METHYLENEMALONIC ALDEHYDES AND THEIR USE IN ORGANIC SYNTHESIS (REVIEW)

L. A. Yanovskaya and G. V. Kryshtal'

UDC 542.91:547.44:547.7:547.8

The review is devoted to the use of methylenemalonic aldehydes in the synthesis of diverse heterocycles — pyrans, dihydropyrans, dihydrofurans, oxazoles, oaxadiazines, pyrazoles, and diazepines.

Methylenemalonic aldehydes of the **1** and **2** type

$$\underset{\mathbf{1}}{RCH{=}C(CHO)_2} \qquad \underset{\mathbf{2}}{R^1R^2C{=}C(CHO)_2}$$

have, until relatively recently, remained difficult to obtain and have not been investigated in detail, although the first representatives of the **1** (R = OH, Me_2N, CO_2Et, CO_2CCl_3) and **2** ($R^1 = Me_2NC_6H_4$, R^2 = Cl or $R^1 = R^2 = CO_2Et$) series [1-8] were obtained in the nineteen sixties. In the early stage of the development of the development of these interesting compounds it was shown that they may be valuable starting reactants in organic synthesis. In particular, the total synthesis of natural cephalosporin C, isolated from *Cephalosporium acremonium*, and its analogs, which have high antimicrobial activity [6-8], was accomplished using **1**. One of the analogs, by the name of cephalovin, has found application in medicine.

As of this writing quite simple methods for the synthesis of **1** and **2** have been developed, and this has led to the rapid development of the chemistry and utilization of methylenemalonic aldehydes (MMA) in organic synthesis [9-11], particularly heterocyclic compounds. And our review is devoted to these problems.

METHODS FOR THE SYNTHESIS OF METHYLENEMALONIC ALDEHYDES

Methylenemalonic aldehydes (MMA) were first obtained in a study of formylation with the Vilsmaier—Haack reagent ($COCl_2$ or $POCl_3$ in dimethylformamide) through the formation of a series of trimethylidyne salts of the $(Me_2N{=}CHCH{=}CXR)^+X^-$ type [for example, $(Me_2N{=}CHCH{=}{-}NMe_2)^+ClO_4^-$ or (4-$Me_2NC_6H_4CCl{=}CHCH{=}NMe_2)^+X^-$] [1-4], carbonyl compounds (aromatic aldehydes or aliphatic-aromatic ketones [1-3, 9-11], haloacetic acids and malonic acid [5]), compounds with an active methylene group (for example, 4-methyl-2,6-diphenylpyran perchlorate) [12], and 2-methyl-3-ethylbenzoxazolium (-selenazolium or -thiazolium) iodide quaternary ammonium salts [13]. However, the above-noted Vilsmaier—Haack reagent is applicable for a limited number of compounds.

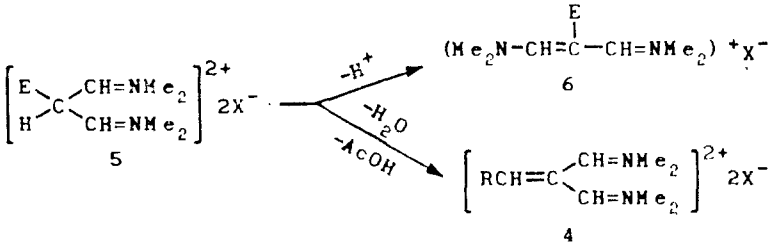
Various approaches developed in the nineteen eighties [9, 14-22] are used as the basis of methods for obtaining MMA, depending on the nature and number of substituents in the β position of these compounds. Diverse aromatic (including heterocyclic or polyene) aldehydes are formylated for the synthesis of **1** (R = aryl, heteryl, or polyenyl) by trimethylidyne salt **3** in acetic anhydride in the presence of protic acids (CH_3COOH or $HClO_4$) or Lewis acids ($TiCl_4$, $BF_3{\cdot}EtO_2$, etc.) with cooling or at room temperature with subsequent hydrolysis of the intermediate diiminium salt with dilute HCl (when R = heteryl or aryl) or in the presence of alkali metal acetates [10, 16] when clearly expressed electropositive substituents are present in the molecule or with water—benzene systems (water—benzene—dichloromethane) system (if R is a polyene chain [18]).

$$\underset{\mathbf{3}}{(Me_2NCH{=}CHCH{=}NMe_2)^+ClO_4^-} \xrightarrow{RCHO} \underset{\mathbf{4}}{\left[R\text{-}CH{=}C(CHNMe)_2\right]^{2+}2X^-} \xrightarrow{H_2O} \underset{\mathbf{1}}{R\text{-}CH{=}C(CHO)_2}$$

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1011-1026, August, 1991. Original article submitted November 6, 1990; revision submitted March 13, 1991.

0009-3122/91/2708-0807$12.50

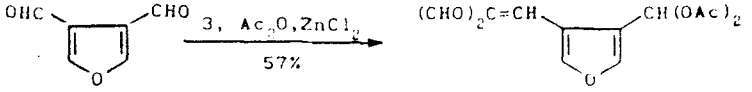
The scheme presented above is confirmed by the isolation of intermediate **4** from the reaction mixture of trimethylidyne salt **3** with 5-nitrofurfural [17]. The reaction scheme is in agreement wit the data obtained in a study of substitution in trimethylidyne salts. Thus the attack of electrophilic agents in acid-catalyzed formylation [2], nitration [23], or deuteration [24, 25] takes place at the central atom of the trimethylidyne salt with the formation of product **5**. The stabilization of **5** is realized by deprotonation with the development of conjugated system **6** (pathway A), while in the case of condensation with an aldehyde, in which the protonated form of the aldehyde, or an adduct of the aldehyde with the Lewis acid, or, most likely, the acylated $RCHOCOCH_3^+$ form (since the reaction is carried out in acetic anhydride) acts as the electrophile, the stabilization of intermediate **5** occurs through dehydration or elimination of AcOH (pathway B) to give salt **4**.



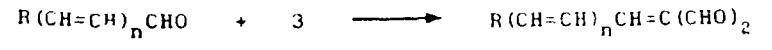
E=D, NO_2 or $(Me_2NCHCl)^+$(pathway A); E=$RCHOH^+$, $RCHBF_3^+$ or $RCHOAc^+$ (pathway B)

Intermediate **4** is very sensitive to water and is readily hydrolyzed to MMA. The yields of MMA **1** depend on the structures of the starting aldehydes. In the case of benzaldehyde and 4-X-benzaldehydes (X = Br, OAc, OMe, etc.) the yields of **1** range from 60% to 65%; 3,4-dimethoxy- and 3,4,5-trimethoxybenzaldehydes form MMA **1** in 81-85% yields; nitrobenzaldehydes and 3-methoxy- and 2,4,6-trimethylbenzaldehydes give **1** in 12-21% yields. Let us note that heterocyclic aldehydes (furfural, 5-methyl-, 5-bromo-, or 5-nitrofurfural, 2-formylthiophene, 3-formylthiophene, etc.) react with trimethylidyne salt **3** to give, in high yields (72-90%), the corresponding 2-heterylmethylenemalonic aldehydes, with the exception of 5-nitro-2-furylmethylenemalonic aldehyde, the yield of which is 30%.

Polyunsaturated aliphatic, aromatic, and heterocyclic dialdehydes react quite readily with trimethylidyne salt **3**; however, even when an excess amount of it is used, formylation takes place only at one aldehyde group, while the second is converted to a diacetate group [19].

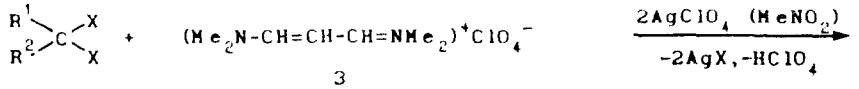


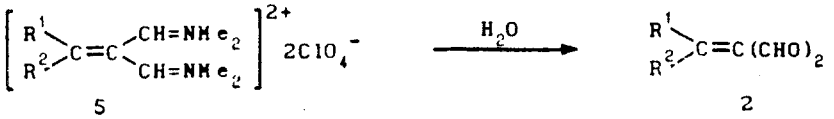
Saturated aldehydes and α,β-unsaturated aldehydes do not react with salt **3**; however, di- and polyene aldehydes react with it to give polyenylidenemalonic aldehydes in yields ranging from 25% to 92% [18, 21, 26]. 2-(2,2-Dichlorocyclopropyl)acrolein also reacts normally [26]:



R=$Me(CH=CH)_n$, n=2,3; $EtO_2C(CH=CH)_n$, n=1—3; $Cl_2C=CH(CH=CH)_n$, n=1—3

A general approach to the synthesis of MMA of the **2** type, where R^1 and R^2 = Ar and (or) Het was realized on the basis of the reaction of geminal dihalo compounds (obtained from the corresponding ketones) with trimethylidyne salt **3** in nitromethane in the presence of silver perchlorate with cooling. As in the case of **1**, the initial product is intermediate **5**, which, upon hydrolysis with dilute HCl, is converted to dialdehyde **2** [10, 14, 23]:

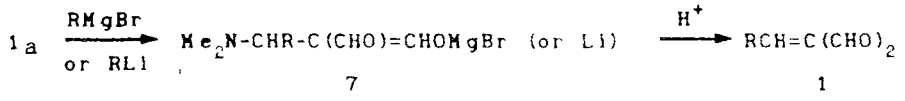




5 2

Diaryl ketones [benzophenone, 4-R-benzophenones (R = Me, Br, MeO), phenyl 1-naphthyl ketone, etc.] form MMA **2** in 50-90% yields; however, 4-nitrobenzophenone forms **2** in 31% yield [14, 22]. Quite high yields of **2** (50-90%) were obtained for 4-pyridyl and 2-thienyl phenyl ketone, as well as for di-2-thienyl ketone [14, 22].

A general synthesis for alkylidenemalonic aldehydes was recently developed on the basis of the reaction of the readily accessible dimethylaminomethylenemalonic aldehyde $Me_2NCH{=}C(CHO)_2$ (**1a**) [27] with Grignard reagents, organolithium compounds, or lithium dialkylcuprates [20, 28] at −40°C. Addition occurs in the 1 and 4 positions of aldehyde **1a**; the aliphatic residue bonds with the carbon atom bearing the Me_2N group. Intermediate **7** (as confirmed by the disappearance of the signal of the CH= group in the PMR spectrum during the reaction) is hydrolyzed by $HClO_4$ at pH 3-4:



7 1

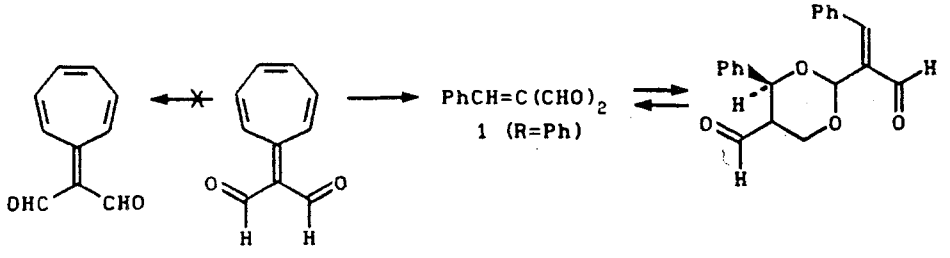
R=Me, *i*-Pr, Bu, RCH=CH, RC≡C, cycloalkyls

Only MMA **1** (R = PrC≡C and R = PhC≡C) proved to be sufficiently stable and were isolated in the form of pure preparations in 30% and 80% yields, respectively. The remaining **1** (R = Me, iso-Pr, Bu, cyclopropyl, cyclopentyl, and cyclohexyl) are extremely unstable and were characterized in the form of adducts with vinyl ethyl ether (see below). The yields of unpurified MMA **1** (R = alkyl, cycloalkyl) ranged from 37% to 80%. 3,3-dimethylacrylaldehyde reacts with **1a**; however, cyclization occurs during isolation of the final MMA, and 2,2-dimethyl-2H-pyran-5-carbaldehyde is formed [26]. It should be noted that the method described above is also suitable for the synthesis of aryl- and heterylmalonic aldehydes [28].

Two other methods have been proposed for the synthesis of aliphatic MMA. The first method includes the condensation of mesoxalic or glyoxylic esters with malonic aldehyde enolate. However, this method is limited and is used only for the production of 2,2-diethoxycarbonylmethylenemalonic aldehyde and 2,2-bis(β,β,β-trichloroethoxycarbonyl)methylenemalonic aldehyde — starting compounds for the synthesis of cephalosporin and its analogs [8].

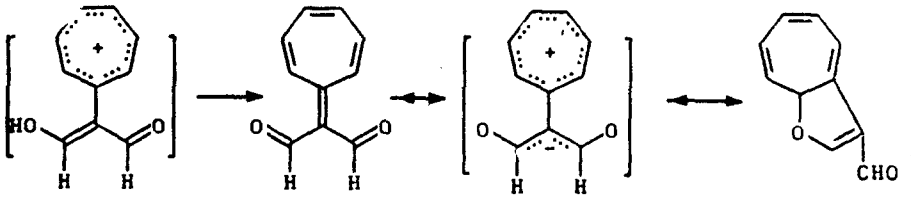
The second method for the synthesis of MMA reduces to the Wittig reaction between acetals of mesoxalic aldehyde and methylene--, alkylene-, dialkylene-, or cycloalkylidenetriphenylphosphoranes and leads to acetals of alkylidene(or cycloalkylidene)malonic aldehydes in 26% to 89% yields. However, the corresponding MMA could not be obtained by hydrolysis of the acetals [29].

Two special instances of the formation of MMA of the **1** and **2** types have been described. Thus oxidation of cycloheptatrienylmalonic aldehyde (with Ag_2O or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone) gave **1** (R = Ph) in equilibrium with a dimeric form (in 88% overall yield) [30, 31]:



However, treatment of cyclohepta-2,4,6-trienylidenemalonic aldehyde hexachloroantimonate with dimethylaminopolystyrene in CH_2Cl_2—CH_3OH (1:1) led to splitting out of hexachloroantimonate and the formation

of an equilibrium mixture of two valence isomers, viz., 8,8-diformylheptafulvalene **8** and 8*a*-cyclohepta[b]furan-3-carbaldehyde **9** [32, 33], the composition of which depends on the solvent:

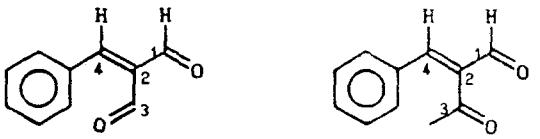


$SbCl_5$ **8** **9**

The MMA are liquids or crystalline solids. The color of the crystals varies from yellow to red. The are unstable at room temperature but can be stored without undergoing any changes at −20°C for several months (except for the alkylidenemalonic aldehydes); **1** and **2** are sensitive to air oxygen.

The spectral data (from the IR and NMR spectra) are in complete agreement with the formulas proposed for **1** and **2** [10, 14, 16-19, 23], while the UV spectra of MMA **1** depend to a marked degree on the nature of the solvent; the pK_a values of MMA **1** lie within the limits that are typical for carboxylic acids, viz., from 3.98 to 5.42. The pronounced effect of the nature of the solvent on the UV spectra of **1** and the high acidities make it possible to classify the MMA as organic Lewis acids [34], which include compounds that contain two electronegative substituents attached to one of the carbon atoms that form the double bond. A comparative study of the rates and equilibrium constants of the reactions of **1** (R = Ph) and the benzylidene derivative of 4,4-dimethyl-3,5-dioxahexane-2,6-dione (Meldrum's acid) with water and OH^- as a function of the pH of the medium showed that **1** (R = Ph) is a stronger acid by a factor of 4.3 than the benzylidene derivative of Meldrum's acid; however, the rate constants for attack by water and OH^- for it are lower than for the derivative of Meldrum's acid, which indicates the higher barrier with respect to nucleophilic attack in **1** (R = Ph) due to delocalization of the negative charge with respect to the carbonyl groups [35, 36].

The following conclusions were drawn on the basis of an analysis of the spin-spin coupling constants (SSCC) (including the long-range values) as a function of the nature of the solvents, the temperature, and the nature of the substituents in the aryl or heteryl rings, as well as in conformity with the results of x-ray diffraction analysis of **1** (R = 3-thienyl) and **2** (R^1, R^2 = Ph, Ph or Ph, 2-thienyl) [37-40] and quantum-chemical calculations of the MO levels (semiempirical methods and ab initio procedures): 1) most of the MMA are conformationally nonhomogeneous; 2) the s-trans,s-cis **1A** conformation is the most stable conformation for $>C=(CHO)_2$ fragment, due to the coulombic repulsion of the oxygen atoms; 3) the cis(E),trans(E) conformation is the most stable conformation for **1** (R = Ph), while the trans(E),cis(Z) conformation is the most stable conformation for the heteryl- and alkylidenemalonic aldehydes; 4) for MMA **1** one can conceive of an equilibrium between two conformations, viz., **1A** and **1B** [10, 40]:



1A **1B**

Dialdehyde **1A** displays a 3-H signal in its PMR spectrum corresponding to the least shielded CHO group in a cis orientation relative to the phenyl ring and is characterized by coupling of the "zigzag"type through four bonds between 3-H and 4-H.

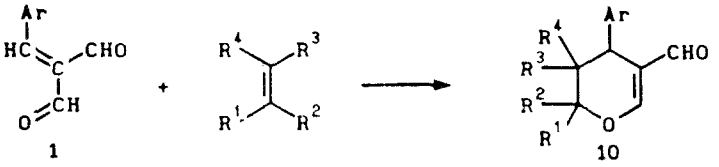
USE OF METHYLENEMALONIC ALDEHYDES IN SYNTHESIS

Inasmuch as they have several reaction centers and peculiar structures, MMA **1** and **2** are capable of diverse transformations. Their reactivities differ appreciably as a consequence of the greater steric hindrance of the double bond in **2**.

For MMA **1** the most typical reactions are 1,4-addition and cycloaddition at the —CH=C(CHO)—CH=O fragment, while reactions involving condensation and cyclocondensation at the β-dicarbonyl $=C<^{CHO}_{CHO}$ fragment. The use of MMA in the synthesis of heterocycles is of particular promise.

1. Synthesis of Dihydropyrans

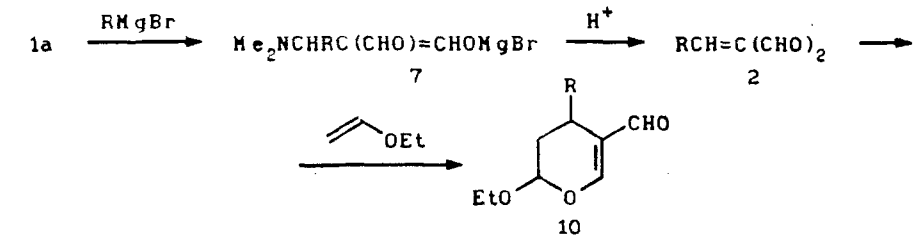
A method for the synthesis of diverse 4-aryl-3,4-dihydro-2H-pyran-5-carboxaldehydes **10** [10, 41] that includes the cycloaddition of MMA of the **1** type as a 4π-component to various olefins, including functionally substituted compounds (ketene acetals, vinylamines, vinyl ethers, and thioketene acetals) has been developed. In most cases the reaction proceeds via simple mixing of the reagents in benzene at room temperature, but sometimes the reaction is carried out in the presence of catalytic amounts of zinc iodide:

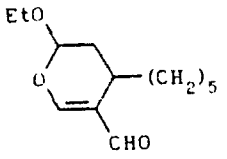
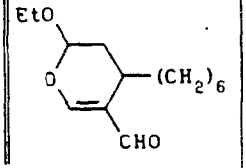


Ar	R¹	R²	R³	R⁴	Yield, %
4-ClC_6H_4	Me	Me	H	H	56
4-ClC_6H_4	H	—$CH_2CH_2CH_2$—		H	40
4-$MeOC_6H_4$	C_6H_5	C_6H_5	H	H	67,5
4-$MeOC_6H_4$	EtO	H	H	H	86,5
4-$MeOC_6H_4$	$O(CH_2CH_2)_2N$—	H	Me	Me	83
4-$MeOC_6H_4$	MeO	MeO	H	H	91,5
2-Thienyl	C_6H_5	C_6H_5	H	H	50
2-Thienyl	$O(CH_2CH_2)_2N$—	H	Me	Me	49
2-Thienyl	MeS	MeS	H	H	89,9

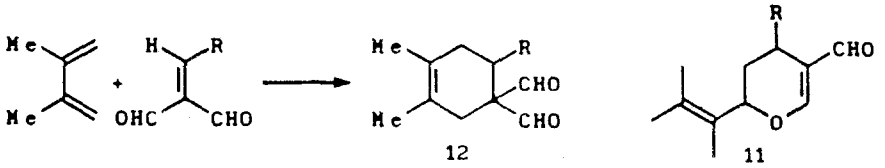
The maximum yields of **10** (83.9-91.5%) were observed in the reaction between **1** (Ar = 4-ClC_6H_4, 4-$MeOC_6H_4$, and 2-thienyl) with vinyl ethyl ether, ketene dimethylacetal, and ketene dimethylthioacetal, as well as 1-morpholino-2,2-dimethylethene; the lowest yields of **10** (40-49%) were obtained in the reaction of MMA **1** (Ar = 2-thienyl) with 1,1-diphenylethene or 1-morpholyl-2,2-dimethylethene. Thus the method makes it possible to obtain substituted 3,4-dihydro-2H-pyrans that contain an aldehyde group. The stereochemistry of the process has been studied only for the reaction of **1** (R = 4-ClC_6H_4) with dimethylvinyl ethyl ether. It was established that a mixture of cis and trans isomers **10A** and **10B** is formed in a ratio of 2.5:1; however, when it is heated in the presence of acids, this ratio changes to favor the trans isomer up to a ratio of 1:2.5 [42].

The ease of formation of dihydropyran [4+2]-cycloadducts of MMA with vinyl ethyl ether has been used to prove the formation of extremely labile MMA with aliphatic and cycloaliphatic substituents obtained as a result of the reaction of dimethylaminomethylenemalonic aldehyde **1a** with organometallic compounds [26, 28]. The method leads to rather good yields of the final dihydropyrans **10** with an extensive set of substituents R:



R	Yield, %	R	Yield, %	R	Yield, %
Me	40		44		53
i-Pr	67				
Bu	73				
Cyclopropyl	47				
Cyclopentyl	67				
Cyclohexyl	76				

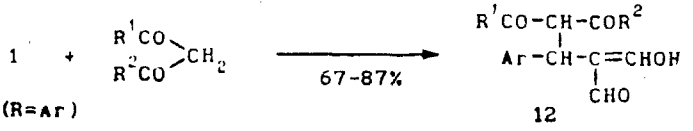
Formyldihydropyrans can also be obtained by the reaction of MMA **1** with cyclic dienes (1,3-cyclohexadiene or cyclopentadiene) under the conditions of the Diels—Alder reaction, which takes place primarily via a pathway of the 1,4-addition type, i.e., in this case also **1** react as 4π-components to give 3-formyl-5,5-dihydropyrans **11** [10, 41]. However MMA **1** react with aliphatic conjugated dienes (1,3-butadiene or 2,3-dimethyl-1,3-butadiene) primarily as 2π-components to give geminal dialdehydes **12** of the cyclohexene series [10, 43]:



	Percentages in the mixtures	
1,3-Butadiene	90	10
2,3-Dimethyl-1,3-butadiene	90	10
1,3-Cyclohexadiene	25	75
Cyclopentadiene	0	100

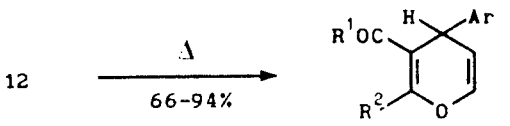
2. Synthesis of 4H-Pyrans

Two methods for the synthesis of 4H-pyrans have been developed based on MMA of the **1** type. In the first method the MMA is subjected to reaction with β-dicarbonyl compounds such as diethyl malonate, ethyl acetoacetate, penta-2,4-dione, etc. via the following scheme [44]:



R	R^1	R^2	Yield, %	R	R^1	R^2	Yield, %
4-$MeOC_6H_4$	OEt	OEt	78,5	3-Thienyl	Me	OEt	82,3
4-ClC_6H_4	Me	OEt	76,6	4-ClC_6H_4	Me	Me	78,6
4-$MeOC_6H_4$	Me	OEt	66,9	3-Thienyl	Me	Me	87,1

The reaction is carried out in the presence of Et_3N and leads to polyfunctionally substituted malonic aldehydes **12**. It has been noted that the reaction is catalyzed by the addition of (2,4-pentadionate)Cu(I) and bis(2,4-pentadionate)Cu(II) in conjunction with $BF_3 \cdot Et_2O$ [45]. In the second step the resulting Michael products **12** are converted to pyrans **13** in the presence of p-toluenesulfonic acid [44]:



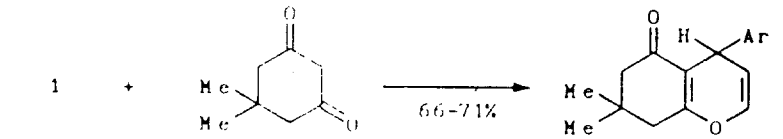
13

Ar, R^1, R^2: 4-ClC_6H_4, Me, Me; 4-$MeOC_6H_4$, Me, Me; 3-thienyl, Me, Me; 4-ClC_6H_4, OEt, Me; 4-$MeOC_6H_4$, OEt, Me; 3-thienyl, OEt, Me

It should be noted that the products (**12**) of the reaction of **1** (R = Ar) with acetoacetic ester are mixtures of stereomers and, possibly, other forms due to enolization and the formation of hydrogen bonds.

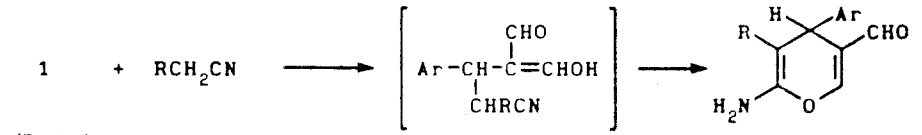
Thus a new two-step convenient approach to the synthesis of 4H-pyrancarboxaldehydes **13** was developed on the basis of MMA of the **1** type.

The second method of synthesis is a one-step process and is based on the spontaneous conversion of malonic aldehydes of the **12** type to pyran derivatives. For example, the reaction of MMA **1** (R = Ar) with 5,5-dimethyl-1,3-cyclohexadione leads directly to the formation of pyran **14** [44]:



(R=Ar) 14

Similarly, the condensation of I (R = Ar) with cyanoacetic ester or malononitrile under the conditions described above for β-dicarbonyl compounds leads immediately to 2-amino-4H-pyran-5-carboxaldehydes **15** in 39-60% yields [44].



(R=Ar) 16 15

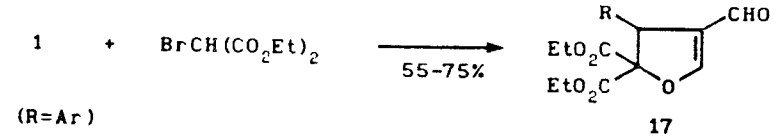
Ar=4ClC_6H_4, 4-$MeOC_6H_4$, 3-thienyl, R=CN, CO_2Me

Intermediate **16** could not be isolated in the pure state, although it was detected in the reaction mixture by TLC, and in the case of the reaction of malonodinitrile with **1** (Ar = 3-thienyl) was characterized by the PMR spectrum as 2-hydroxy-3-(3-thienyl)methylenepropanal **16** (Ar = 3-thienyl, R = CN).

3. Synthesis of Formyl-4,5-dihydrofurans

Functionally substituted 2,3-dihydrofurans are potentially physiologically active substances and are of interest for the synthesis of natural compounds. However, methods for the synthesis of their formyl derivatives have not been adequately worked out.

A study of the reaction of MMA **1** (R = Ar) with bromomalonic ester under interphase-catalysis conditions in a liquid—solid phase system (K_2CO_3—DMF—TEBAC) showed that the only products in this case are 4-aryl-3-formyl-5,5-diethoxycarbonyl-4,5-dihydrofurans **17** [46, 47]:



(R=Ar) 17

R	Yield, %	R	Yield, %
C_6H_5	51	trans-C_6H_5CH=CH	55
4-ClC_6H_4	60	2-Thienyl	75
4-$MeOC_6H_4$	74	$CH_3(CH$=$CH)_2$	60

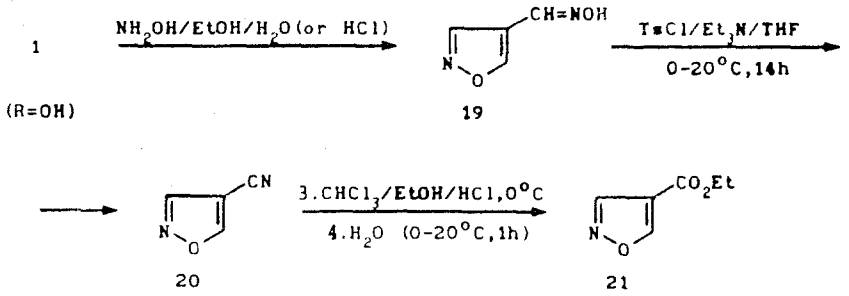
It is most likely that the initially formed $CBr(CO_2Et)_2$ carbanion adds to the double bond of **1** via a mechanism of the Michael reaction type, which is followed by the ejection of bromine and 1,5-cyclization. Calculations of the cross section of the potential-energy surface by the MNDO method for a model system of addition of the CH_2Br carbanion to α,β-unsaturated aldehydes have shown that the formation of dihydrofurans is associated with thermodynamic control of the reaction [48]. This reaction is the first example of the formation of dihydrofurans by the addition of bromomalonic ester to α,β-unsaturated aldehydes (MMA) and can be used as a simple method for the synthesis of 3-formyldihydrofurans.

Yet another possible method for the synthesis of formyldihydrofurans **18** is based on the addition of diphenylcarbene (generated from diphenyldiazomethane) to MMA of the **1** type [10]:

18

4. Synthesis of 4-R-Isoxazoles

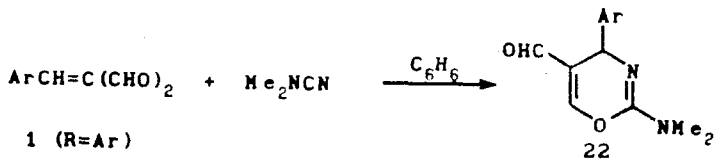
It has been shown that **1** (R = OH) can be used in the synthesis of difficult-to-obtain 4-substituted isoxazoles. The method includes condensation of **1** (R = OH) with hydroxylamine hydrate or hydrochloride; a mixture of E- and Z-oximes of 4-formylisoxazole **19** is formed, the dehydration of which makes it possible to easily obtain 4-cyanoisoxazole **20** and then 4-ethoxycarbonylisoxazole **21** in high yields [49]:



1. $NH_2OH/EtOH/H_2O$ (or HCl); 2. TsCl/Et_3N/ THF (0→20 °C); 3. $CHCl_3$/EtOH/HCl, 0 °C; 4. H_2O (0→20 °C)

5. Synthesis of 1,3-Oxazine-5-carbaldehydes

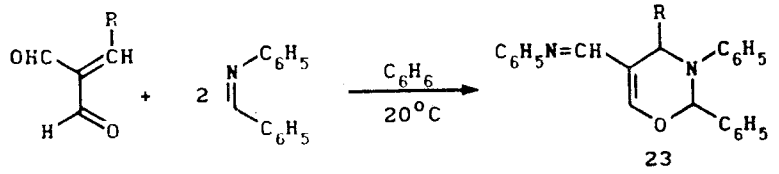
In the reaction with dimethylcyanamide (refluxing in benzene) **1** (R = Ar) act as 4π-components; 4-aryl-2-dimethylamino-4H-1,3-oxazine-5-carbaldehydes **22** are formed in 42-80% yields:



22

Ar	Ph	4-ClC_6H_4	4-$NO_2C_6H_4$	2-Thienyl
Yield, %	78	42	62	80

The proposed method is a new valuable contribution to the chemistry of oxazines. A similar reaction occurs at room temperature between MMA of the **1** type and benzaldehyde phenylimine [10] and leads to 2,3-diphenyl-4-R-5-formyldihydrooxazines **23** [10, 49]:

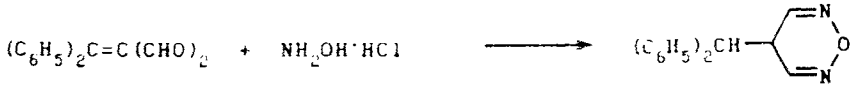


23

R=4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-thienyl

6. Synthesis of 1,2,6-Oxadiazines

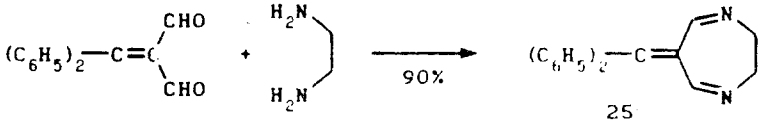
The MMA of the **2** type undergo cycloaddition readily particularly readily. 4H-4-Diphenylmethyl-1,2,6-oxadiazine **24** is formed in 97% yield when **2** ($R^1 = R^2 = C_6H_5$) is refluxed in acetone with hydroxylamine hydrochloride [45]:



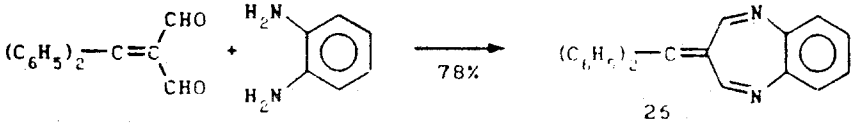
24

7. Synthesis of Pyrazoles and Diazepines

The MMA of the **2** type can also be used successfully in the synthesis of nitrogen heterocycles with two nitrogen atoms. Thus **2** ($R^1 = R^2 = C_6H_5$) reacts at room temperature with hydrazine hydrate or its hydrochloride to give 4-diphenylmethylpyrazole (56% yield), while the corresponding diazepines **25** and **26** are formed in the case of refluxing in acetonitrile (in the presence of an ether solution of HCl for 12-18 h) with 1,2-diaminoethane or 1,2-diaminobenzene [49, 50]:



25



25

These methods are undoubtedly promising for the synthesis of nitrogen heterocycles, particularly diazepines.

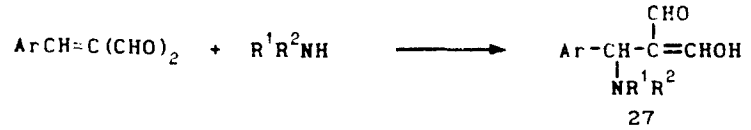
8. Other Reactions of MMA

Among the other reactions of MMA, of particular interest are reactions involving the formation of diverse functionally substituted malonic aldehydes, which, in turn, can be used in the synthesis of other MMA.

SYNTHESIS OF SUBSTITUTED MALONIC ALDEHYDES

The synthesis is based on the 1,4-addition reactions that are typical for MMA. Thus the addition to **1** of proton-containing nucleophiles (water, alcohols, thiols, and primary and secondary amines) leads to the corresponding substituted malonic aldehydes. The reactions involving the formation of adducts with water and alcohols are typical reversible reactions [34, 35]. Sulfides are formed in reactions with thiols. Thus benzenethiol adds to MMA **1** (R = Ph) in the presence of small amounts of concentrated HCl to give 2-hydroxymethylene-3-thiophenyl-3-phenylpropanal [10, 30], which is a mixture of cis and trans isomers in a ratio of 1:3; the overall yield of the sulfide reaches 85%.

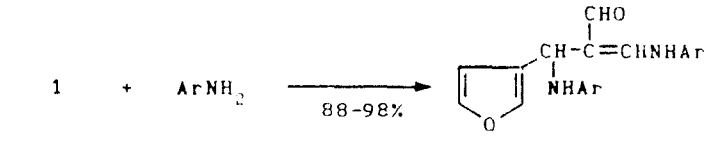
Primary and secondary amines give amino-substituted malonic aldehydes **27** in 84-93% and 35-98% yields, respectively [51]:



27

Ar, R^1, R^2: 4-ClC_4H_4, $—(CH_2)_2O(CH_2)_2—$; 4-$MeOC_6H_4$, $—(CH_2)_2O(CH_2)_2—$; 2-thienyl $—(CH_2)_2O(CH_2)_2—$; 4-ClC_6H_4, Me, Me; 4-$MeOC_6H_4$, Me, Me; 3-thienyl, Me_3C, H; 3-thienyl, 4-$NO_2C_6H_4$, H

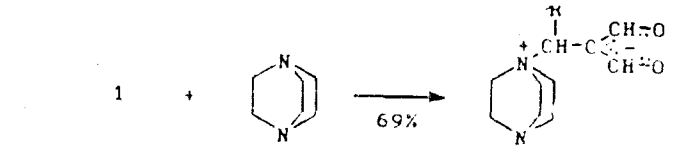
The yields of the products in the reaction of aniline and 4-nitroaniline with **1** are low (≈35%). Carrying out the reaction in alcohols in the presence of small amounts of concentrated HCl leads to 3-alkoxy-2-(4-nitrophenylamino)methylene-3-phenyl-1-propanal in the form of a mixture of E and Z isomers in a ratio of 6:1 and an overall yield of 93% (in MeOH) or 85% (in EtOH). The initial step is evidently the addition of the alcohol to the 1 and 4 positions, after which the resulting enol of the [(alkoxy)-2-phneylmethyl]malonic aldehyde reacts at the enol group with 2-nitroaniline to give the final product. In fact, the reaction of MMA **1** (R^1 = 2-furyl) with aromatic amines in the presence of $BF_3 \cdot Et_2O$ (20°C, 2 h) gives 2-arylamino-2-(2-furyl)malonic aldehyde derivative **28**, in which the enol group is replaced by an arylamino group [51]:



(R=2-furyl) 28

Ar=Ph; 4-ClC_6H_4; 4-BrC_6H_4; 4-IC_6H_4; 4-$MeOC_6H_4$; 4-$NO_2C_6H_4$; 1(or 2)-naphthyl

The reaction of **1** with tertiary amines leads to bipolar compounds. Thus 1,4-diazabicyclo[2.2.2]octane reacts with **1** (R = 4-ClC_6H_4) at 20°C to give adduct **29** [52]:



(R=4-ClC_6H_4) 29

Bipolar adducts **30** are also formed in the reaction of MMA **1** (R = Ar) with tributylphosphine [10, 51]:

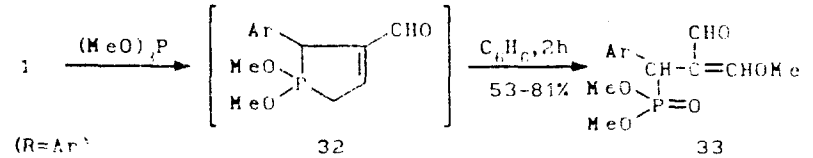
(R=Ar) 30

The formation of bipolar adducts **31** occurs in the reaction of a number of inorganic salts (KCN, KN_3, KNCO, KNCS) in tert-butyl alcohol with **1** at 20°C [44]:

(Ar=4-ClC_6H_4) 31

$X=CN^-, N_3^-, NCO^-, NCS^-$

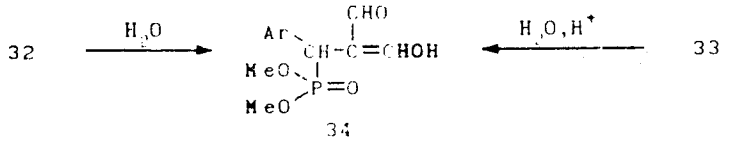
In contrast to tributylphosphine, the reaction of MMA **1** (R = Ar) with trimethoxyphosphine is exothermic and is accompanied by the Arbuzov rearrangement [52, 53]:



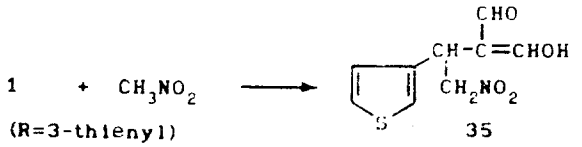
(R=Ar) 32 33

Ar=4ClC_6H_4; 4-$NO_2C_6H_4$; 4-$MeOC_6H_4$; 2- thienyl

The formation of intermediate **32** was detected in the mixture by spectral methods. In addition, **32** (Ar = Ph) was isolated and its structure was confirmed by the ^{1}H, ^{31}P, and ^{13}C spectra [54]. Treatment of product **32** with water immediately leads to the formation of malonic aldehyde **34**; the latter is also obtained by treatment of **33** with acids:



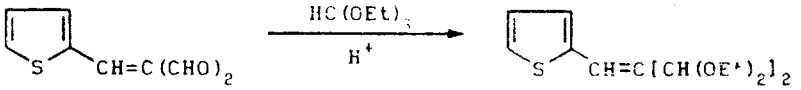
The 1,4-addition of CH acids to I is of particularly great interest. Many CH acids in this case form substituted malonic aldehydes. For example, nitromethane adds to MMA **1** (R = 3-thienyl) to give the corresponding malonic aldehyde **35** [44]:



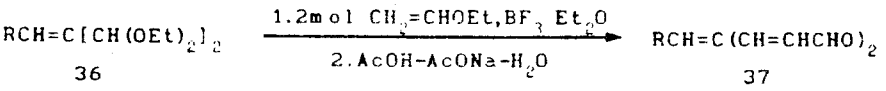
It should be noted that the 1,4-addition reactions of MMA lead not only to the formation of substituted malonic acids that are suitable for the synthesis of heterocycles (see sections 1-7) but can also be used for the creation of functional chains in heterocycles by means of subjecting heterylmethylenemalonic aldehydes to 1,4-addition with suitable components (see the syntheses of **27**, **28**, **29**, and **35** cited above).

REACTIONS OF MMA AT THE ALDEHYDE GROUPS

The aldehyde groups in MMA **1** and **2** are acetalized by orthoformic ester under the conditions that are usual for α,β-unsaturated aldehydes or in the presence of trace amounts of $HClO_4$ [56]; the yields of the acetals are 22-66% (in the first method) and 85-90% (in the second method). For example,

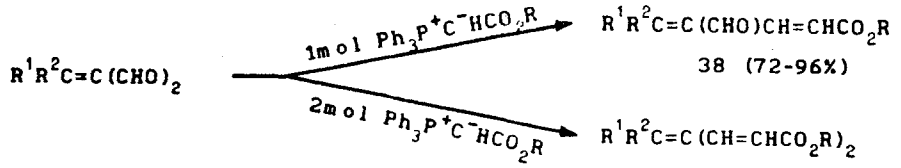


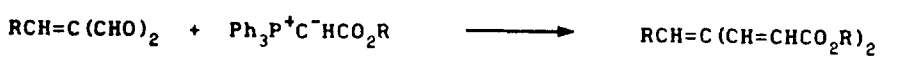
Methylenemalonic aldehyde (MMA) acetals **36** are valuable starting compounds for the synthesis of cross-conjugated aldehydes, since they are capable of adding, via both acetal groups, to vinyl ethyl ether in the presence of $BF_3 \cdot Et_2O$, and the resulting diacetals upon hydrolysis give cross-conjugated aldehydes **37** [42]:



R = 2-thienyl, 60%; Ph, 67%; 4-$MeOC_6H_4$, 87% [42]

The Wittig reaction between MMA **1** (or **2**) and phosphoranes, particularly carbalkoxymethylenetriphenylphosphoranes, can also be used for the transition to cross-conjugated compounds [42]. It should be noted that, depending on the reactant molar ratio, dialdehydes **2** form products involving the reaction at on (**38**) or both (**39**) aldehyde groups, while MMA **1**, regardless of the amount of phosphorane, give only products of condensation (**40**) at both aldehyde groups, with the exception of **1** (R = 4-$MeOC_6H_4$), which behaves like MMA **2** and, depending on the amount of phosphorane, forms mono- (**41**) or dicondensation (**42**) products [56]:



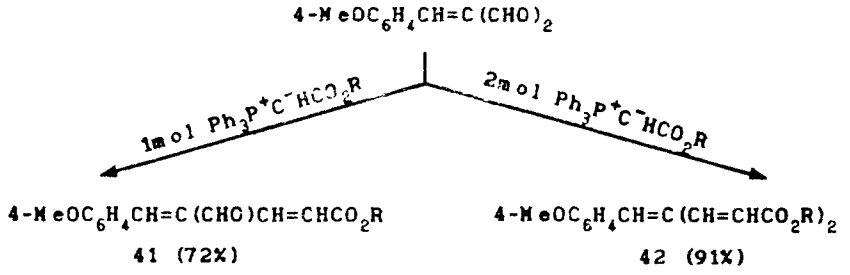


R^1,R^2 = Ph, Ph; 2-thienyl, Ph; Ph, 4-$MeOC_6H_4$

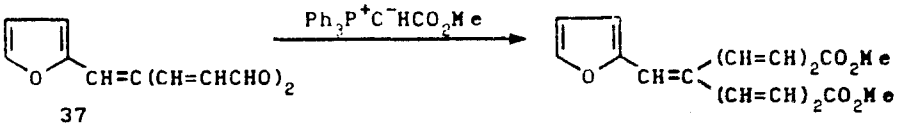
or

$$RCH{=}C(CHO)_2 + Ph_3\overset{+}{P}{-}\overset{-}{C}HCO_2R \longrightarrow \underset{40}{RCH{=}C(CH{=}CHCO_2R)_2}$$

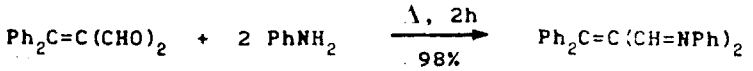
R = Ph, 2-thienyl, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4, PhCH=CH, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$



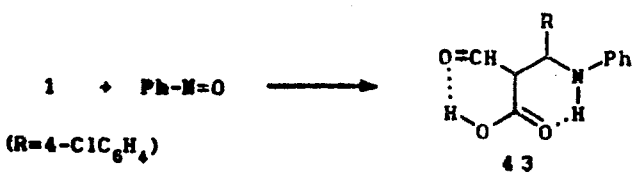
One can also make the transition to cross-conjugated esters by subjecting cross-conjugated aldehydes **37** to the Wittig reaction with carbomethoxymethylenetriphenylphosphorane [57]; the yields are 62-69%:



Methylenemalonic aldehydes (MMA) also undergo reaction at the aldehyde groups with primary amines; **1** forms complex mixtures, while aldehydes **2** give Schiff bases readily in high yields [22]:



Finally, a peculiar redox reaction occurs between MMA **1** and nitrosobenzene [10, 58] to give adduct **43** with a 1:1 composition:



CONCLUSION

It is apparent from the information set forth in this review that, starting from quite accessible methylenemalonic aldehydes of the **1** and **2** types, a number of new methods have been developed for the synthesis of difficult-to-obtain or previously inaccessible compounds that hold promise for use in precision organic synthesis, particularly in the synthesis of natural and physiologically active compounds. At the beginning of our review we mentioned the synthesis of cephalosporin C and its analogs, and one should also note that some alkylidenemalonic aldehydes have been used in situ in the synthesis of iridoids and secoiridoids, particularly secologanine monoterpenylglycoside — the key product in the biosynthesis of most indole, cinchonine, ipecacuine, and pyrroloquinoline alkaloids. A number of compounds obtained from secologanine are used as pharmaceutical

preparations, such as leucocrystine (vincristine) [59, 60], which have found application for the treatment of acute leukemia. It is apparent that MMA are particularly valuable in the synthesis of substituted malonic aldehydes and, chiefly, heterocycles (pyrans, dihydropyrans, dihydrofurans, dihydropyridines, isoxazoles, pyrazoles, oxadiazoles, diazepines, and many other systems).

LITERATURE CITED

1. Z. Arnold, *Coll. Czech. Chem. Comm.*, **25**, 1308 (1960).
2. Z. Arnold, *Coll. Czech. Chem. Comm.*, **25**, 1328 (1960).
3. Z. Arnold and A. Hóly, *Coll. Czech. Chem. Comm.*, **28**, 869 (1963).
4. Z. Arnold, *Coll. Czech. Chem. Comm.*, **26**, 3051 (1961).
5. Z. Arnold, *Coll. Czech. Chem. Comm.*, **25**, 1313 (1960).
6. R. B. Woodward, *Angew. Chem.*, **78**, 557 (1966).
7. R. B. Woodward, K. Heusler, J. Gosteli, et al., *J. Am. Chem. Soc.*, **88**, 852 (1966).
8. R. B. Woodward, French Patent No. 14,950,147; *Chem. Abstr.*, **69**, 51,640 (1968).
9. Z. Arnold, Summaries of Papers Presented at the 6th International Conference on Organic Synthesis [in Russian], Moscow (1986), pp. 12, 34.
10. Z. Arnold, *Organic Synthesis. Modern Trends and Reactivities. Methylenemalonic Aldehydes: Synthesis and Reactivity* [Russian translation], O. Chizov (ed.), Moscow (1987), p. 191.
11. G. A. Reinolds and J. A. Van Appau, *J. Org. Chem.*, **34**, 2736 (1969).
12. V. Dressler and K. Bodendorf, *Arch. Pharm.*, 481 (1970).
13. J. Ciernik, *Coll. Czech. Chem. Commun.*, **37**, 2273 (1972).
14. V. Král and Z. Arnold, *Synthesis*, No. 10, 823 (1982).
15. Z. Arnold, V. Král, and D. Dvořak, *Tetrahedron Lett.*, **23**, 1725 (1982) .
16. Z. Arnold, D. Dvořak, and V. Král, *Coll. Czech. Chem. Commun.*, **49**, 2602 (1984).
17. Z. Arnold, D. Dvořak, and V. Král, *Coll. Czech. Chem. Commun.*, **49**, 2613 (1984).
18. L. A. Yanovskaya, G. V. Kryshtal' (Kryshtal), D. Dvořak, et al., *Coll. Czech. Chem. Commun.*, **50**, 1306 (1985).
19. L. A. Yanovskaya, G. V. Kryshtal' (Kryshtal), D. Dvořak, et al., *Coll. Czech. Chem. Commun.*, **50**, 2270 (1985).
20. Z. Arnold, G. V. Kryshtal' (Kryshtal), V. Král, et al., Abstracts of the Poster Session of the 2nd Belgian Organic Synthesis Symposium, A. 4, Brussels (1988).
21. D. Dvořak, G. V. Kryshtal' (Kryshtal), V. Kryshtal' (Kryshtal), V. Král, et al., Chech. Autorske Osvedceni, No. 240,371; *Chem. Abstr.*, **111**, 94,515 (1989).
22. V. Král, L. Jelinek, and D. Šaman, *Coll. Czech. Chem. Commun.*, **54**, 2721 (1989).
23. J. Kučera and Z. Arnold, *Coll. Czech. Chem. Commun.*, **32**, 1704 (1967).
24. D. Lloid and H. McNab, *Angew. Chem.*, **88**, 1704 (1976).
25. G. Scheibe, C. Jutz, Seifert, et al., *Angew. Chem.*, **76**, 270 (1964).
26. G. V. Kryshtal', V. Král, D. Dvořak, et al., *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 9, 2172 (1990).
27. Z. Arnold, *Coll. Czech. Chem. Commun.*, **30**, 2125 (1965).
28. Z. Arnold, G. V. Kryshtal' (Kryshtal), V. Král, et al., *Tetrahedron Lett.*, **29**, 2861 (1988).
29. C. Reichardt, W. Pressler, and E. I. Würthewein, *Angew. Chem.*, **88**, 88 (1976).
30. C. Reichardt and K.-Y. Yun, *Tetrahedron Lett.*, **23**, 3163 (1982).
31. C. Reichardt, K.-Y. Yun, W. Massa, et al., *Ann.*, No. 10, 1987 (1985).
32. C. Reichardt and K.-Y. Yun, *Angew. Chem.*, **94**, 69 (1982).
33. C. Reichardt, K.-Y. Yun, W. Massa, et al., *Ann.*, No. 10, 1980 (1985).
34. O. Polansky, P. Schuster, and F. Weselly, *Tetrahedron*, Suppl. 8, 2 (1966).
35. C. F. Bernasconi and M. W. Stronach, *J. Org. Chem.*, **51**, 2144 (1986).
36. C. F. Bernasconi and G. B. Leonardussi, *J. Am. Chem. Soc.*, **104**, 5133 (1982).
37. V. Král, R. Laatikainen, and Z. Arnold, *Tetrahedron*, **41**, 4919 (1985).
38. E. Kohenaine, R. Laaitikanen, and V. Král, *Magn. Reson. Chem.*, **41**, 498 (1986).
39. T. A. Pakkanen, V. Navalinen, V. Král, et al., *Coll. Czech. Chem. Commun.*, **52**, 714 (1987).
40. R. Laatkainen and V. Král, *J. Chem. Soc., Perkin* 2, No. 8, 1091 (1985).

41. D. Dvořak and Z. Arnold, *Tetrahedron Lett.*, **23**, 4401 (1982).
42. G. V. Kryshtal', D. Dvořak, Z. Arnold, et al., *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 11, 2614 (1987).
43. D. Dvořak and Z. Arnold, *Nucl. Acid Res. Symp. Ser.*, No.14 (31).
44. D. Dvořak, D. Šaman, J. Hodačova, et. al., *Coll. Czech. Chem. Commun.*, **52**, 2687 (1987).
45. D. Dvořak, Z. Arnold, and V. Král, *Proceedings of the 9th Symposium of the Chemistry of Heterocyclic Compounds*, Bratislava, Czechoslovakia (1987), Elsevier, Amsterdam (1988).
46. Z. Arnold, V. Král, G. V. Kryshtal', et al., *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 9, 2162 (1985).
47. Z. Arnold, G. V. Kryshtal' (Kryshtal), V. Král, et al., *Synthesis*, No. 11, 974 (1984).
48. K. Ya. Burshtein, G. V. Kryshtal', and L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 6, 1422 (1985).
49. R. O. Agnus, N. R. Bryce, and Z. Kheschavar, *Synthesis*, No. 9, 746 (1988).
50. Z. Arnold and D. Dvořak, *Coll. Czech. Chem. Commun.*, **50**, 2265 (1985).
51. V. Král, L. Jellinek, and D. Šaman, *Coll. Czech. Chem. Commun.*, **54**, 2721 (1989).
52. D. Dvořak and Z. Arnold, *Coll. Czech. Chem. Commun.*, **52**, 2699 (1987).
53. P. Safář and J. Covač, *Coll. Czech. Chem. Commun.*, **54**, 2433 (1989).
54. D. Dvořak, D. Šaman, M. Buděšsinský, et al., *Coll. Czech. Chem. Commun.*, **52**, 2926 (1987).
55. P. Kocovsky and D. Dvořak, *Coll. Czech. Chem. Commun.*, **53**, 2667 (1988).
56. G. V. Kryshtal', D. Dvořak, Z. Arnold, et al., *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 4, 921 (1986).
57. Z. Arnold, V. Král, G. V. Kryshtal', et al., *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 2, 457 (1984).
58. D. Dvořak, M. Buděšsinský, D. Šaman, et al., *Coll. Czech. Chem. Commun.*, **50**, 2260 (1985).
59. L. F. Tietze, K. H. Glüsenkamp, and W. Rolla, *Angew. Chem.*, **94**, 793 (1982).
60. L. F. Tietze, *Angew. Chem.*, **95**, 841 (1983).