14, 15, 23] (Scheme 54). According to [22], the proposed scheme is supported by the isolation of formamide transamination

Scheme 54.



Scheme 55.



R = Me, Et; Y = N, O, S.

products, dialkylformamides (in reactions with 1-dialkylamino-1-alken-3-ynes). Decarbonylation of **170** could give reactive imine **173** which undergoes cyclization via addition of the second formamide molecule at the C^3 atom (it is known that primary amines readily add to such systems in a similar way) [22]. Guethner and Graml [124] patented a procedure for the preparation of 4-methylpyrimidine (**172**) by reaction of acetal **4a** with formamidinium salts (e.g., formamidinium acetate) at a molar ratio of 0.5–2 in ether or alcohols at 110–150°C with removal of the solvent. Functionalization of pyrimidine **172** and application of the functionalized derivatives as antiviral agents were also patented [125–129].

Urea derivatives **174** react with dimethoxybutanone **4a** to afford pyrimidine derivatives [6, 17, 22, 130, 131] (Scheme 55). The reaction is believed to involve transamination to intermediate **175** and subsequent intramolecular condensation with participation of the primary amino group and carbonyl group (intermediate **176**) [22]; as a result, pyrimidines **177** and **178** are formed.

The condensation of 4-diethylamino-3-buten-2-one (**80**) with *S*-alkylisothiuronium salts **179** was performed in the presence of a catalytic amount of a mineral acid (60–90°C, 1 h); the products were 2-alkylsulfanyl-4-methylpyrimidines **180** [132] (Scheme 56). A large number of pyrimidines **177** and **178** were obtained from dimethoxybutanone **4a** and alkoxybutenones **3a** and **3b** [6, 14, 22, 130, 131]. The syntheses were performed mostly in alkaline medium (100–200°C, Na, EtOH, 15 h). 2-Amino-4-methylpyrimidine was obtained from ethoxybutenone **3b** and guanidine, whereas from dimethoxybutanone **4a** the yield was 96% [16, 23]. 4-Methyl-2-phenylpyrimidine was synthesized from ketone **3b** and benzamidine [16]. Presumably, alkaline medium favors condensation of the carbonyl and amino groups in the reactants, though a path similar to reactions of enamino ketones cannot be ruled out [22].

Katoch *et al*. [133] reported on the reaction of *N*-benzyloxyurea with acetal **4a**, which afforded

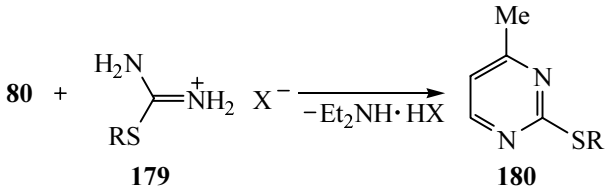
1-benzyloxy-4-methyl-1,2-dihydropyrimidine-2-one; hydrolysis of the latter in 30% hydrochloric acid gave 1-hydroxy-4-methyl-1,2-dihydropyrimidin-2-one [134]. The same authors synthesized amino acids **181** containing a pyrimidin-2(1*H*)-one fragment by chemical modification of α-glutamic acid **182** via condensation with acetal **4a** [135] (Scheme 57).

Amines of the pyrimidine series are widely used in pharmaceutical industry [14, 136]. For example, anilinopyrimidines were identified as potential corticotropine antagonists [137]. A series of coagulants (protease inhibitors) based on 4-methyl-2-aminopyrimidine was patented [138]; *N*-(2-pyrimidinyl)phosphoric triamide is used as a reagent for control of urea hydrolysis [139]; a series of pharmaceutical agents [140–142], including those inhibiting thrombosis, was patented [143–145]; (1-adamantylamino)pyrimidines were patented as α-TNF-stimulators [146].

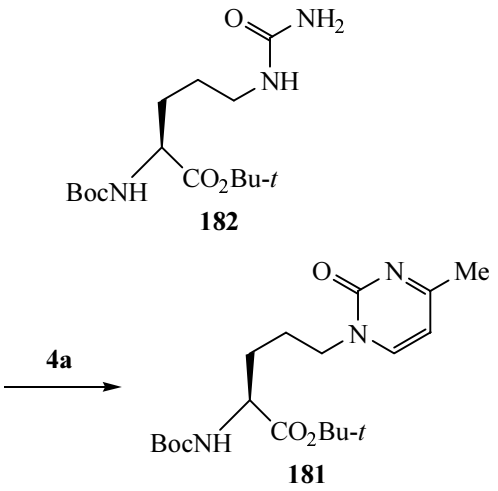
Intermediate products for the synthesis of sulfonamide drugs, e.g., 2-(4-aminophenylsulfonylamino)-4-methylpyrimidine (sulfamerazine), can be obtained in high yield from acetals **4a** and **4b** and 4-aminophenylsulfonylguanidine [14, 15]. Pyrimidine derivatives obtained from acetal **4a** were patented as antitumor agents [147].

Protein tyrosine kinase inhibitors [148], vitronectin receptor antagonists [149], effective psychotropic agents [150], new fungicides [151], and perfume [152, 153] and cosmetic compositions [154, 155] were developed on the basis of pyrimidine derivatives **177** and **178**. The reaction of pyridine-2-carboximidamide (**183**) with acetal **4a** through intermediate **184** gave 4-methyl-2-(2-pyridyl)-pyrimidine (**185**) as potential chelating ligand capable of forming complexes with iron [22, 156] (Scheme 58).

Scheme 56.

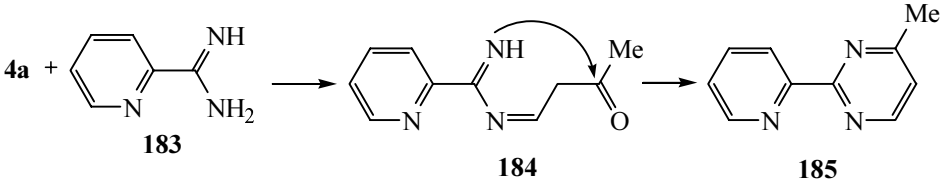


Scheme 57.

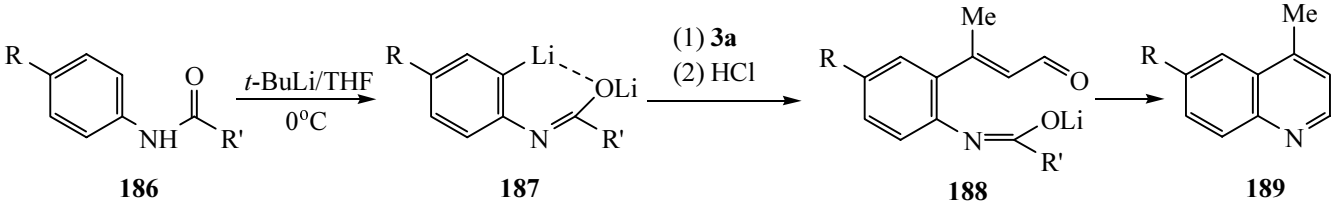


Polycyclic guanidines (1-iminohexahydropyrrolo-[1,2-*c*]pyrimidines) were synthesized by polycondensation of acetal **4a** with ionic species generated from α-phenylsulfanyl carboximidamides by the action of $Cu(OTf)_2$ [157]. 4-Methyl-1,2-dihydropyrimidine-2-thione and 4-methyl-1,2-dihydropyrimidin-2-one were used as a basis for development of new pharmaceuticals [158, 159], cytokine inhibitors [160–162], and corrosion inhibitors [163]. Cho *et al*. [164] synthesized 4-methylquinolines **189** by a modified Friedländer reaction of methoxy-

Scheme 58.

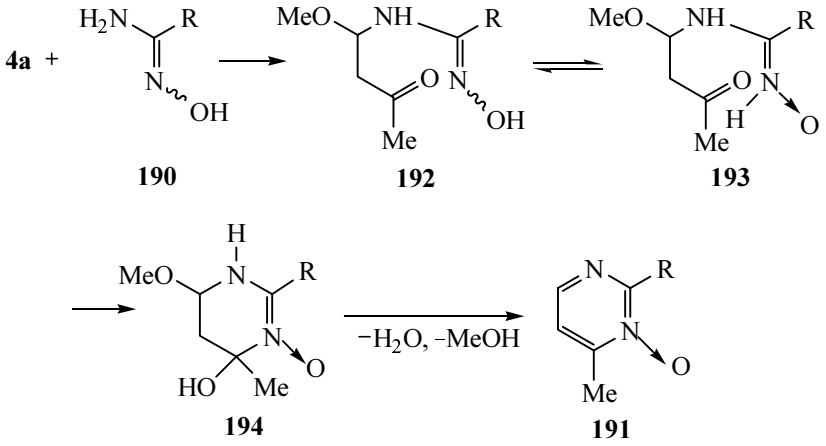


Scheme 59.



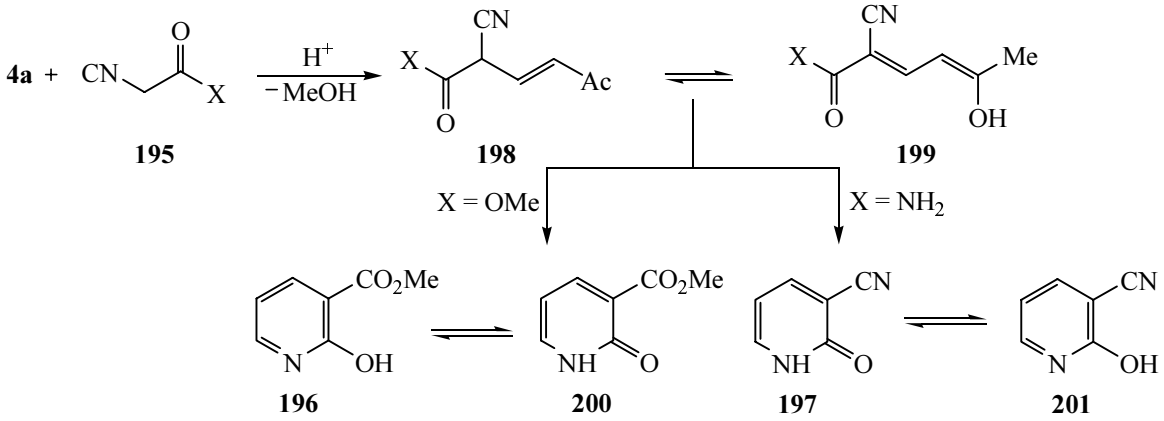
R = H, MeO, Ph, Cl, F; R' = OBu-*t*, *t*-Bu.

Scheme 60.



R = $ClCH_2$, 4-$F_3CC_6H_4$, 2-$MeOC_6H_4CH_2$.

Scheme 61.



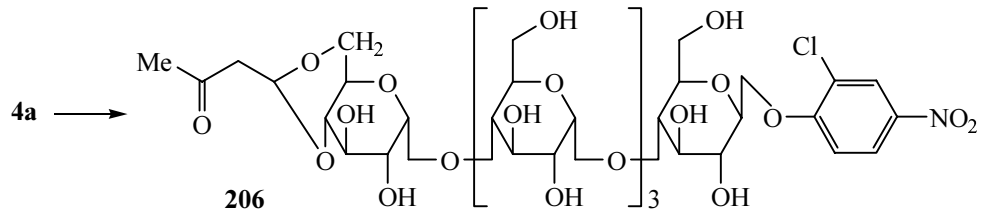
X = NH_2, OR'; R' = Me, Et.

butenone **3a** with *ortho*-lithiated *N*-(*tert*-butoxycarbonyl)-aniline derivatives **187** (–20°C, THF, pentane, 2 h) which were obtained from anilines **186** (Scheme 59). Misak *et al*. [165] patented pharmacological application of quinoline derivatives synthesized on the basis of acetal **4a**.

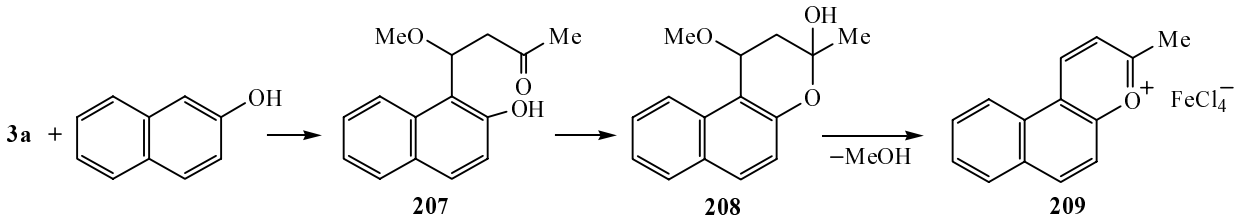
A procedure for the preparation of pyrimidine *N*-oxides from carboxamide oximes was reported in [166, 167]. Direct oxidation of pyrimidines is inconvenient for the synthesis of unsymmetrically substituted pyrimidines, for it leads to formation of a mixture of oxidation products (1- and 3-oxides). Acetal **4a** reacts with carboxamide oximes **190** (*i*-PrOH, CF_3CO_2H, 2–17 h) in a regioselective fashion, yielding pyrimidine *N*-oxides **191** via initial attack on the acetal fragment in **4a** by the amino group (intermediate **192**) rather than by the oxime moiety (Scheme 60). The subsequent intramolecular addition of the nitrone moiety at the carbonyl group in intermediate **193** (which is tautomeric to oxime **192**) and aromatization of tetrahydropyrimidine *N*-oxide **194** via elimination of water and methanol molecules results in formation of final pyrimidine *N*-oxide **191** [22, 166]. The reactions of acetal **4a** with cyanoacetic acid derivatives **195** (X = OR', NH_2) give pyridines **196** and **197**, respectively [6, 14, 15, 22, 23] (Scheme 61). It was presumed [22] that in the first stage intermediate **198** is formed as a result of replacement of the methoxy group in **4a** by the CH-acid fragment and elimination of methanol. Enol intermediate **199** undergoes cyclization along two pathways, depending on the X substituent. When X = OR', the attack is directed at the cyano group to give methyl 2-oxo-1,2-dihydropyridine-3-carboxylate (**200**) (or its lactim tautomer **196**). In the reaction with cyanoacetamide (**195**, X = NH_2), intramolecular ring closure in **199** leads

Scheme 62.

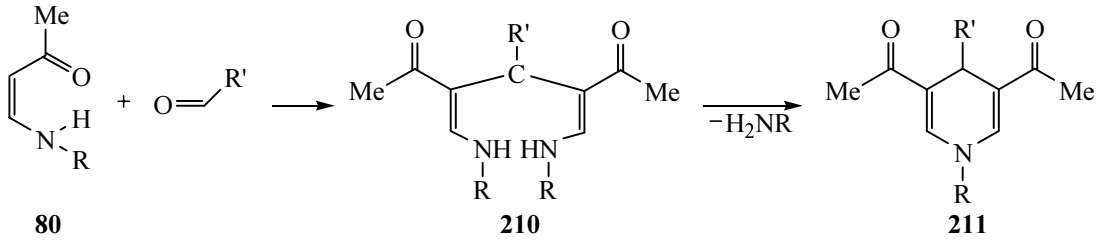
Scheme 63.



Scheme 64.



Scheme 65.



R = H, Alk; R' = Alk, Ph.

to 2-oxo-1,2-dihydropyridine-3-carbonitrile (**197**) [22]. The synthesis of 4-ethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile by reaction of acetal **4a** with malonodinitrile was covered by patent [168].

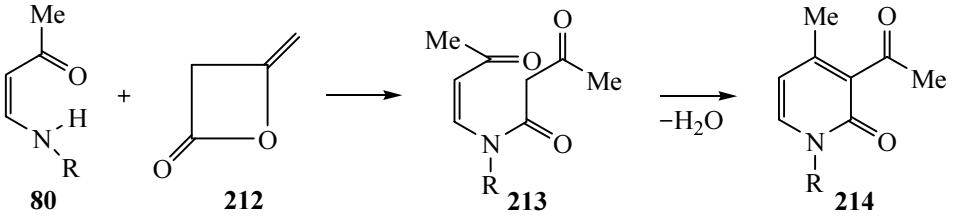
7.4. Reactions with oxygen- and sulfur-containing reagents. Acetal **4a** reacts with ethylene glycol (**202**) following the transacetalization pattern with formation of 2-substituted dioxolane **203** [22]; analogous reaction with 2-butene-1,4-diol (**204**) yields 2-substituted 1,3-dioxepines **205** [15, 22] (Scheme 62).

1,3-Dioxane derivatives obtained from methoxybutenone **3a** and glycols are used as fungicides and squalene synthetase inhibitors [169]. Reactions of mono- and oligosaccharides with acetal **4a** and its analogs lead to formation of, respectively, 3-oxobutylidene-maltopentose (purity 99%) [170] or maltooligosaccharides **206** which are used as substrates for clinical analysis of α-amylose [171–174] (Scheme 63).

In the reaction of methoxybutenone **3a** with 2-naphthol, catalyzed by $FeCl_3$/HCl, the latter adds at the double bond of the former to give adduct **207** which undergoes intramolecular ring closure to hemiacetal **208**; elimination of methanol molecule from **208** yields 2-methylnaphtho-[2,1-*b*]pyrylium tetra-chloroferrate(III) (**209**) [15, 22] (Scheme 64). 3-Aryl-4-hydroxy-1-benzopyran-4-ones were synthesized from acetals **4** and 4-hydroxy-1-benzopyran-2-ones [175].

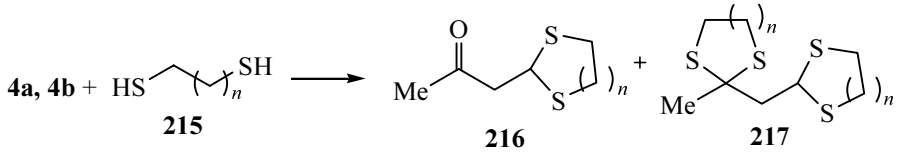
(*Z*)-Aminobutenones **80** possessing at least one hydrogen atom on the nitrogen react with aldehydes (EtOH,

Scheme 66.



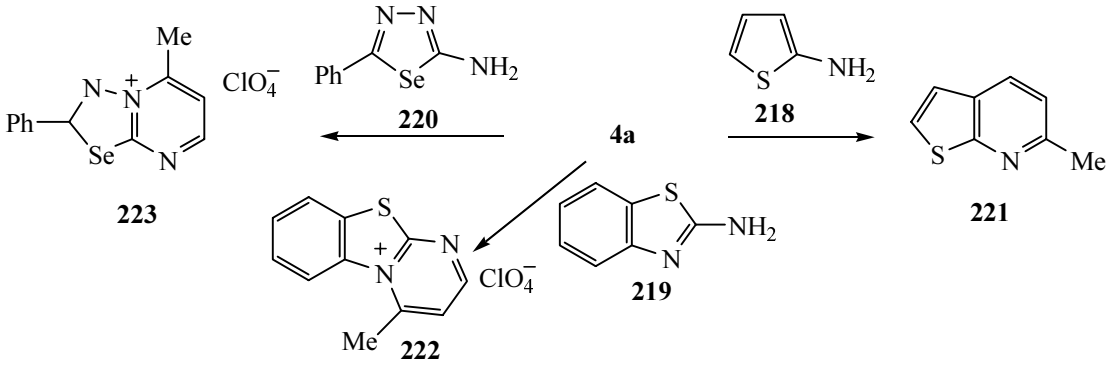
R = H, Me, Et, *i*-Pr, Bu.

Scheme 67.



n = 1, 2.

Scheme 68.



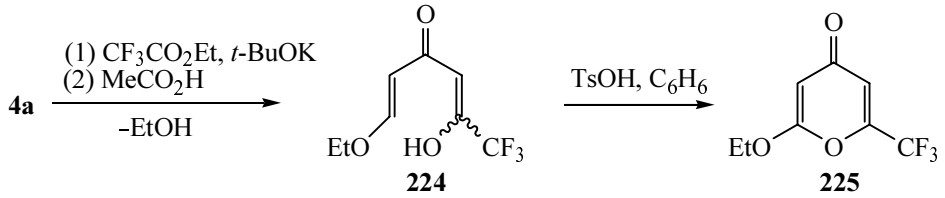
piperidinium acetate, 25°C, 12 h) at a ratio of 2 : 1. Presumably, the reaction involves formation of bis-adduct **210** whose cyclization in acid medium yields 1,4-dihydropyridine **211** (Scheme 65). An analogous reaction with methoxybutenone **3a** was also reported; it occurred in the presence of ammonia, presumably via transamination of the alkoxy group [16, 22]. 3-Acetyl-4-methyl-1,2-dihydropyridin-2-ones **214** were obtained from monoalkylaminobutenones **80** and diketene (**212**) in benzene through intermediate amides **213** [16, 22] (Scheme 66).

Acetal **4a** reacts with 1,2-etanedithiol (**215**, *n* = 1) (benzene, *p*-toluenesulfonic acid, 16 h, reflux) to give 1-(1,3-dithiolan-2-yl)-2-propanone (**216**, *n* = 1) and 2-methyl-2-(1,3-dithiolan-2-ylmethyl)-1,3-dithiolane (**217**, *n* = 1) [15, 16] (Scheme 67). The conditions of this reaction were optimized using natural kaolines as catalyst [176, 177]. 1,3,5,7-Tetramethyl-2,4,6,8-tetrathiaada-mantanes were synthesized from acetal **4a**, hydrogen sulfide, and 3-methylpentane-2,4-dione [17]. Thieno-[3,2-*b*]-pyridines having a functional group in the β-position of the pyridine ring were obtained from β-(3-amino-2-thienyl)-α,β-unsaturated ketones prepared from dimethoxybutanone **4a** or methoxybutenone **3a** [178]. 2-Sulfonyl-4-methoxypyridines were synthesized from acetals **4** or alkoxyvinyl ketones **3** and benzenesulfonyl cyanide (BuOH, toluene, 110°C, 4 h); 2,4-dihydroxypyridine was obtained from the latter [179, 180].

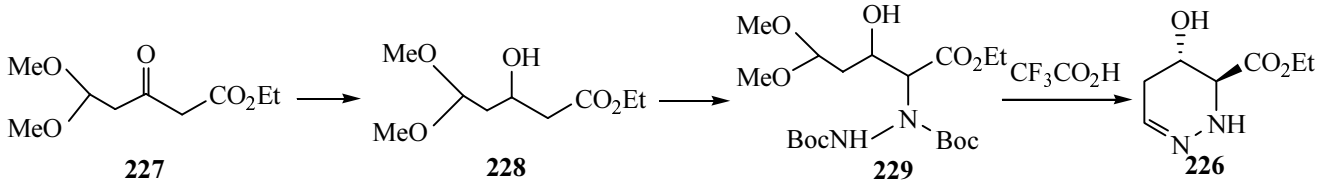
Reactions of acetal **4a** with 2-aminothiophene (**218**), 2-aminobenzothiazole (**219**), and 5-amino-2-phenyl-1,3,4-selenadiazole (**220**) were reported to afford, respectively, 2-methylthieno[2,3-*b*]pyridine (**221**), 4-methylpyrimido[2,1-*b*][1,3]benzothiazol-5-ium perchlorate (**222**), and 7-methyl-2-phenyl[1,3,4]selenadiazolo[3,2-*a*]pyrimidinium perchlorate (**223**) [17] (Scheme 68).

Synthetic approaches were developed for introduction of perfluoroalkyl groups into six-membered hetero-

Scheme 69.

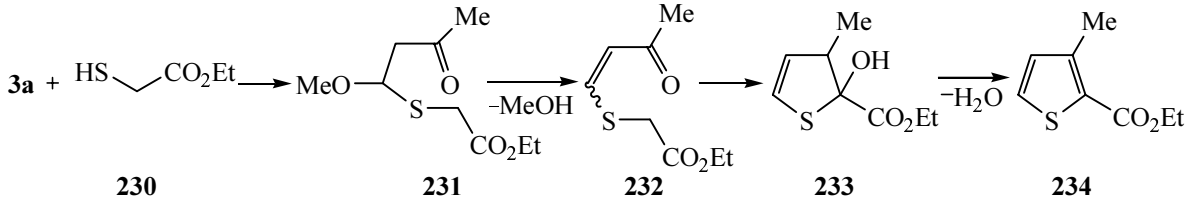


Scheme 70.

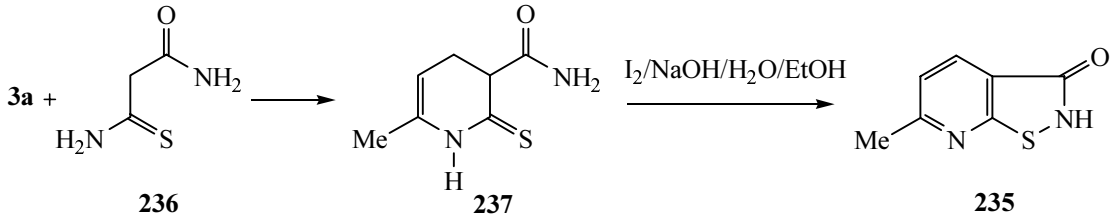


Boc = *t*-BuOCO.

Scheme 71.



Scheme 72.

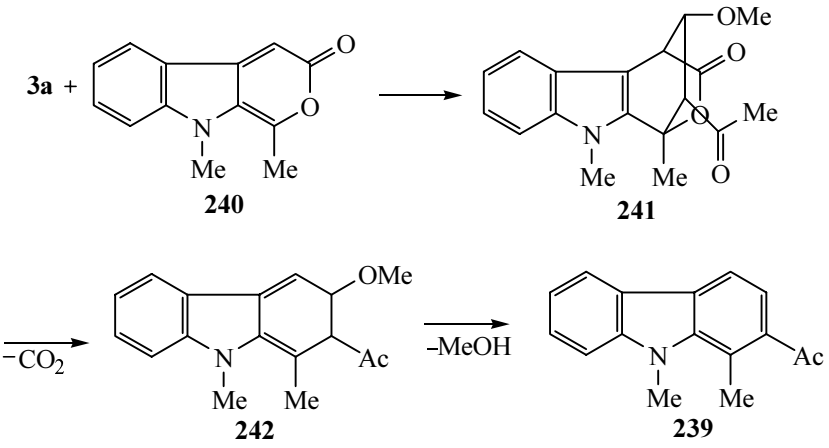


cycles of the pyran and pyridine series with the use of ethoxybutenone **3b** or diethoxybutanone **4b**. For example, 2-ethoxy-6-trifluoromethyl-4*H*-pyran-4-one (**225**) was synthesized by condensation of ethyl trifluoroacetate with ethoxybutenone **3b** or diethoxybutanone **4b** through intermediate **224** [181, 182] (Scheme 69).

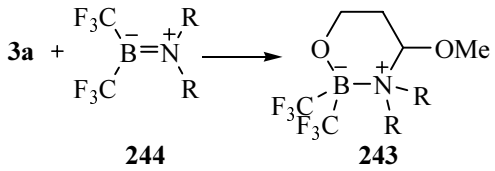
Ciufolini and Xi [183] described a five-step scheme for the synthesis of tetrahydropyridazinecarboxylate **226** which is used to build up luzopeptin fragments. From acetal **4a** keto ester **227** was obtained; its reduction with $NaBH_4$ (EtOH, –78°C) gave alcohol **228** which reacted with di-*tert*-butyl azodicarboxylate to form two stereoisomeric adducts. The latter were quickly converted into ester **226** by treatment with trifluoroacetic acid (THF, –78°C) (Scheme 70).

Replacement of the methoxy group in **3a** by sulfanyl via reaction with ethyl sulfanylacetate (**230**) gave ethyl (1-methoxy-3-oxobutylsulfanyl)acetate (**231**) which was converted into ester **232** by elimination of methanol; the subsequent intramolecular cyclization and dehydration of intermediate **233** afforded ethyl 3-methylthiophene-2-carboxylate (**234**) [22] (Scheme 71). 6-Methyl-2,3-dihydroisothiazolo[5,4-*b*]pyridin-3-one (**235**) was synthesized from thiomalonamide (**236**) and methoxybutenone **3a**. The primary condensation product (piperidinium acetate, EtOH, 10 h), 2-thioxo-1,2-dihydro-pyridine-3-carboxamide **237** was oxidized to isothiazolo-pyridine **235** [22, 184] (Scheme 72). A synthesis from dimethoxybutanone **4a** of 7-(2,6-difluorophenyl)-2-phenyl-4,7-

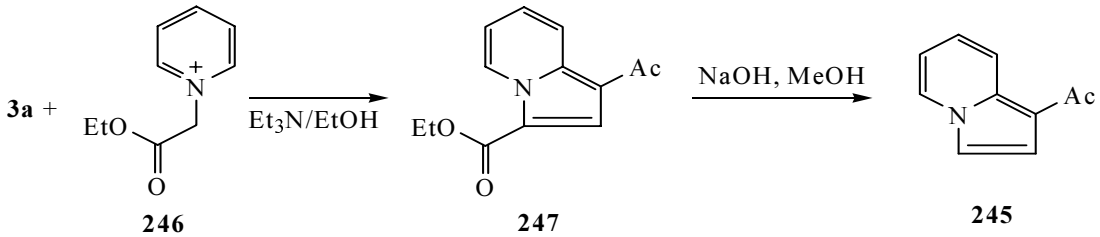
Scheme 73.



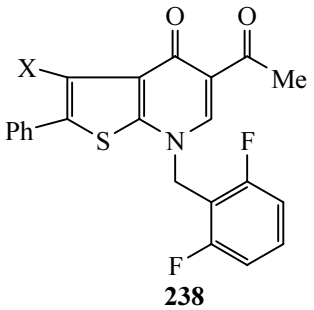
Scheme 74.



Scheme 75.



dihydrothieno[2,3-*b*]pyridin-4-ones **238**, which act as GnRH blockators, was described in [185].



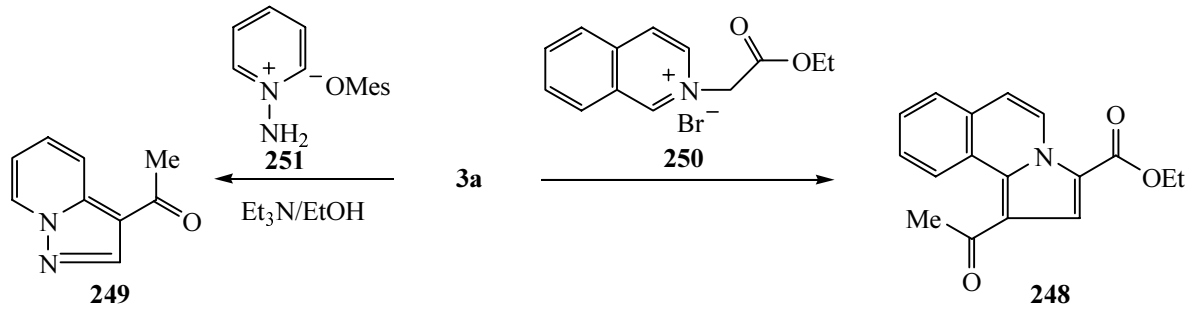
X = H, Hlg.

8. CYCLOADDITION

Functionally substituted isoxazoles, pyrazoles, and triazoles were obtained by cycloaddition of alkoxybutenones **3** to benzonitrile *N*-oxides, *C*-acetyl- and *C*-ethoxycarbonyl-*N*-phenylnitrile imines, and *p*-methoxyphenyl azide [186–189]. Alkoxybutenones **3** react with 1,3-dipoles only at the C=C bond, and the negatively charged atom of the 1,3-dipole adds to the C^4 atom, while the positive center, to C^3. Ring closure is accompanied by elimination of the alkoxy group.

1-Amino(or methoxy)-3-trialkylsiloxy-1,3- butadienes **30** and **33** derived from dialkoxybutanones **4a** and **4b** are widely used in syntheses of diastereoisomeric compounds. These reagents are readily involved in cycloaddi-

Scheme 76.



Mes = 2,4,6-$Me_3C_6H_2SO_2$.

tion reactions with electron-deficient dienophiles [35, 40–43, 190–192]. The process occurs under mild conditions, and the corresponding adducts are formed with high *endo*-selectivity. Diels–Alder reaction of pyrano[3,4-*b*]indol-3-one **240** with methoxybutenone **3a** as electron-rich olefin gives rise to adduct **241** which eliminates CO_2 molecule to give 2-acetyl-3-methoxy-1,9-dimethyl-2,3-dihydrocarbazole (**242**), and the latter loses methanol molecule to afford 2-acetyl-1,9-dimethylcarbazole (**239**) [193] (Scheme 73).

Ansorge *et al*. [194] described [2+4]-cycloaddition of dialkylaminobis(trifluoromethyl)boranes **244** to methoxybutenone **3a** (0°C, pentane, 1 h), which led to formation of new six-membered oxygen–boron–nitrogen heterocycles **243** (Scheme 74). The reaction of pyridinium salt **246** with methoxybutenone **3a** (Et_3N/EtOH, 30°C, 9 h) gave 1-acetylindolizine-3-carboxylate **247** which was then transformed into 1-acetylindolizine **245** [195] (Scheme 75). An analogous reaction with isoquinolinium salt **250** afforded ethyl 1-acetylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate **248** (Scheme 76). 1-Acetylpyrazolo-[1,5-*a*]pyridine (**249**) was synthesized by reaction of pyridinium salt **251** with methoxybutenone **3a** (25°C, 5 h) [195].

9. CONCLUSION

The amount of diacetylene formed in the manufacture of acetylene by electrocracking and oxidative pyrolysis of natural gas, as well as by plasma processes, reaches 5% of the overall efficiency [1]; however, the problem concerning utilization of diacetylene has not been solved as yet [1, 14, 22]. It is now quite obvious that diacetylene can be used in effective small-scale production of thiophene [196], vitamins A and PP, geraniol and phytol derivatives, and various pyrazoles, pyrimidines, and pyridines [14, 22]. Development of new technologies should increase the significance of products obtainable from diacetylene. The first step toward industrial utilization of diacetylene may be manufacture of chemicals based thereon [6, 22, 45, 197, 198].

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