Russian Chemical Reviews **83** (7) 620 – 637 (2014) © 2014 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2014v083n07ABEH004441

Acyl Meldrum's acid derivatives: application in organic synthesis

K Janikowska, J Rachoń, S Makowiec

Faculty of Chemistry, Gdansk University of Technology
Narutowicza 11/12, 80-233 Gdansk, Poland

This review is focused on an important class of Meldrum's acid derivatives commonly known as acyl Meldrum's acids. The preparation methods of these compounds are considered including the recently proposed and rather rarely used ones. The chemical properties of acyl Meldrum's acids are described in detail, including thermal stability and reactions with various nucleophiles. The possible mechanisms of these transformations are analyzed.
The bibliography includes 134 references.

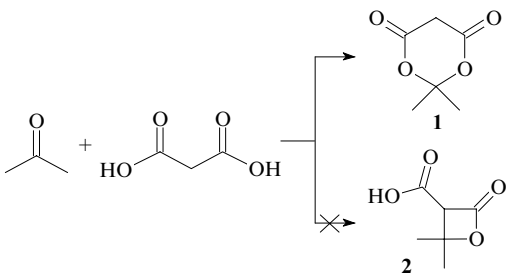
Contents

I. Introduction 620
II. Preparation of acyl Meldrum's acid derivatives 621
III. Properties of acyl Meldrum's acid derivatives 623
IV. Reactivity of acyl Meldrum's acid derivatives 627
V. Conclusion 635

I. Introduction

2,2-Dimethyl-4,6-dioxo-1,3-dioxane **1** is a very useful reagent in the synthesis of heterocyclic compounds. This molecule is commonly known as Meldrum's acid with the name from its discoverer, Scottish scientist Andrew Norman Meldrum. It was synthesized in 1908 by the reaction between acetone and malonic acid in the presence of acetic anhydride and sulfuric acid (Scheme 1).[1] Taking into account the results of elemental analysis and the acidity ($pK_a = 4.83$ in water)[2,3] of the final compound, Meldrum misidentified its structure as the β-lactone of β-hydroxyisopropylmalonic acid (β,β-dimethyl-α-carboxy-β-propiolactone **2**). Only 40 years later, Davidson and Bernhard determined the correct structure of Meldrum's acid **1**.[4] This structure was finally confirmed in 1985 when the first crystal structure analysis of Meldrum's acid was carried out.[5] In addition, this investigation established the boat conformation of the six-membered ring of Meldrum's acid, which had been previously postulated based on the measured dipole moment.[6,7]

Scheme 1



Despite the fact that more than 100 years has passed from the discovery of Meldrum's acid, this reagent is still very important and popular in organic synthesis. It can react with various electrophiles at C(5) and nucleophiles at C(4) and C(6) atoms. It has been used as a reactant in the synthesis and design of a vast range of organic compounds having utility in the context of drugs and pharmaceuticals. The chemistry of Meldrum's acid and its derivatives has been described in comprehensive reviews[8–10] and in one very short review.[11] There are also some specialized subject reviews, like for example: Meldrum's acid in the synthesis of natural products,[12] Meldrum's acid in domino and multicomponent reactions,[13–15] Meldrum's acid in catalytic carbon–carbon bond forming processes[16] and Meldrum's acids in flash vacuum pyrolysis techniques.[17–19] The current review is focused solely on the chemistry of an important class of Meldrum's acid derivatives, acylated Meldrum's acids.

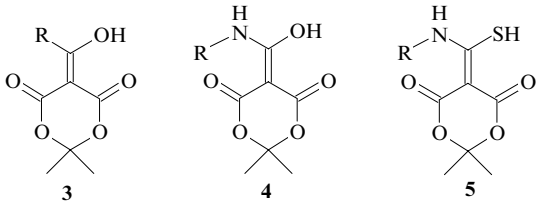
K.Janikowska Ph.D., assistant of the Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology.
Telephone: (48-58) 347 28 83,
e-mail: karolina.janikowska@pg.gda.pl
Current research interests: organic synthesis, asymmetric synthesis.
J.Rachoń Professor of the same Department.
Telephone: (48-58) 347 12 34, e-mail: januszrachon@pg.gda.pl
Current research interests: reaction mechanisms, organosulfur chemistry, organophosphorus chemistry.
S.Makowiec Ph.D., adjunct of the same Department.
Telephone: (48-58) 347 28 83, e-mail: mak@pg.gda.pl
Current research interests: reaction mechanisms, organic synthesis, organic conductors.

Received 5 November 2013
Uspekhi Khimii **83** (7) 620 – 637 (2014)

II. Preparation of acyl Meldrum's acid derivatives

A group of acylated Meldrum's acids is presented below, namely, 5-[alkyl(aryl)(hydroxy)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (parent acyl Meldrum's acid **3**), 5-[alkyl(aryl)amino(hydroxy)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (carbamoyl Meldrum's acid **4**) and 5-[alkyl(aryl)amino(sulfanyl)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (thiocarbamoyl Meldrum's acid **5**).

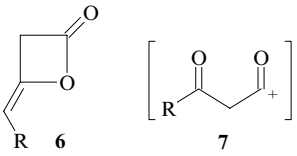
Structures 3–5



R = Alk, Ar

Owing to the formation of intramolecular hydrogen bonds, all of acyl Meldrum's acid derivatives exist in aprotic solvents (CDCl3, DMSO) mainly in their enol form.[20–22] Another characteristic feature of these compounds is their thermal instability. Thermolysis of acyl Meldrum's acids leads to the corresponding ketenes, acetone and carbon dioxide.[23] 5-Acyl Meldrum's acids **3** can serve as synthetic equivalents of mixed diketenes **6**,[24] which are usually not available. Alcoholysis of compounds **3** provides easy preparation of acylacetyc acids containing moiety **7**.

Structures 6, 7



R = Alk, Ar

In contrast to the typical acyl Meldrum's acid **3**, carbamoyl **4** and thiocarbamoyl **5** Meldrum's acids are poorly described in the chemical literature. Compared with acyl Meldrum's acids **3**, carbamoyl and thiocarbamoyl derivatives are characterized by higher stability and slower thermolysis.[22] This is because of the presence of two (instead of one) intramolecular hydrogen bonds in their molecules. Preparation methods of compounds **3**, **4** and **5** are also different.

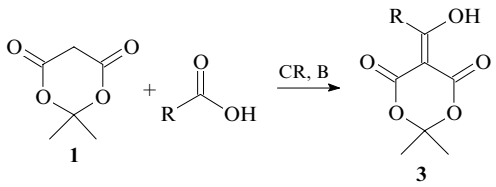
The preparation of 5-acyl Meldrum's acid derivatives was shortly described in general reviews.[8,9] This review provides additional main and less popular procedures for obtaining this class of compounds, special attention being paid to new methods.

1. Synthesis from carboxylic acids and their derivatives

a. Preparation from carboxylic acids

One of the most common method for the synthesis of 5-acyl derivatives **3** is the reaction between Meldrum's acid (**1**) and carboxylic acid with coupling reagents (CR) such as dicyclohexylcarbodiimide (DCC),[25] isopropenyl chloroformate (IPCF)[26] or diethyl cyanophosphonate (DEPC)[27] in the presence of a base (Scheme 2).

Scheme 2



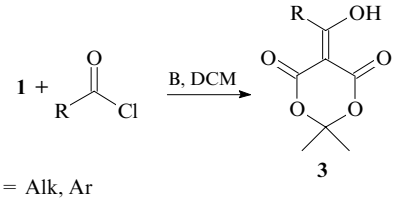
R = Alk, Ar; B is base

Using this method it is also possible to synthesize N-protected-α-amino-5-acyl Meldrum's acids, which can serve as substrates in the synthesis of tetramic acids.[28] However, in the case of acid-labile N-protecting groups like, for example, Boc, significant self-decomposition of **3** is observed.[25] Up to 24% of BocGlu derivative of Meldrum's acid decomposes within 6 month at room temperature.[27] This instability is attributed to the acidic nature of **3**, and therefore an alternative protocol for preparation of N-Boc-α-amino-acyl Meldrum's acid was developed by Baer and co-workers.[28] The carboxylic acid was treated with equimolar amounts of DCC and 4-dimethylaminopyridine (DMAP), and after the reaction, the product was isolated as a DMAP salt. The free acid **3** was released using ion exchange resin immediately before subsequent reactions.[28]

b. Preparation from acyl halides

The first 5-[alkyl(aryl)(hydroxy)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-diones were prepared by Yonemitsu and co-workers[24] in 1978 by the reaction between Meldrum's acid and acyl chlorides in dichloromethane (DCM) in the presence of pyridine (Py) (Scheme 3). This method is still a common way to synthesize 5-acyl Meldrum's acids.[29] The ^{1}H NMR spectrum of the final products exhibited only single signals corresponding to the enol forms of these compounds (enolization of acyl Meldrum's acid derivatives became a subject of many publications[20–22]). Instead of pyridine, other bases like, for example, DMAP can be used.[30,31]

Scheme 3

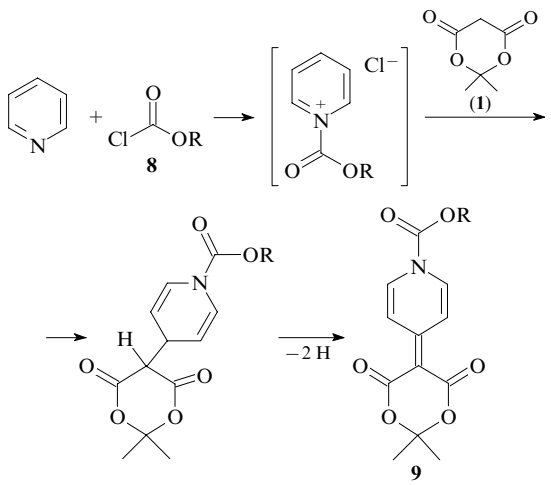


R = Alk, Ar

Moreover, in place of acyl chlorides, it is also possible to use acyl bromides.[32] A major drawback of the method proposed by Yonemitsu is the limitation to use only alkyl acid halides. In the case of aromatic acid halides, it is necessary to replace pyridine by DMAP; nonetheless, the yield of the product obtained is still lower than when the method with carboxylic acids is applied.[33]

In 1992 Henning *et al.*[34] noticed that if alkyl chloroformates **8** are used as acylating agents in the reaction proposed by Yonemitsu, the reaction mechanism completely changes. In this case, 5-[1-alkoxycarbonyl-4(1*H*)-pyridinylidene]-1,3-dioxane-4,6-dione (**9**) is formed (Scheme 4).

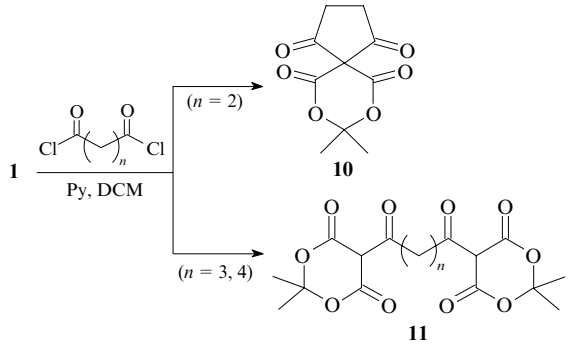
Scheme 4



R = Me, Et, Bu^{i}, Bu^{s}, All

Bis-acylation of Meldrum's acid is very difficult, because of enolization of the monoacylated compound. Nevertheless, it is possible to obtain cyclic bis-acylated Meldrum's acid **10** by the reaction of Meldrum's acid with succinic acid dichloride (Scheme 5). With higher homologues such as glutaryl and adipyl dichlorides, dimeric products **11** are predominantly formed (see Scheme 7).[35]

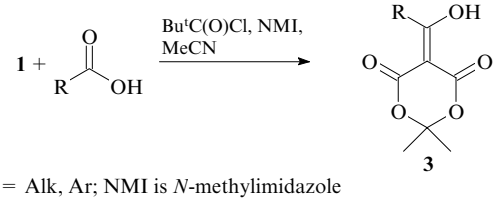
Scheme 5



c. Preparation from mixed carboxylic anhydrides

Methods for the synthesis of acyl Meldrum's acids based on the reaction of mixed carboxylic anhydrides with Meldrum's acid in the presence of a base were also reported in the literature. Mixed anhydrides in this transformations are usually obtained *in situ* by treating carboxylic acid with pivaloyl chloride (Scheme 8).[36–38]

Scheme 6

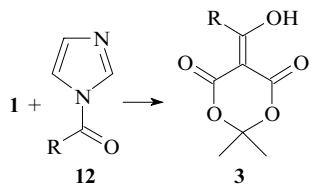


R = Alk, Ar; NMI is *N*-methylimidazole

d. Preparation from acyl imidazoles

Upon the addition of 1,1′-carbonyldiimidazole (CDI) to a reaction mixture composed of Meldrum's acid and carboxylic acid, acyl imidazolide **12** is formed *in situ*. This compound can also serve as a very good acylating agent for the preparation of acyl Meldrum's acids (Scheme 7).[39,40]

Scheme 7

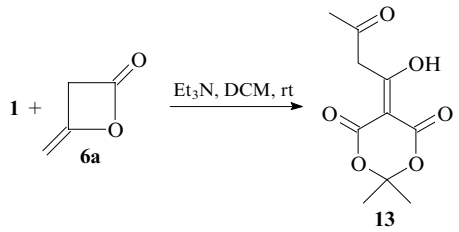


R = Alk, Ar

2. Synthesis from diketenes

Diketene **6a** is one more commercially available acylating agent. It reacts with Meldrum's acid at room temperature in the presence of triethylamine and DCM to give 5-(1-hydroxy-3-oxobutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**13**) (Scheme 8).[41–43]

Scheme 8

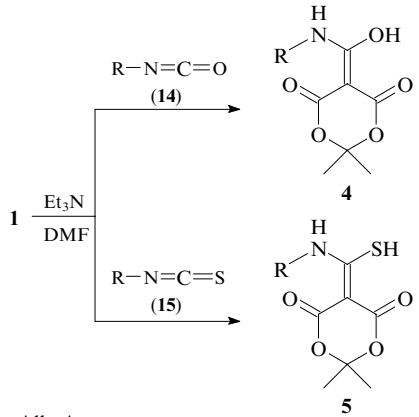


rt is room temperature

3. Synthesis from isocyanates

Carbamoyl (**4**) and thiocarbamoyl (**5**) Meldrum's acid derivatives are obtained by reactions of Meldrum's acid with isocyanates **14**.[20,21,44–47] and isothiocyanates **15**[20,48] (Scheme 9). The synthesis is usually carried out in DMF in the presence of triethylamine. Aryl isocyanates react with Meldrum's acid at room temperature in almost quantitative yield, while alkyl isocyanates react much more slowly under the same conditions. Despite the long reaction time (60 to 72 h), no by-products are formed.[47]

Scheme 9



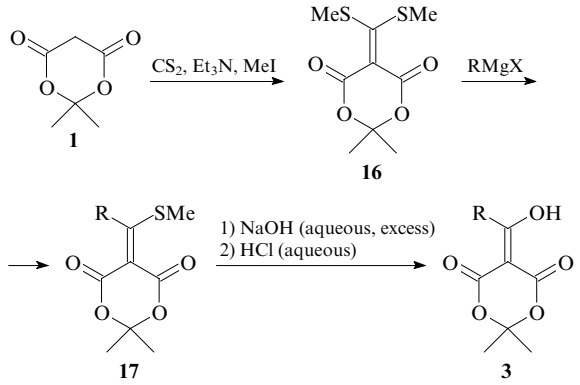
R = Alk, Ar

4. Synthesis from 5-[bis(methylsulfanyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione

The 5-[bis(methylsulfanyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**16**) is usually prepared in one-pot process by the reaction of Meldrum's acid with carbon disulfide and triethylamine with subsequent treatment with methyl

iodide.[49] The reaction of Grignard reagents with compound **16** affords α-alkyl(aryl)-α-(methylsulfanyl)methylidene Meldrum's acids **17**.[50, 51] Compounds **17** can be saponified to give acyl Meldrum's acids **3** (Scheme 10).[50, 52–54]

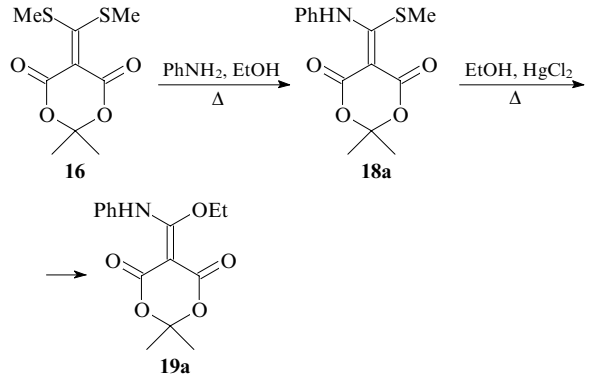
Scheme 10



R = Alk, Ar

The reaction of compound **16** with aryl or alkyl amines in boiling EtOH leads to the formation of 5-[alkyl(aryl)amino](methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **18**.[53, 55] These compounds react with alcohols in the presence of $HgCl_2$ to give 5-[alkyl(aryl)amino]alkoxymethylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **19**, which are O-alkylated carbamoyl Meldrum's acid derivatives.[53] As an example, Scheme 11 shows the reaction with phenylamine and ethanol, which gives compounds **18a** and **19a**.

Scheme 11

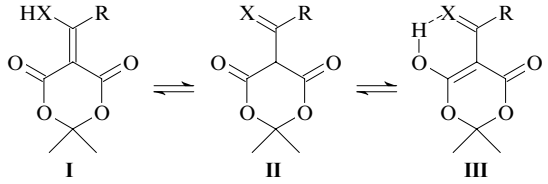


III. Properties of acyl Meldrum's acid derivatives

1. Enolic structure of acyl Meldrum's acids

The acyl Meldrum's acids represent a specific kind of compounds having formally an active methine hydrogen surrounded by three electron-withdrawing groups. Such a constitution allows for existence of various tautomeric forms. Generally, three tautomeric forms **I**–**III** should be considered (Scheme 12). Rappoport and co-workers[21, 22] have performed a thorough study of the tautomeric equilibrium of carboxylic acid amides (carbamoyl Meldrum's acids) by NMR spectroscopy and X-ray diffraction analysis. First, they excluded the existence of structure **II** since the ^1H NMR spectrum ($CDCl_3$) exhibits two broad singlets at 11.16 ppm from NH and at 15.70 ppm from OH. The ^{13}C NMR spectra also did not confirm the presence of methine carbon (C_β) with a large coupling constant, which also excludes structure **II**. Naturally, X-ray diffraction data provide the strongest arguments, and they point to structure **I** with a $C_\alpha-C_\beta$ bond lengh of 1.426(5) Å, which is longer than a double and shorter than a single C–C bond; a C–N bond length of 1.333 Å typical of enamines; and finally the length of 1.300 Å for side-chain carbonyl groups, which is close to a single C–O bond as expected for structure **I**.[21, 22]

Scheme 12



X = S, O; R = Alk, Ar, RNH, ArNH

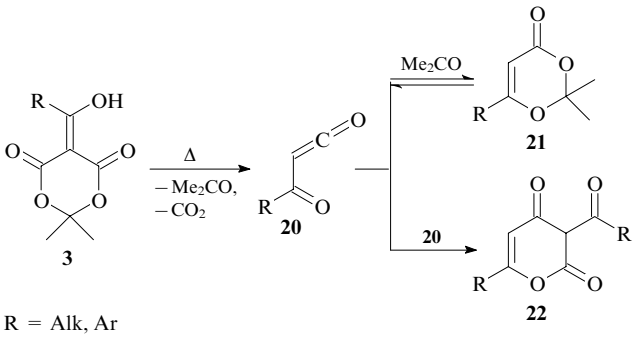
The same research group has studied similar equilibria of thioenols and thioamides substituted by two electron-withdrawing groups. In the case of thiocarbamoyl Meldrum's acids, on the basis of X-ray data, a thioenol structure was established with the $C_\alpha-C_\beta$ bond lengh of 1.425(3) Å, which is very close to the oxygen analogue, the C–N bond of 1.324 Å, which is typical of enamines, and the C–S bond lengh of 1.739 Å, which is close to a typical single C–S bond.

It should be stressed that acyl Meldrum's acid derivatives represent a unique type of non-aromatic compounds in which the enol form predominates, especially in the case of carbamoyl and thicarbamoyl Meldrum's acids, which are rare examples of stable enol forms of amides and thioamides.

2. Pyrolysis of acyl Meldrum's acid derivatives

Pyrolysis of Meldrum's acid derivatives is well known and is widely used. Thermal decomposition of acyl Meldrum's acid derivatives leads to the formation of oxoketenes **20**, CO_2 and acetone.[56–59] Also, the formation of 1,3-dioxin-4-ones **21** and oxoketene [4+2]-dimer is possible (Scheme 13).[58, 59] The formation of compounds **21** is reversible. Oxoketenes serve as key intermediates in the synthesis of various products formed upon reactions with nucleophiles.[56, 57]

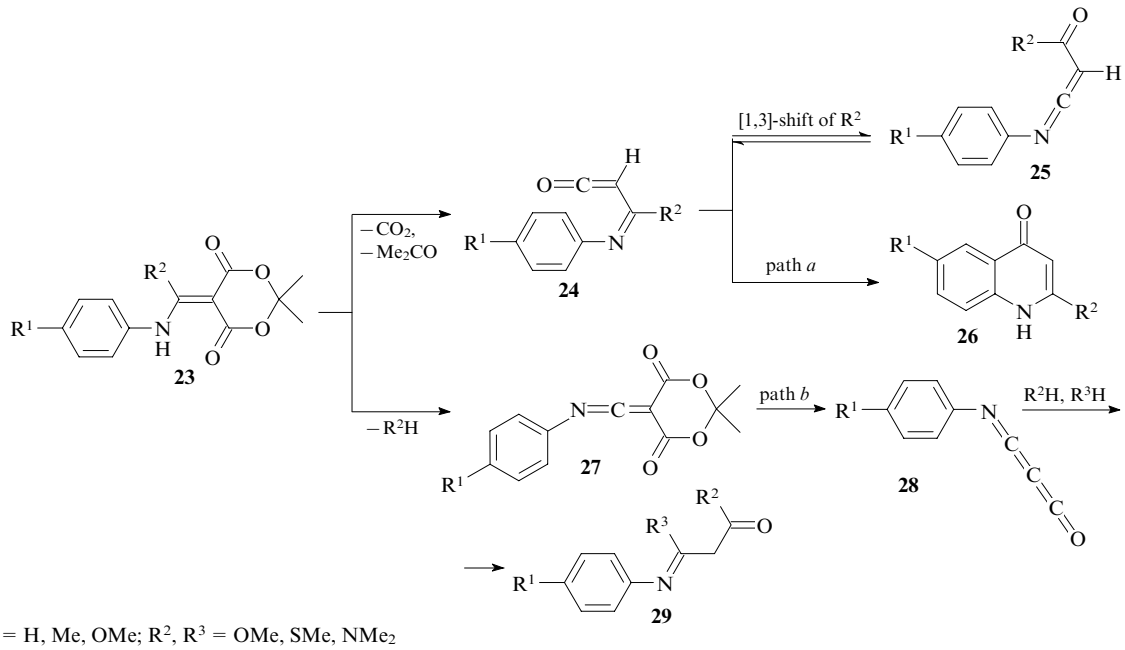
Scheme 13



R = Alk, Ar

One of special methods used for the thermal decomposition of Meldrum's acid derivatives is flash vacuum pyrolysis (FVP).[19] In this technique, acyl Meldrum's acid is heated to temperatures higher than 400 °C during a short

Scheme 14



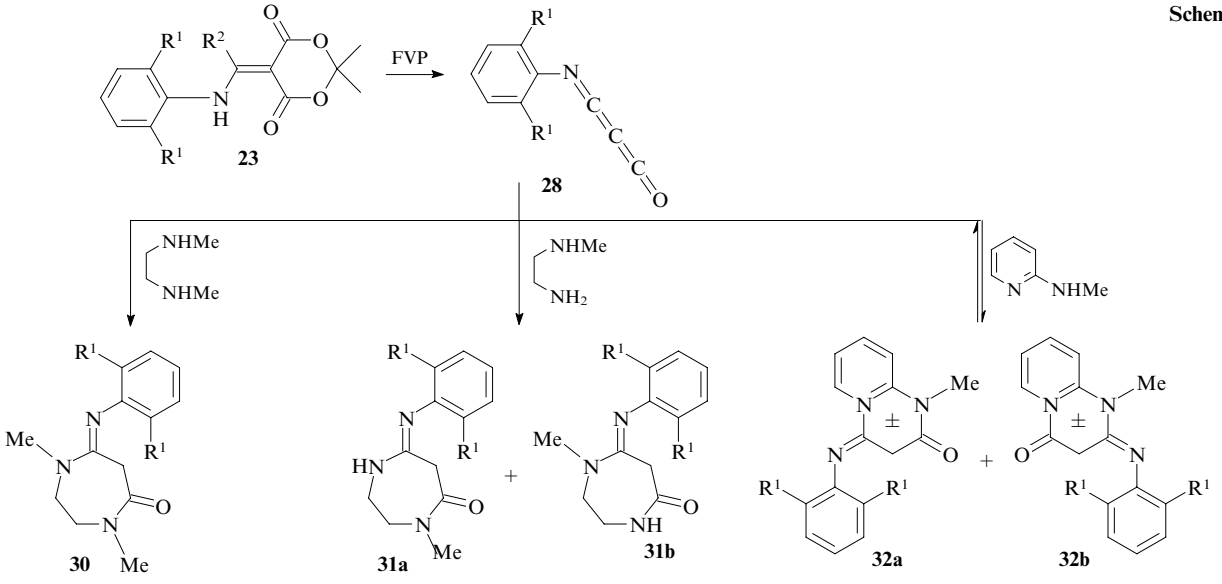
R^1 = H, Me, OMe; R^2, R^3 = OMe, SMe, NMe_2

period under reduced pressure (1 Pa). Under these conditions, the listed intermediates are not trapped by nucleophiles and can be frozen in an argon matrix for subsequent spectroscopic analysis.[60, 61]

In the case of carbamoyl derivatives of Meldrum's acids, thermolysis process is much more complicated with a broad range of possible products. Wentrup and co-workers [23] found that the product distribution for the thermolytic reaction of carbamoyl Meldrum's acid depends on types of substitution in the Meldrum's acid derivative as well as on the reaction conditions. Series of FVP experiments performed on compound **23** supported by the IR spectroscopic study of the products provided interesting results. In lower temperature range (200 – 360 °C), the formation of ketene **24** together with ketimine **25** resulting from its rearrangement was mainly observed. The final product of this reaction route was quinolone **26**. Higher temperatures (400 – 600 °C) promoted an alternative reaction pathway through initial formation of ketimine **27**, which eliminated acetone and CO_2 to form aryliminopropadienone **28**. The latter can be trapped by methanol or other nucleophilic species present in the reaction mixture to yield compound **29** (Scheme 14). Note that for $R^2 = NMe_2$, pathway *b* becomes predominant at temperatures as low as 300 °C.[23]

Aryliminopropadienones generated from various precursors including also carbamoyl Meldrum's acid derivatives have found a synthetic application. Reactions of compounds **28** with bis-nucleophiles afford perhydrodiazepines **30** and **31a**,**b** as well as pyridopyrimidine derivatives **32a**,**b**, which itself can be a source of aryliminopropadienones (Scheme 15).[62]

Scheme 15

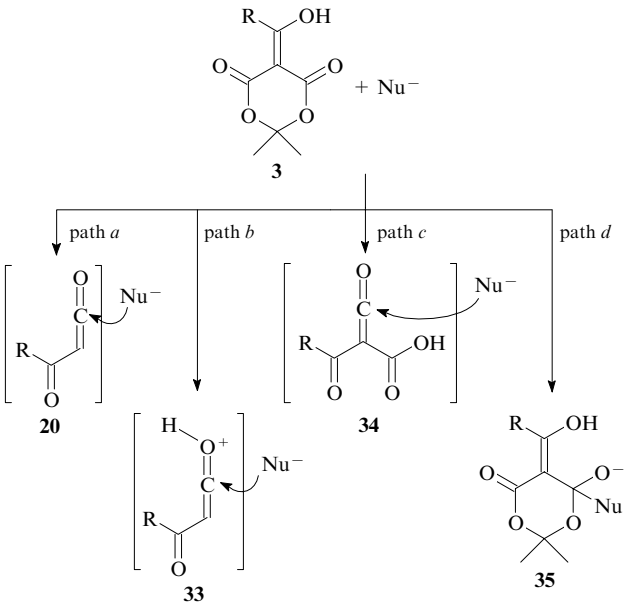


R^1 = F, Et; R^2 = OMe, SMe, NMe_2

3. Reactions with nucleophiles: mechanistic consideration

Acyl Meldrum's acid derivatives may react with a variety of nucleophiles. This can be used to obtain various heterocyclic compounds such as β-lactams,[46, 63] 1,3-oxazinones,[33] pilicides,[30, 64] isoxazololes,[29] tetramic acid derivatives,[65] cyclic nitrones,[66, 67] analogues of prodigiosin family antibiotics[68] and substituted pyridines.[69] Also valuable noncyclic 1,3-dicarbonyl compounds can be easily synthesized using acylated Meldrum's acids. We can cite, for example, 1,3-diones,[70] keto esters,[71–73] and keto amides.[74, 75] The mechanism of formation of final products in the nucleophilic reactions of acyl Meldrum's acids depends on the reactants and reaction conditions. Despite numerous attempts to study this mechanism, it still remains a matter of controversy. In the chemical literature, one can find four proposed routes of the reaction between acyl Meldrum's acids and nucleophiles (Scheme 16). These include intermediate formation of α-oxoketenes **23** (path *a*), protonated α-oxoketenes **33** (path *b*), non-decarboxylated α-oxoketenes **34** (path *c*) and a mechanism *via* addition–elimination of the nucleophile to give acyl Meldrum's adduct **35** (path *d*).

Scheme 16



R = Alk, Ar; Nu^- is nucleophile

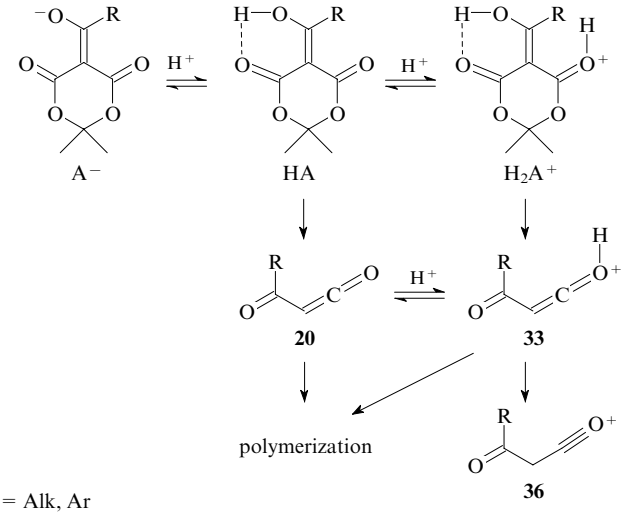
As mentioned above, the formation of α-oxoketenes **20** from the corresponding Meldrum's acid derivatives was observed upon thermolysis, which was carried out in boiling diphenyl ether (259 °C)[76] or under flash vacuum pyrolysis condition (600 °C, 0.01 Torr).[57, 60]

The major route of reactions of Meldrum's acid derivatives with nucleophiles is connected with the tendency of the latter to form ketenes upon thermal decomposition. Once formed, ketene may react with various types of nucleophiles. When the nucleophile is an alcohol or amine, the ketene simply forms an SN-acylated product. When the nucleophile is an imine, vinyl ether or another π-electron system, [4 + 2]- or [2 + 2]-cycloaddition reactions can occur.

In 2004, Grabowski *et al.*[38] postulated the mechanism of decomposition of acylated Meldrum's acid **3** *via* α-oxoketenes **20** (path *a*, Scheme 16). They undertook a detailed mechanistic study of the synthesis of β-ketoamides from acyl Meldrum's acids and various amines. The essential task for this study was to determine the Meldrum's acid form (anionic or free acid), which was achieved using IR spectroscopy. It was found that acyl Meldrum's acids are unstable in acidic media at ambient temperature but are stable in basic solutions. The observations suggested that decarboxylation/amination of acyl Meldrum's acids required acidic medium to achieve optimal results; hence, the free acid form of acyl Meldrum's acid HA is the reactive intermediate, whereas the anionic form A^- is not responsible for nucleophilic addition or decomposition.

Grabowski and co-workers[38] first studied the kinetics of decomposition of acyl Meldrum's acid in the absence of nucleophiles in order to check the influence of acids or bases on the reaction rate and then studied the decomposition of acyl Meldrum's acid in the presence of various nucleophiles. They proposed a reaction mechanism according to which decomposition can proceed *via* α-oxoketene **20** or *via* protonated α-oxoketene **33**, which can subsequently rearrange to its tautomeric form **36** (Scheme 17).

Scheme 17



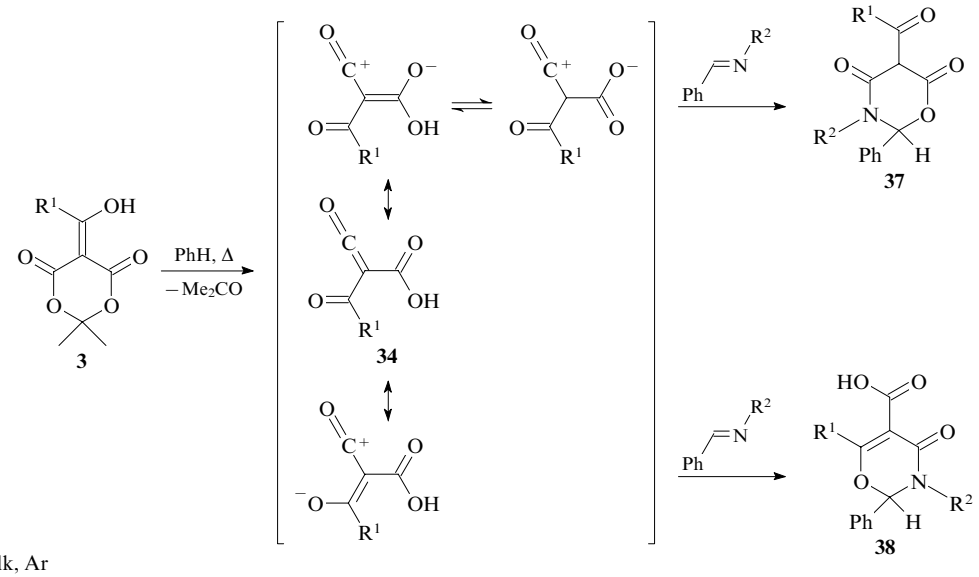
R = Alk, Ar

During the experiments they obtained results that strongly suggested the first order for decomposition reaction with respect to HA. Meanwhile, from the chemical literature concerning the stability of ketenes, it is well known[57, 77] that acylium ion **36** is lower in energy than the protonated α-oxoketene **33**. Moreover, protonation of oxoketene **20** to compound **33** has a high energy barrier making this process unlikely.

In the presence of nucleophilic species, the alternative pathway of the reaction should be taken into consideration in which the addition of nucleophile to the carbonyl carbon of the 1,3-dioxa-4,6-dione ring is the rate limiting step. In this case, the reaction rate should depend on the [HA] and nucleophile concentrations. However, the kinetic studies of the decomposition of Meldrum's acid performed in the presence of nucleophiles, for example BocNHOBoc, indicated again a first-order kinetics with respect to HA.

Therefore, considering the results obtained by the Grabowski group, it should be emphasized that irrespective of the presence or the absence of a nucleophile as well as irrespective of the acidic or basic properties of the reactants, the reaction always proceeds *via* α-oxoketene intermediate **20**.

Scheme 18



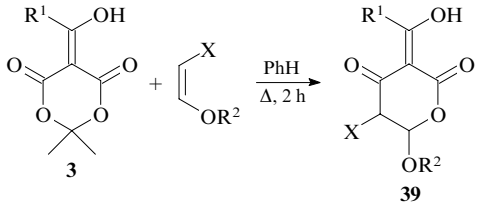
R^1, R^2 = Alk, Ar

An alternative mechanism for the reaction of acyl Meldrum's acid with nucleophiles was proposed by Almqvist and co-workers.[30] They observed the formation of 2-pyridinones in the reaction of acyl Meldrum's acid with thioazolines in the presence of gaseous HCl. The aurthors postulated the formation of protonated α-oxoketene **33** as an intermediate in this transformation. However, this mechanism has never been proven experimentally (see path *b*, Scheme 16).[30]

However, if a nucleophile is able to react with acyl Meldrum's acid derivative before it can be converted to a corresponding ketene intermediate **20** or **33**, then the reaction pathway has to be different. For instance, Yamamoto and Watanabe[33,63] used the reaction of acyl Meldrum's acid with imines to synthesize 1,3-oxazinediones **37** and oxazin-4-ones **38** (Scheme 18). The structure of the products obtained ruled out the possibility of formation of α-oxoketene **20** or protonated α-oxoketene **33** intermediates in the reaction medium (in this case, β-lactams should have formed). To explain the formation of compounds **37** and **38** and the fact that decarboxylation did not occur throughout the reaction time, the authors proposed a mechanism including the intermediate formation of non-decarboxylated α-oxoketene **34** or its zwitterionic tautomer (path *c* in Scheme 16, Scheme 18).

Similarly, Zawacki and Crimmins[78] have observed that treatment of acyl Meldrum's adducts with vinyl ethers in refluxing benzene results in the formation of pyrandiones **39** rather than pyranones, which would be formed if the reaction proceeded *via* the ketene intermediate (Scheme 19).

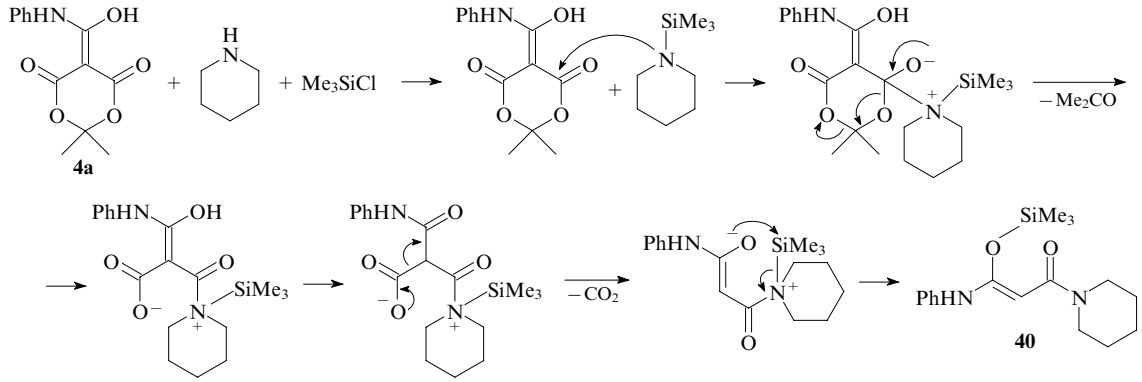
Scheme 19



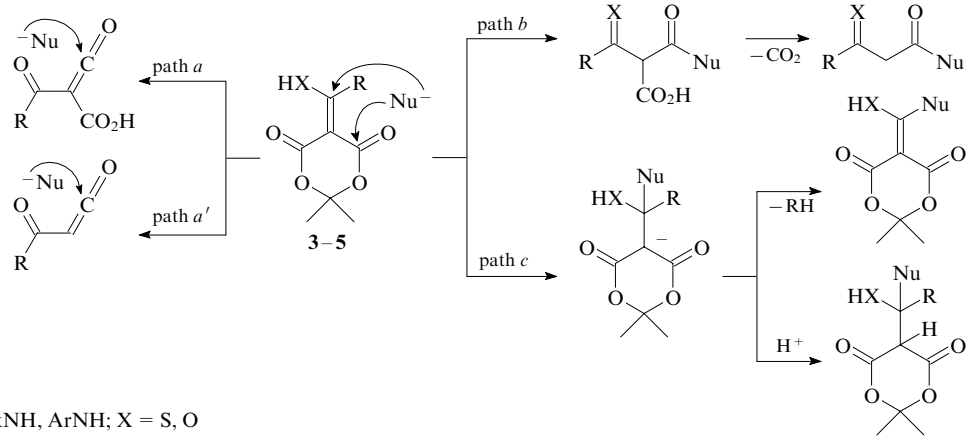
R^1 = Alk, Ar; R^2 = Alk; X = H, Alk

Our own research seems to indicate that the reaction of acyl Meldrum's acid with nucleophiles may take places even before the loss of acetone and carbon dioxide through the addition–elimination mechanism (see path *d* in Scheme 16).[79] In the reaction of carbamoyl Meldrum's acid **4a** with amines in the presence of trimethylsilyl chloride (TMSCl), we observed high yields and reduction of the reaction time in the synthesis of unsymmetrical malon-

Scheme 20



Scheme 21



R = Alk, Ar, AlkNH, ArNH; X = S, O

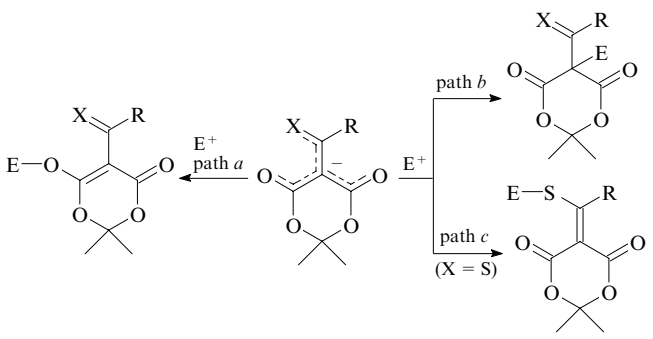
amides **40**. It was found that the formation of *N*-trimethylsilylated amines is directly responsible for this acceleration. In addition, we have noticed that TMSCl has no influence on the rate of decompostion of carbamoyl Meldrum's acid derivative. All these facts strongly suggest that *N*-trimethylsilylated amines react with carbamoyl Meldrum's acid derivatives according to the addition–elimination mechanism rather than *via* the formation of free ketenes as in the reaction with non-silylated amines (Scheme 20).[79]

IV. Reactivity of acyl Meldrum's acid derivatives

Acyl Meldrum's acid as a multifunctional molecule has a wide range of possibilities to react with both nucleophiles and electrophiles. Most explored and having the broadest variety of synthetic applications is the thermal decomposition to give ketene type of species, which can subsequently react with nucleophiles (paths *a*, *a*′ in Scheme 21). As noted above, acyl Meldrum's acid can also react with nucleophilic reagents before the loss of acetone and CO_2. In this situation, two alternatives exist, the first one being a nucleophilic attack on the carbonyl carbons of the 1,3-dioxane-4,6-dione system followed by ring opening (path *b*). The second, more frequently observed possibility is the nucleophilic attack on the β-carbon of the conjugated vinyl bond (path *c*), which may lead to reduction or substitution in the side chain of the molecule.[53]

The last but not negligible opportunity is the electrophilic attack on the anionic form of acyl Meldrum's acid (Scheme 22). Here, three possible scenarios should also be considered: an attack on the carbonyl oxygen of the 1,3-dioxane-4,6-dione ring (path *a*), the reaction of an electrophile with the methine carbon atom (path *b*)[80] and, in the case of thiocarbamoyl Meldrum's acids, alkylation of sulfur in the side chain (path *c*).[81]

Scheme 22

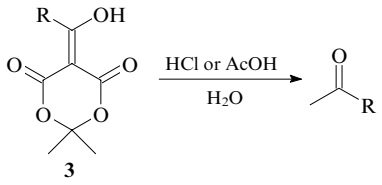


R = Alk, Ar, AlkNH, ArNH; X = S, O; E^+ is electrophile

1. Reactions with acids

The reactions of acyl Meldrum's acid with dilute acids such as HCl or HOAc provide an efficient synthesis of the corresponding methyl ketones, important intermediates in many organic transformations (Scheme 23).[82,83] Currently, a number of methods for the preparation of methyl ketones are known, for example, alkylation of acetone derivatives, palladium-catalyzed oxidation of 1-olefins,[84,85] synthesis from olefins and acetylenes using mercury compounds.[86,87] The synthesis from acyl Meldrum's acid derivatives is one of the non-organometallic alternatives and easy going methods, which can be carried out under mild conditions.

Scheme 23



R = Alk, Ar

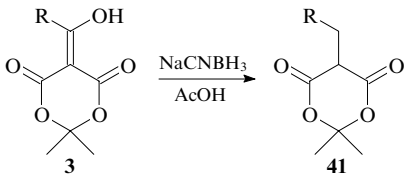
2. Reactions with nucleophiles

Acylated Meldrum's acids can react with H-, O-, S-, N- and C-nucleophiles. N-Nucleophiles similarly to O-nucleophiles can be introduced into the reaction medium from outside or can be parts of the 5-acyl side chain of Meldrum's acid. In all transformations described in this section (with the exception of the reaction with H-nucleophiles), the carbonyl group of the 5-acyl moiety of Meldrum's acid remains intact. O-, S-, N- and C-nucleophiles react formally with the 1,3-dioxane-4,6-dione moiety of the compound rather than with the 5-acyl fragment.

a. Reactions with H-nucleophiles

In the reactions of acyl Meldrum's acid derivatives with H-nucleophiles, the hydride ion selectively attacks the β-carbon atom of the conjugated system of the acylated Meldrum's adduct. The starting compounds **3** are reduced to the alkyl Meldrum's acid derivatives **41** (Scheme 24). As H-nucleophiles, sodium cyanoborohydride ($NaCNBH_3$)[88] or sodium borohydride ($NaBH_4$)[89] can be used.

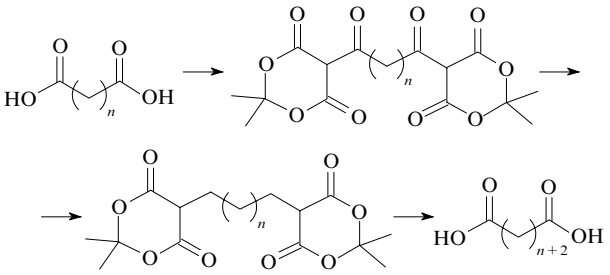
Scheme 24



R = Alk, Ar

This method has been elegantly applied by Obaza and Smith[90] for chain elongation in dicarboxylic acids (Scheme 25). Because of the simplicity of this method, it is still widely used in the synthesis of long-chain dicarboxylic acids.[91]

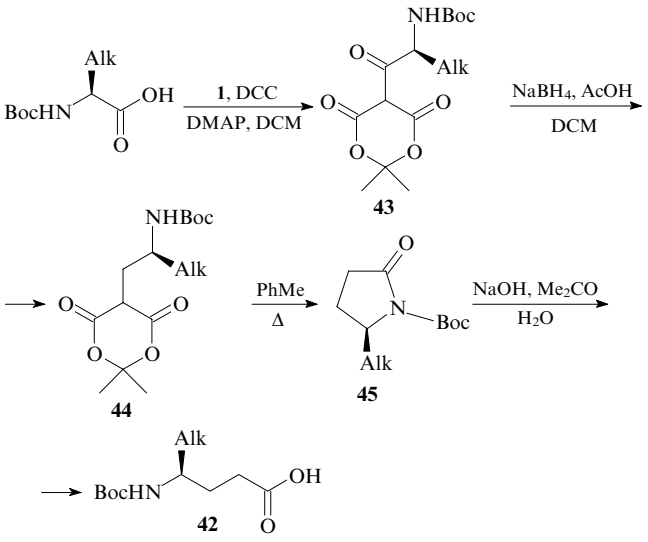
Scheme 25



n = 11, 13, 15

In 1997, γ-substituted γ-amino acids **42** were prepared in this way from the corresponding α-amino acids.[92] The key step of the procedure is complete reduction of the keto functionality of α-amino acyl Meldrum's acid **43** by sodium triacetoxyborohydride. The resulting amino alkyl derivative **44** undergoes thermal decarboxylation with ring contraction to give 5-substituted pyrrolidone **45**, which yields the corresponding γ-amino acid **42** after alkaline hydrolysis (Scheme 26). A similar approach using β-amino acids as starting materials provides *N*-Boc-protected-α,δ-disubstituted δ-amino acids.[93]

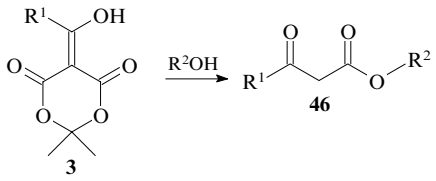
Scheme 26



b. Reactions with alcohols

Concurrently with the discovery of acyl Meldrum's acid derivatives, it was also noticed that these substances can serve as very efficient substrates for the synthesis of β-keto esters **45** in boiling alcohol (Scheme 27).[24]

Scheme 27

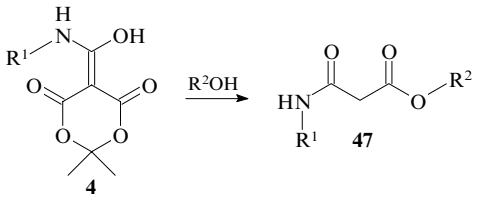


R^1 = Alk, Ar; R^2 = Alk

This methodology has been extensively used in organic synthesis, including the total syntheses of a number of natural products or compounds with biological activity. Alcoholysis of Meldrum's acid is, for instance, one of the steps of the synthesis of phenylpyrazolodiazepin-7-ones,[94] which possess antiproliferative action on cancer cells.

In our research, we have found that, similarly to typical acyl Meldrum's acids **3**, carbamoyl Meldrum's acids **4** can also react with O-sp^3 nucleophiles giving malonamic acid (malonic acid monoamide) esters **47** in good to excellent yields (Scheme 28).[45] Even weakly nucleophilic *tert*-butyl alcohol gave malonamic acid *tert*-butyl esters in high yield. The alcoholysis of carbamoyl Meldrum's acids was carried out in refluxing ethylbenzene with a high excess of alcohol. However, in the case of ethyl and *tert*-butyl alcohols as nucleophiles, the boiling point of the reaction mixture decreased from about 130 °C to 80 °C, which increased the reaction time from 2 h up to 24 h.

Scheme 28



R^1 = Alk, Ar; R^2 = Alk

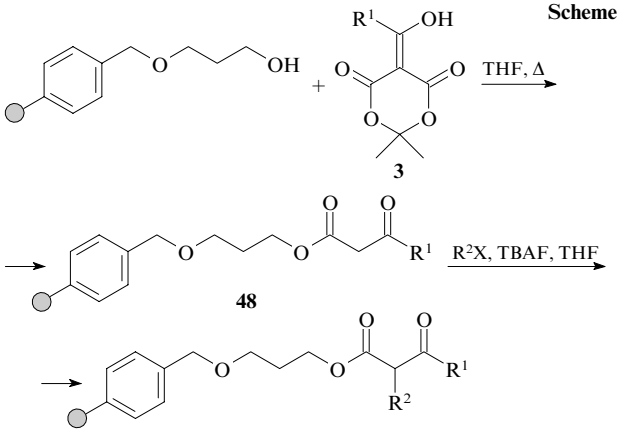
In 1996, Tietze *et al.*[95,96] have developed the solid-phase synthesis of polymer-bound β-keto esters **48**. The polystyrene resin containing free hydroxyl groups was treated with acyl Meldrum's acid in boiling THF, leading to the formation of new modified resin containing β-ketoester side chains. The process was monitored with IR spectroscopy where the absorption band from the carbonyl group was observed. They additionaly found that the β-ketoester moieties introduced in the resin can be further modified by alkylation with haloalkanes in the presence of tetra-n-butylammonium fluoride (TBAF) (Scheme 29).

β-Ketoester-modified resins prepared by Tietze *et al.*[95,96] can be used for the synthesis of biologically active pyrazoles.

If the 5-acyl moiety of Meldrum's acid derivative has a hydroxy group, an intramolecular reaction may occur producing lactones **49** (Scheme 30).[97]

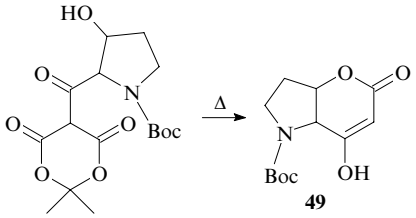
In 1992, Weiler and co-workers[98] developed a new method for the synthesis of macrocyclic β-keto lactones by cyclization of acyl Meldrum's acid derivatives with intramolecular hydroxy group (Scheme 31). This approach involves thermolysis of acyl Meldrum's acid and lactonization through intramolecular alcoholysis. This approach

Scheme 29



R^1 = Alk, Ar; R^2 = Alk; X = Hal; ◯ is polymeric substrate

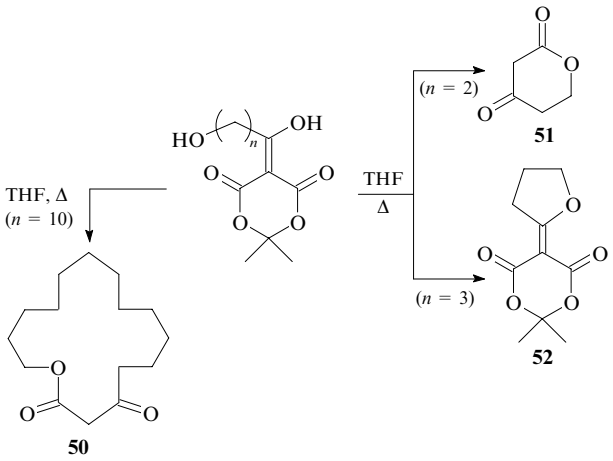
Scheme 30



gives a modest yield of macrocyclic system **50** and a good yield of unsubstituted 3-oxopentan-5-olide **51**. To minimize the intermolecular reaction, a dilute THF solution of Meldrum's adduct was slowly added to boiling THF. However, no monomeric lactones were detected for any of systems except those with $n = 2$ and 10. When $n = 3$ the enol ether **52** was obtained in a 80% yield, demonstrating the strong kinetic preference for the formation of 5-memberd rings over 7-memberd rings.

The O-sp3 intramolecular ring closure reaction in which the enolic hydroxy group attacks the carbonyl group of acyl Meldrum's acid was described by Haüsler [43] and two years later by Kang *et al.*[99] In 1999, Lokot *et al.*[100] described the synthesis of 4-hydroxy-6-methyl-2-pyrones **53** (Scheme 32). The process includes the formation of β-alkyl-substituted acyl Meldrum's acid **54** and its subsequent thermal transformation *via* the formation of α-oxo ketene as a key

Scheme 31



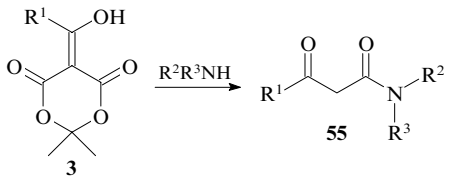
intermediate followed by its intramolecular reaction with the enolic hydroxy group.

The same research group [100] used this approach in a seven-step synthesis of germicidin. The method gave germicidin in an optically active form.

c. Reactions with amines

In 1978, it was proposed [24, 101] to use acyl Meldrum's acid **3** for the preparation of β-oxo-amides **55**. However an efficient and versatile method for the synthesis of these compounds was developed and described only in 1992 (Scheme 33).[75] The reaction involves direct aminolysis of a slight excess of acyl Meldrum's acid **3** in benzene under reflux for approximately 4 h.

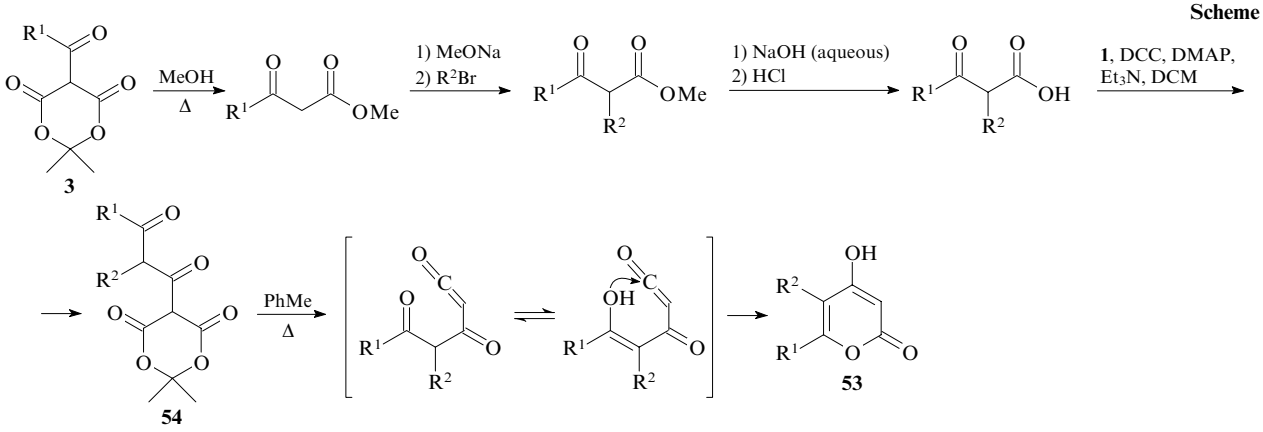
Scheme 33



R^1 = Alk, Ar; R^2, R^3 = H, Alk, Ar, SO_2Ar

Weakly nucleophilic amines such as 2-aminopyridine or 2-nitroaniline reacted as good as aliphatic primary and secondary amines, all the β-oxo-amides were obtained in

Scheme 32

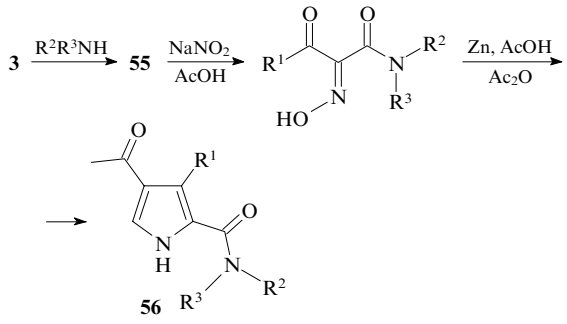


R^1 = Alk, Ar; R^2 = Alk

good yields, irrespective of the type of amine. Under similar reaction condition (boiling benzene), the reaction between acyl Meldrum's acids and various carboxamides affords imides in satisfactory yields.[102]

The method proposed by Pak *et al.*[75] is used very often in chemical synthesis; it can be applied for instance in the three-step synthesis of substituted pyrroles **56** (Scheme 34).[103]

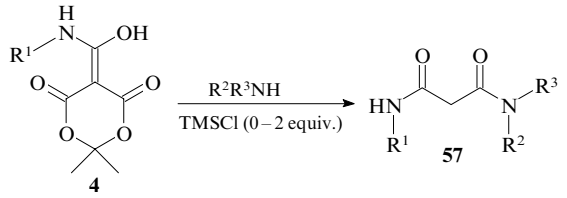
Scheme 34



R^1, R^2, R^3 = H, Alk, Ar

The use of carbamoyl Meldrum's acid derivatives **4** as acetyl group donors in the synthesis of unsymmetrical malonamides **57** according to this method was also reported (Scheme 35).[47] The procedure is analogous to that used for the preparation of β-oxo-amides **55**. However, Pak's paper[47] deals only with weakly basic N-nucleophiles such as aromatic amines with electron-withdrawing groups or even amides. In our research we have found that the use of more basic secondary amines such as diethylamine or piperidine in this reaction results in lower yields and longer reaction time. These difficulties can be eliminated by adding trimethylsilyl chloride to the reaction medium. Also, we also have noticed that the reaction mechanism changes if TMSCl is used.

Scheme 35

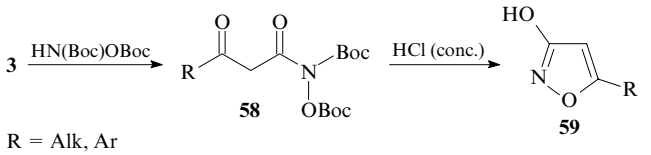


R^1, R^2, R^3 = H, Alk, Ar

Acylated Meldrum's acid can also react with hydroxylamine derivatives.[104] Krogsgaard-Larsen and co-workers[29] have presented a versatile three-step procedure in which acyl Meldrum's acid **3** is converted to *N*,*O*-di-Boc-protected β-keto hydroxamic acid **58** upon aminolysis with *N*,*O*-bis(*tert*-butoxycarbonyl)hydroxylamine, and compound **58** is cyclized to give 5-substituted 3-isoxazole **59** (Scheme 36). What is surprising, in this process acyl Meldrum's acid reacts efficiently with sterically hindered hydroxylamine containing two Boc groups, suggesting that an unselective strongly acylating intermediate is present during the reaction.[29]

1,3-Dimethylurea and -thioures (**60**) are two more examples of N-sp^3 nucleophiles which can react with acyl Meldrum's derivatives. The reaction of **60** with trifluoro-

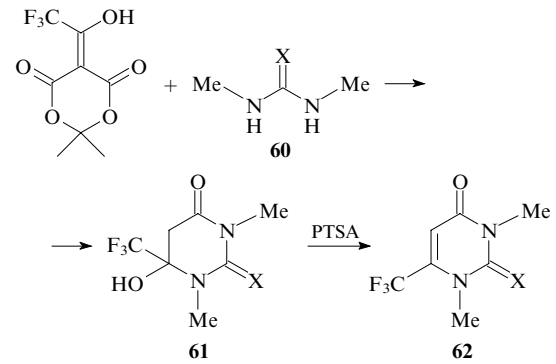
Scheme 36



R = Alk, Ar

acetyl Meldrum's acid leads to the formation of dihydro(thio)uracil derivatives **61**, which can be dehydrated to 6-trifluoromethyl(thio)uracil **62**. It is significant that in the case of thiourea derivatives, the yields are twice higher than for urea derivatives (Scheme 37).[71]

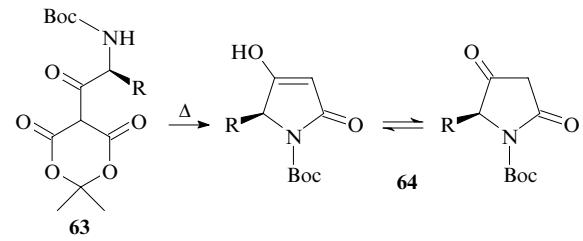
Scheme 37



X = O, S; PTSA is *p*-toluenesulfonic acid

All the examples described so far were associated with the attack of an N-nucleophile from the outside of the molecule but the attack may also be intramolecular. The reaction described by Jouin *et al.*[105] in 1987 is an example of intramolecular reaction of acyl Meldrum's acid with N-sp^3 nucleophile. It was found that the condensation of Boc-protected amino acids and Meldrum's acid followed by deprotection and decarboxylation could produce pyrrolidine-2,4-diones **64** (commonly named as tetramic acids), without racemization (Scheme 38).[65, 105] These molecules are important precursors of β-hydroxy-γ-amino acids. The proposed[105] method has been applied to the synthesis of several biologically active molecules.[106–108] However, the reaction conditions are rather elusive and, as reported, by the authors, any change in the procedure leads to lower yields.

Scheme 38

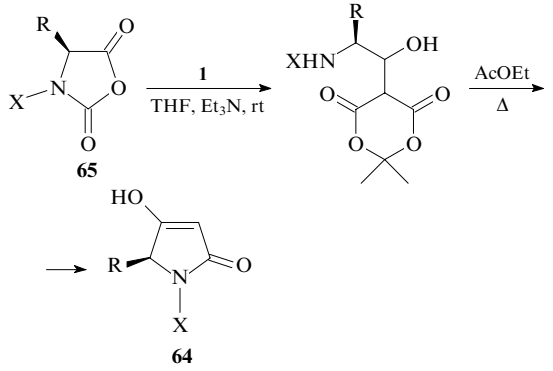


R = Alk

Tetramic acids can be also obtained in high yields by the reaction of Meldrum's acid with *N*-urethane-*N*-carboxy anhydrides (UNCAs) **65** followed by cyclization (Scheme 39).[109] This procedure is applicable to Boc-, Fmoc- and Z-carboxy anhydrides (Fmoc is fluorenylmethoxycarbonyl, Cbz is benzyloxycarbonyl). Meldrum's acid **1** readily reacts

with UNCAs **65** in the presence of tertiary amine (triethylamine, *N*,*N*-diisopropylethylamine, *N*-methylmorpholine, *etc.*) to afford in a few minutes corresponding acyl Meldrum's acid. The crude material is next cyclized according to Jouin *et al.*[105] and yields the corresponding enantiomerically pure tetramic acid derivative **64**.

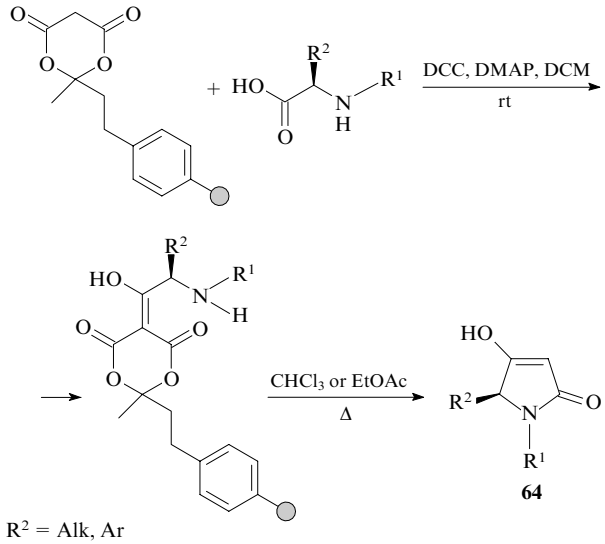
Scheme 39



R = Alk; X = Boc, Cbz, Fmoc

Yet another efficient method for the assembly of the tetramic acid core is the solid-phase synthesis using Meldrum's acid attached to a polymer support (Scheme 40).[110, 111]

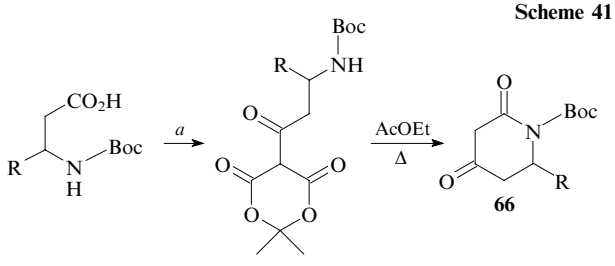
Scheme 40



R^1, R^2 = Alk, Ar

Another, method very similar to that discovered by Jouin *et al.*[105] was described in 2007 by Orsini *et al.*[112] This is the intramolecular reaction for the synthesis of piperidine-2,4-diones **66** (Scheme 41). In this case, instead of α-amino acids, the β-homologues are used. It was also noted that to increase the molecular diversity of compounds **64** as building blocks, selective 5-alkylation with lithium hexamethyldisilazide (LiHMDS) is possible.[112]

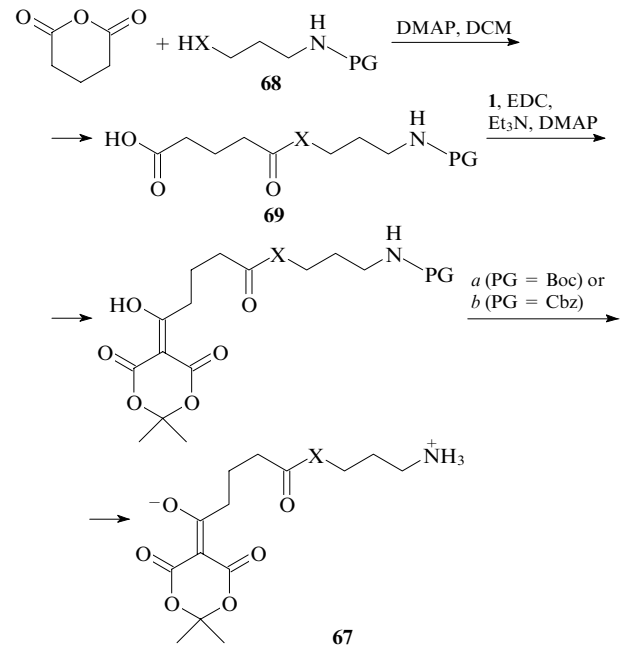
Scheme 41



(*a*) **1**, EDC, DMAP, DCM, 0 °C → rt; R = Alk

In 2011, Kurth and co-workers[113] described the synthesis of macrocyclic lactams from 5-acyl Meldrum's acids. Carboxylic acid intermediates **67** for this reaction were prepared by opening pentane-1,5-dioic acid anhydride with carbamate-protected amino alcohol or diamine **68** with protected amino group. The resulting compounds **69** were next coupled to Meldrum's acid **1** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC). The removal of the nitrogen protecting group delivers zwitterions of acyl Meldrum's acids **67** (Scheme 42). As protecting groups, both Boc and Cbz were explored. It was found that Boc deprotection with SnCl4 proceeds more smoothly than Cbz hygrogenolysis.

Scheme 42



(*a*) $SnCl_4$, DCM, EtOAc; (*b*) H_2, Pd/C, EtOH, 30 min; X = O or NH; PG = Boc or Cbz

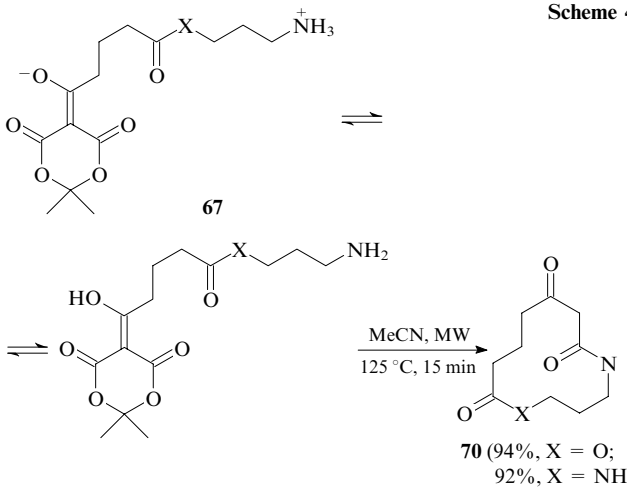
The cyclization of compounds **67** was carried out in MeCN at 125 °C for 15 minutes under microwave (MW) radiation. Zwitterions **67** exist as an internal ion pair with geometries that resemble the respective macrocyclic products **70** (Scheme 43). This pre-organization perhaps aids ring closure, explaining high macrocyclization yields (92% – 94%).[113]

The same research group utilized similar macrolactams as intermediates in the multicomponent cyclization (Scheme 44). The resulting macrolactams **70** were made to condense with a formaldehyde equivalent, yielding a methylene derivative, which reacted as a dipolarophile in a $KHCO_3$-initiated nitrile oxide (from a chloro oxime) 1,3-dipolar cycloaddition to furnish spiro-fused macrolactams **71** in very good yields (70% – 74%).[112]

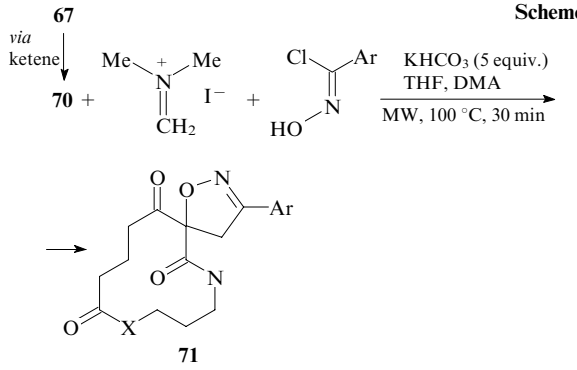
d. Reactions with thiols

Woodward and Ley[32] were the first to report the possibility of reaction between acyl Meldrum's acid derivatives **3** and

Scheme 43



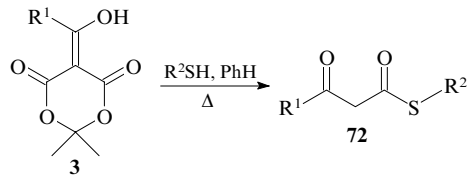
Scheme 44



X = O, NH; DMA is *N*,*N*-dimethylacetamide

thiols. This reaction gave β-keto thioesters **72** (Scheme 45). However, in the chemical literature, there are few examples of the reaction of acyl Meldrum's acid derivatives with S-sp^3 nucleophiles.

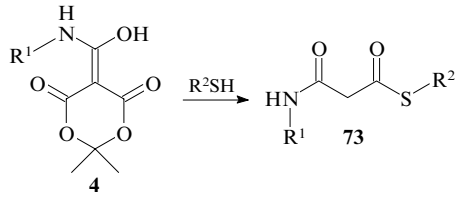
Scheme 45



R^1, R^2 = Alk, Ar

We have found that carbamoyl Meldrum's acid derivatives **4** can react with thiols in a similar way giving β-keto thiomalonamides **73** in 31% to 65% yields (Scheme 46).[45]

Scheme 46



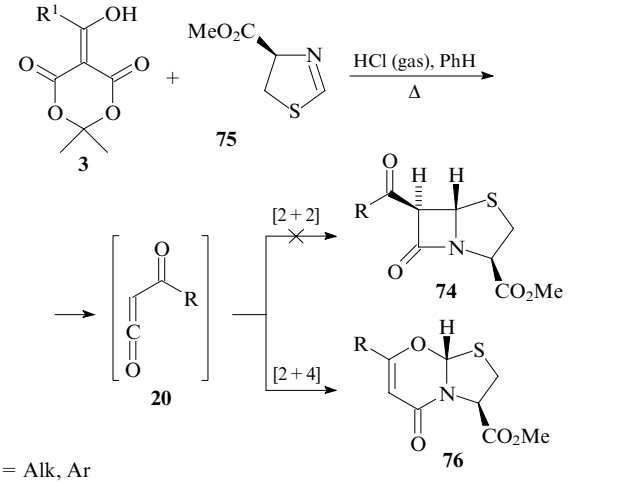
R^1, R^2 = Alk, Ar

e. Reactions with cyclic and non-cyclic imines

Imines can react with acyl Meldrum's acid as N-sp^2-nucleophiles. This reaction type is described most widely in the chemical literature dealing with the reactivity of acyl Meldrum's acids. In these reactions, the carbonyl function of Meldrum's acid adduct acts as an electrophilic reaction centre, and the 5-acyl Meldrum's acid introduces three carbon atoms into the forming heterocyclic core.

Almqvist and co-workers[114] attempted to assemble bicyclic β-lactam **74** directly by a Staudinger cycloaddition of acylketenes **20** generated from acyl Meldrum's acids **3** to optically active Δ^2-thiazoline **75** under acidic conditions. After structure elucidation of the product, it was found that the reaction gave rise to chiral 1,3-oxazinones **76** rather than 6-acylpenames **74** as was initially reported (Scheme 47).[115, 116]

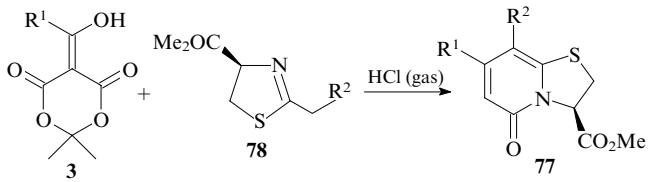
Scheme 47



R = Alk, Ar

Enantioselective synthesis of thiazoline **77** fused to highly substituted 2-pyridinone was performed by the same research group in 2001 (Scheme 48). The reaction was discovered when 2-alkyl-Δ^2-thiazoline **78** and Meldrum's acid derivative **3** were saturated with HCl gas at 5 °C and subsequently refluxed in benzene at 78 °C. Further refinement of the synthetic protocol revealed that the use of dichloroethane (DCE) as a solvent at 0 to 64 °C leads to 2-pyridinones in good yields and with excellent enantioselectivity.[30, 117]

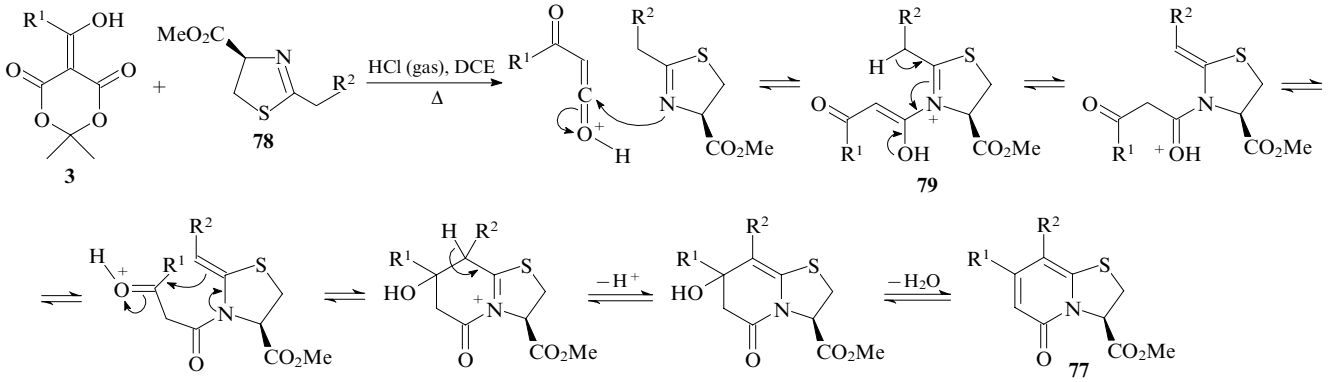
Scheme 48



R^1, R^2 = Alk, Ar

A tentative mechanistic explanation to the formation of 2-pyridinones **77** is presented in Scheme 49: the imine reacts with the corresponding ketene and [1,5]-sigmatropic rearrangement results in enamide **79**. Then an intramolecular attack on the β-carbonyl group closes the six-membered ring. After subsequent removal of a proton and water, thiazolopyridinone **77** is formed. This reaction was used, for instance, as a key step for the generation of diverse

Scheme 49



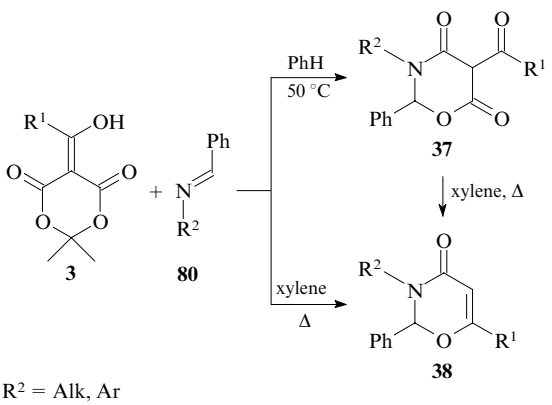
R^1, R^2 = Alk, Ar

bioactive molecules, including in particular, pilicides based on thiazolopyridones.[64, 118–120]

Besides the above-mentioned methods, the Almqvist research group has developed two other innovative methods for the preparation of 2-pyridinones, one using solid-phase synthesis with thiazoline esters bound to the resin [121] and the other using microwave radiation.[122]

Kato and co-workers [123] described the reaction of acetyl Meldrum's acid with benzylideneimines **80**. When a solution of Meldrum's acid adduct with appropriate imine was refluxed in benzene, the exchange reaction between the C–O moiety of the dioxane ring in acyl Meldrum's acid and the C=N moiety of the Schiff base took place with loss of acetone to produce the 1,3-oxazinedione **37** derivative with a small amount of oxazin-4-one **38** (Scheme 50).

Scheme 50

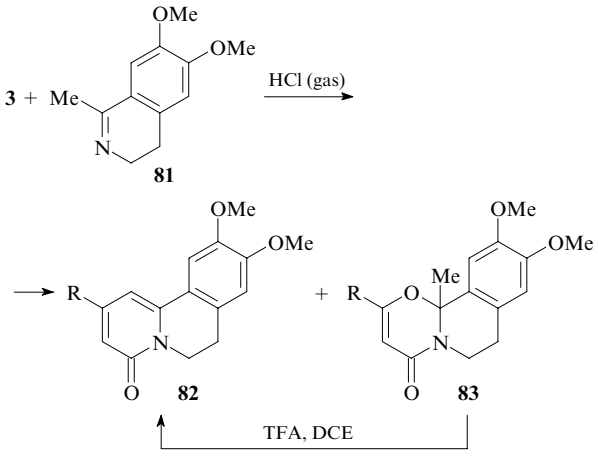


R^1, R^2 = Alk, Ar

Yamamoto and Watanabe [63] continued this work, which was focused on this type of reactivity of acyl Meldrum's acid derivatives. It was found that the product ratio of **37** and **38** depends on the reaction temperature. Treatment of acyl derivatives **3** with imines **80** in benzene at 50 °C for 4 h gave exclusively diones **37** in good yields. They also studied the possibility of transformation of 1,3-oxazinedione **37** to oxazin-4-one **38**. Dione **37** was converted to ketone **38** by refluxing in benzene or xylene, or directly by treatment of acyl Meldrum's acid derivatives **3** with imine **80** in boiling xylene.[63]

Almqvist's research group described a similar reaction.[124] They performed a set of experiments between dihydroisoquinoline **81** and acyl Meldrum's acid derivatives **3** (Scheme 51). In the presence HCl or trifluoroacetic acid (TFA), they obtained 2-pyridone **82** as the only product, whereas under neural conditions, both products, 2-pyridone **82** and 1,3-oxazin-4-one **83**, were observed. When triethylamine was introduced into the reaction mixture, oxazinone **83** was formed predominatly. In this set of experiments, Almqvist and co-workers also found that the formation of **83** is a reversible process, and under microwave irradiation in the presence of TFA, **83** can dissociate to ketene and imine, which form 2-pyridone **82.** This result clearly explains the observation that under acidic conditions only one product **82** is formed, whereas under basic conditions, **83** is formed in excess but not as the only product.[124]

Scheme 51

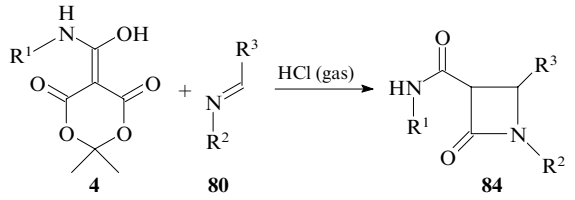


R = Alk, Ar

Yamamoto and Watanabe [63] used acyl Meldrum's acid derivatives in the reaction with aldimines for the preparation of monocyclic β-lactams. In the course of our own study we discovered [46] that it is possible to obtain the β-lactam moiety with retro-amide side chain **84** (Scheme 52). First, we chose benzene as a reaction medium based on the experiments of Yamamoto and Watanabe.[63] However, it turned out that carbamoyl Meldrum's acids **4** decompose much more slowly than compounds **3**. When we replaced the benzene solvent by toluene, we obtained a series of β-lactams with retro-amide side chain **84** in good yields, even when highly hindered di(*tert*-butyl)aldimine was used as a substrate. We have found one limitation to this method: if *N*-alkyl (cyclohexyl or ethyl) carbamoyl Meldrum's acids were used instead of aryl derivatives, no desired β-lactams

were obtained; instead, complicated mixtures of products were formed.

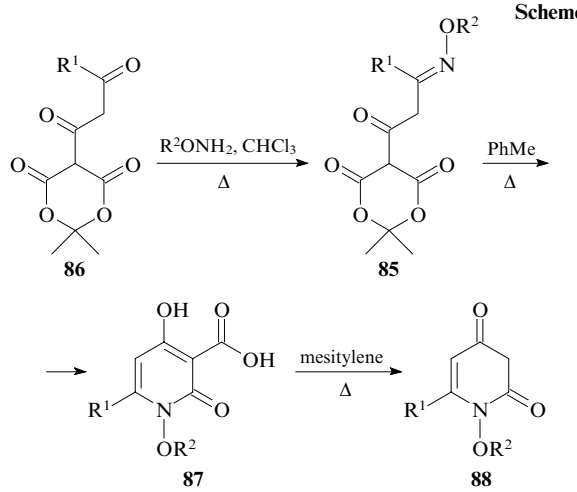
Scheme 52



R^1, R^2 = Alk; R^3 = Alk, Ar

In 2010, Rubinov *et al.*[125] have studied the intramolecular reaction of 2,2-dimethyl-5-[3-(alkoxyimino)alkanoyl]-1,3-dioxane-4,6-diones **85** (Scheme 53). It was found that acyl Meldrum's acid derivatives **86** react with alkoxyamines regioselectively at the β-keto group of the side acyl chain affording the corresponding tricarbonylimines **85**, which are converted upon refluxing in toluene to products of intramolecular cyclization, *N*-alkoxy-2,4-dioxopirydine-3-carboxylic acids **87**. These compounds are completely enolized, and their structure is stabilized by two intramolecular hydrogen bonds. The decarboxylation of acids **87** in mesitylene at 160–165 °C gives *N*-alkoxypyridine-2,4-diones **88** in 85%–90% yields.[125]

Scheme 53

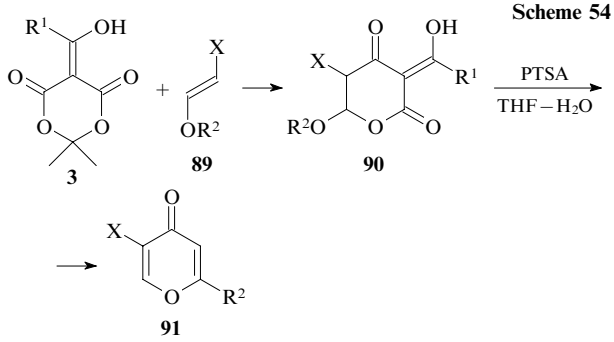


R^1 = Alk, Ar; R^2 = Alk

f. Reactions with vinyl ethers

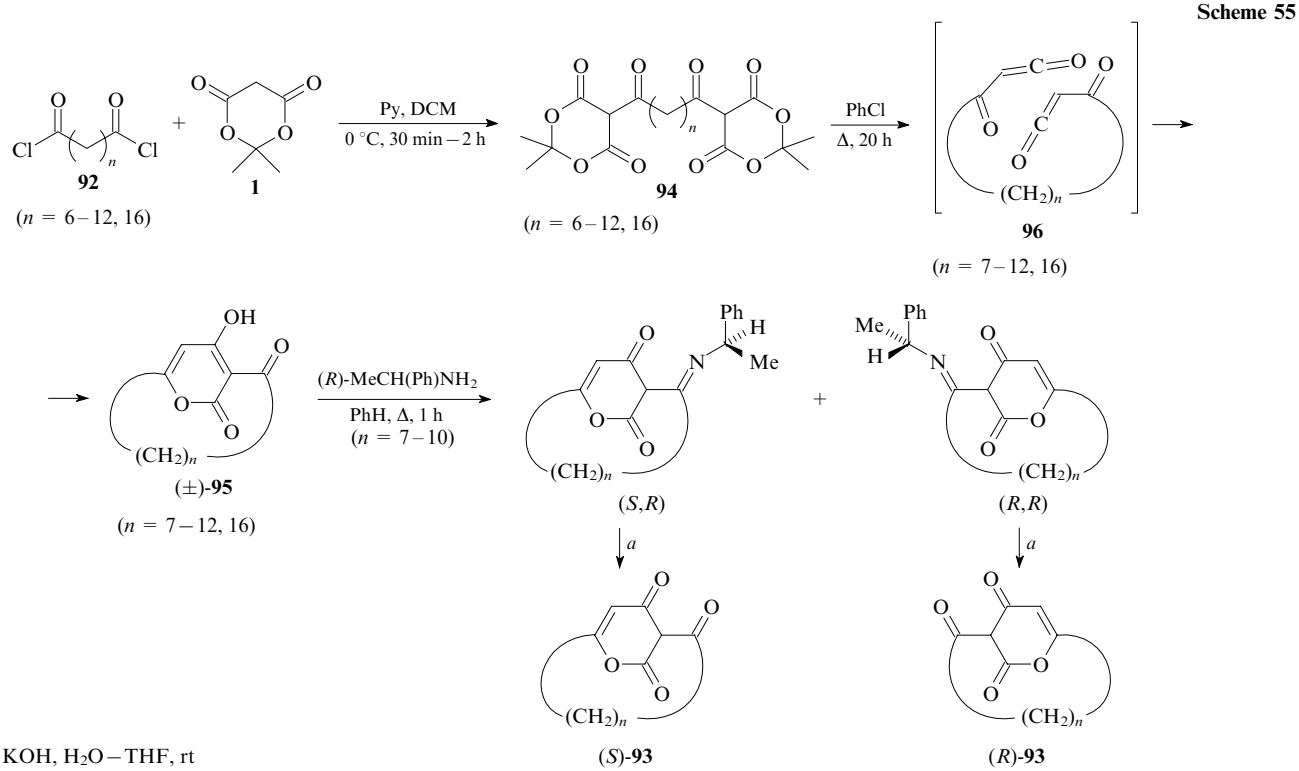
Acyl Meldrum's acids **3** react with vinyl ethers **89** in refluxing benzene to give compounds **90** analogous to pyrandiones (Scheme 54).[78] The latter are readily transformed into γ-pyrones **91** on treatment with PTSA in a 4 : 1 THF : H_2O mixture at reflux. A variety of acyl Meldrum's acids and vinyl ethers have been used to construct mono-, di- and trisubstituent pyrones.[78, 126] Substituted pyrones can be used, for instance, in the synthesis of polyacetate- and

Scheme 54



R^1 = Alk, Ar; R^2 = Alk; X = H, Me, $(CH_2)_3OH$

Scheme 55



(*a*) KOH, H_2O–THF, rt

spiroketal-containing natural products and as cycloaddition substrates for the construction of polycyclic systems.

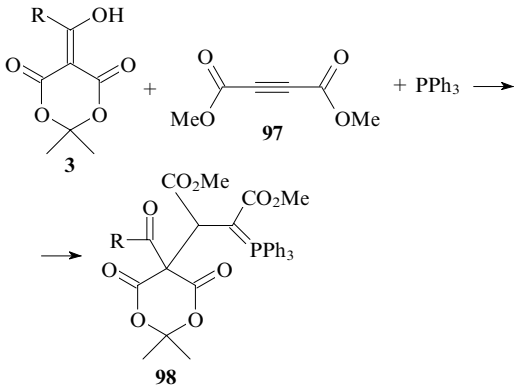
3. Carbocyclization

Sato *et al.*[127] used diacid dichlorides **92** and acyl Meldrum's acid derivatives **3** to synthesize, in four steps, optically pure cyclophanes **93** possessing the 1,3-dicarbonyl moiety (Scheme 55). First, dis(4,6-dioxo-1,3-dioxanes) **94** ($n = 6-12$, 16) were synthesized from the corresponding diacid dichlorides **92** ($n = 6-12$, 16), according to a reported procedure,[24] in the presence of pyridine at 0 °C to room temperature. The slow addition of compounds **94** into refluxing chlorobenzene under highly dilute conditions (1×10^{-4} mol litre^{-1}) gave (±)-cyclophanes **95** ($n = 7-12$, 16) generally in high yields. At temperatures higher than 130 °C, bis(4,6-dioxo-1,3-dioxanes) **94** lose acetone and carbon dioxide generating bis(acylketenes) **96**. The intramolecular [4+2]-cycloaddition of bis(acylketenes) **96** proceeds smoothly, giving (±)-cyclophane pyranones **95** in high yields. Cyclophanes ($n = 7-11$) were readily separated from oligomeric compounds by distillation. Higher homologues ($n = 12$, 16) were isolated by chromatography on neutral silica gel. Racemic cyclophanes **95** containing 7–10 bridging methylene units were resolved into enantiomers *via* diastereoisomeric imine formation with (*R*)-1-phenylethylamine followed by alkaline hydrolysis. This optically active cyclophanes **93** can form complexes with metals such as copper and europium.[127]

4. Acyl Meldrum's acids as nucleophiles

Reactions between Meldrum's acid derivatives and electrophiles are widely described in the chemical literature. However, there are few reactions related to electrophilic addition to 5-acylated Meldrum's acis. In 2012, Habibi *et al.*[128] found that triphenylphosphine and dialkyl acetylenedicarboxylate **97** react smoothly in the presence of 5-acyl Meldrum's acids **3** in dichloromethane at room temperature. This reaction type leads to the synthesis of new stable ylide derivatives **98** (Scheme 56).

Scheme 56

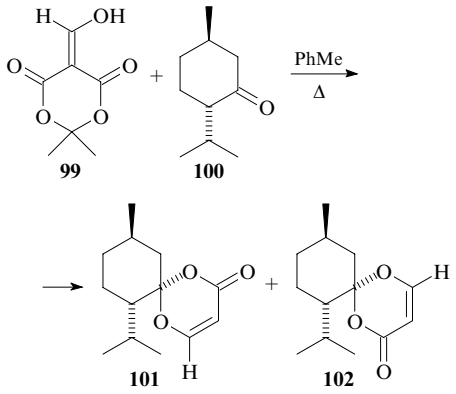


R = Alk, Ar

5. Miscellaneous reactions

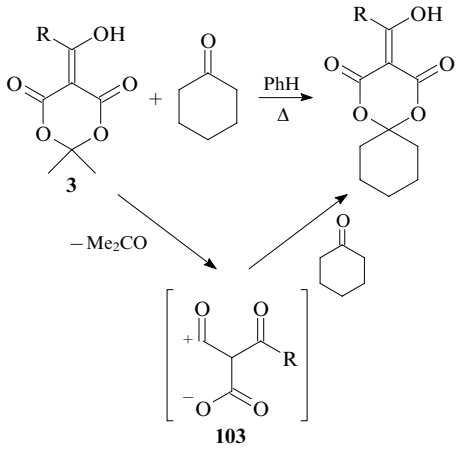
In 1990, Sato *et al.*[129] found that acyl Meldrum's acid derivatives can react with ketones in a similar way as diols giving acetals. The reaction of 5-formyl Meldrum's acid **99** with L-menthone **100** in refluxing toluene for 0.5 h gave products **101** and **102** in a 27% total yield (Scheme 57). 2,2-Dimethyl-1,3-dioxin-4-one is formed as a reactive intermediate and then exchanges the acetone moiety with L-menthone to form spirocyclic dioxinone.

Scheme 57



Yamamoto and Watanabe[63] assumed that acyl Meldrum's acid derivatives **3** may lose acetone to give intermediate **103**. This was proven by exchange of the acetone moiety in acyl Meldrum's acid **3** with a cyclohexanone moiety on refluxing acyl Meldrum's acid and cyclohexanone in benzene (Scheme 58).

Scheme 58



R = Alk, Ar

V. Conclusion

In the light of this review, it is clear that practical applications of Meldrum's acid derivatives in organic synthesis are still extending despite the fact that Meldrum's acid was discovered over one hundred years ago. A survey of recent chemical literature indicates that the key trend of synthetic applications of acyl Meldrum's acids is focused on the preparation of biologically active compounds as, for example, β-lactams, pilicides, isooxazol-3-ols, tetramic acid derivatives or analogues of prodigiosin family antibiotics. Acyl Meldrum's acid derivatives gradually find use in peptide chemistry, especially the topic concerning application of 1,3-dioxa-4,6-dione moiety as a kind of activating agent seems to be promising. However, the well-known strongly acidic properties of acyl Meldrum's acids can be an obstacle for peptide strategies using a weakly acid labile protecting group.

Another recently observed thread with growing importance is the reactivity of Meldrum's acid with organometal-

lic reagents. Fillion research group has given particular attention to this topic.[130–134] Meanwhile, the issue concerning the mechanistic aspect of the reactivity of acyl Meldrum's acid derivatives should be systematized and thoroughly explored because despite the presence of some publications dealing with the mechanistic problems of Meldrum's acid reactions, one can find a lot of data from experiments which cannot be explained with presently known theories about the reactivity and decomposition of acyl Meldrum's acids.

References

1. A N Meldrum *J. Chem. Soc.* **93** 598 (1908)
2. K Byun, Y Mo, J Gao *J. Am. Chem. Soc.* **123** 3974 (2001)
3. E M Arnett, J A Harrelson Jr *J. Am. Chem. Soc.* **109** 809 (1987)
4. D Davidson, S A Bernhard *J. Am. Chem. Soc.* **70** 3426 (1948)
5. C E Pfluger, P D Boyle *J. Chem. Soc., Perkin Trans. 2* 1547 (1985)
6. E N Klimovitskii, L K Yuldasheva, B A Arbuzov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1577 (1973) [a]
7. D Köberl, P Schuster *Monatsh. Chem.* **103** 1483 (1972)
8. H McNab *Chem. Soc. Rev.* **7** 345 (1978)
9. B C Chen *Heterocycles* **32** 529 (1991)
10. V V Lipson, N Y Gorobets *Mol. Divers.* **13** 399 (2009)
11. V D B Bonifacio *Synlett* 1649 (2004)
12. A S Ivanov *Chem. Soc. Rev.* **37** 789 (2008)
13. J Gerencsér, G Dormán, F Darvas *QSAR Comb. Sci.* **25** 439 (2006)
14. C Simmon, T Constantieux, J Rodriguez *Eur. J. Org. Chem.* 4957 (2004)
15. I Yavari, M Sabbaghasn, Z Hossaini *Mol. Divers.* **11** 1 (2007)
16. A M Dumas, E Fillion *Acc. Chem. Res.* **43** 440 (2010)
17. H McNab *Aldrichimica Acta* **37** 19 (2004)
18. A E A M Gaber, H McNab *Synthesis* 2059 (2001)
19. D Cantillo, H Sheibani, C O Kappe *J. Org. Chem.* **77** 2463 (2012)
20. A Basheer, Z Rappoport *J. Phys. Org. Chem.* **21** 483 (2008)
21. Y X Lei, D Casarini, G Cerioni, Z Rappoport *J. Phys. Org. Chem.* **16** 525 (2003)
22. J K Mukhopadhyaya, S Sklenák, Z Rappoport *J. Am. Chem. Soc.* **122** 1325 (2000)
23. C Wentrup, V V R Rao, W Frank, B E Fulloon, D W J Moloney, T Mosand *J. Org. Chem.* **64** 3608 (1999)
24. Y Oikawa, K Sugano, O Yonemitsu *J. Org. Chem.* **43** 2087 (1978)
25. J Maibaum, D H Rich *J. Med. Chem.* **32** 1571 (1989)
26. W R Ewing, M M Joullié *Heterocycles* **27** 2843 (1988)
27. Y Hamada, Y Kondo, M Shibata, T Shioiri *J. Am. Chem. Soc.* **111** 669 (1989)
28. S P Raillard, W Chen, E Sullivan, W Bajjalieh, A Bhandari, T A Baer *J. Comb. Chem.* **4** 470 (2002)
29. U S Sørensen, E Falch, P Krogsgaard-Larsen *J. Org. Chem.* **65** 1003 (2000)
30. H Emtenäs, L Alderin, F Almqvist *J. Org. Chem.* **66** 6756 (2001)
31. C E McInnis, H E Blackwell *Bioorg. Med. Chem.* **19** 4820 (2011)
32. S V Ley, P R Woodward *Tetrahedron Lett.* **28** 345 (1987)
33. Y Yamamoto, Y Watanabe *Chem. Pharm. Bull.* **35** 1860 (1987)
34. H-G Henning, G Stemplinger, K Rothe *Liebigs Ann. Chem.* 813 (1992)
35. P P Mahulikar, R B Mane *Synth. Commun.* **35** 2139 (2005)
36. M Birch, S Challenger, J P Crochard, D Fradet, H Jackman, A Luan, E Madigan, J S Mathew, N McDowall, K Meldrum, C M Gordon, P Peach, S Yeo *Org. Process Res. Dev.* **15** 1358 (2011)
37. J H Ahn, M S Shin, M A Jun, S H Jung, S K Kang, K R Kim, S D Rhee, N S Kang, S Y Kim, S K Sohn, S G Kim, M S Jin, J O Lee, H G Cheon, S S Kim *Bioorg. Med. Chem. Lett.* **17** 2622 (2007)
38. F Xu, J D Armstrong III, G X Zhou, B Simmons, D Hughes, Z Ge, E J Grabowski *J. Am. Chem. Soc.* **126** 13002 (2004)
39. D Alker, S F Campbell, P E Cross, R A Burges, A J Carter, D G Gardiner *J. Med. Chem.* **32** 2381 (1989)
40. S Hamilakis, A Tsolomitis *Heterocycl. Commun.* **11** 325 (2005)
41. T Sifferlen, C Boss, E Cottreel, R Koberstein, M Gude, H Aissaoui, T Weller, J Gatfield, C Brisbare-Roch, F Jenck *Bioorg. Med. Chem. Lett.* **20** 1539 (2010)
42. M M Tamarez, R W Franck, A Geer *Tetrahedron* **59** 4249 (2003)
43. J Haüsler *Monatsh. Chem.* **113** 1213 (1982)
44. M Augstin, E Günther *Monatsh. Chem.* **121** 1005 (1990)
45. K Janikowska, S Makowiec *Synth. Commun.* **42** 975 (2012)
46. K Janikowska, N Pawelska, S Makowiec *Synthesis* 69 (2011)
47. H K Lee, J P Lee, G H Lee, C S Pak *Synlett* 1209 (1996)
48. K Janikowska, S Makowiec, J Rachoń *Helv. Chim. Acta* **95** 461 (2012)
49. X Huang, B-C Chen *Synthesis* 967 (1986)
50. C F Bernasconi, S D Brown, M Ali, Z Rappoport, H Yamataka, H Salim *J. Org. Chem.* **71** 4795 (2006)
51. X Huang, B-C Chen *Synthesis* 480 (1987)
52. Z T Huang, X Shi *Synth. Commun.* **20** 1321 (1990)
53. F C Ye, B C Chen, X Huang *Synthesis* 317 (1989)
54. B E Fulloon, C Wentrup *J. Org. Chem.* **61** 1363 (1996)
55. H Bibas, D J W Moloney, R Neumann, M Shtaiwi, P V Bernhardt, C Wentrup *J. Org. Chem.* **67** 2619 (2002)
56. A R Far *Angew. Chem., Int. Ed.* **42** 2340 (2003)
57. C Wentrup, W Heilmayer, G Kollenz *Synthesis* 1219 (1994)
58. I R Gudipati, D V Sadasivam, D M Birney *Green Chem.* **10** 275 (2008)
59. R J Clemens, J A Hyatt *J. Org. Chem.* **50** 2431 (1985)
60. C O Kappe, M W Wong, C Wentrup *J. Org. Chem.* **60** 1686 (1995)
61. R H Zuhse, M W Wong, C Wentrup *J. Phys. Chem.* **100** 3917 (1996)
62. M Shtaiwi, C Wentrup *J. Org. Chem.* **67** 8558 (2002)
63. Y Yamamoto, Y Watanabe *Chem. Pharm. Bull.* **35** 1871 (1987)
64. M Sellstedt, F Almqvist *Org. Lett.* **10** 4005 (2008)
65. S Pirc, D Bevk, R Jakše, S Rečnik, L Golič, A Golobič, A Meden, B Stanovnik, J Svete *Synthesis* 2969 (2005)
66. N Katagiri, M Okada, C Kaneko *Tetrahedron Lett.* **37** 1801 (1996)
67. N Katagiri, H Sato, A Kurimoto, M Okada, A Yamada, C Kaneko *J. Org. Chem.* **59** 8101 (1994)
68. G A Hunter, H McNab, K Withell *Synthesis* 1707 (2010)
69. A R Renslo, R L Danheiser *J. Org. Chem.* **63** 7840 (1998)
70. A Cantin, P Moya, M A Miranda, J Primo, E Primo-Yufera *J. Agric. Food Chem.* **46** 4748 (1998)
71. Y Morita, R Kamakura, M Takeda, Y Yamamota *Chem. Commun.* 359 (1997)
72. G P McGlackena, C M McSweeneya, T O'Brienb, S Lawrencea, C J Elcoatea, F J Reenc, F O'Garac *Tetrahedron Lett.* **51** 5919 (2010)
73. F Yuste, F K Breña, H Barrios, S Sánchez-Obregón, Ortíz, F Walls *Synth. Commun.* **18** 735 (1988)
74. P Punda, S Makowiec *Synth. Commun.* **43** 1362 (2013)
75. C S Pak, H Yang, E B Choi *Synthesis* 1213 (1992)
76. R Cassis, R Tapia, J A Valderrama *Synth. Commun.* **15** 125 (1985)
77. R H Nobes, W J Bouma, L Radom *J. Am. Chem. Soc.* **105** 309 (1983)

78. F J Zawacki, M T Crimmins *Tetrahedron Lett*. **37** 6499 (1996)
79. K Janikowska, S Makowiec, J Rachoń *Helv. Chim. Acta* **96** 978 (2013)
80. A Basheer, Z Rappoport *J. Org. Chem*. **73** 184 (2008)
81. M Augustin, E Günther *Z. Chem*. **27** 68 (1987)
82. T A Hase, K Salonen *Synth. Commun*. **10** 221 (1980)
83. H Fritz, J Lehmann, P Schlesselmann *Carbohydr. Res*. **113** 71 (1983)
84. J Tsuji, H Nagashima, H Nemoto *Org. Synth*. Coll. Vol. **7** 137 (1990)
85. J Tsuji, H Nagashima, H Nemoto *Org. Synth*. **62** 9 (1984)
86. H R Rogers, J X McDermott, G M Whitesides *J. Org. Chem*. **40** 3577 (1975)
87. R J Thomas, K N Campbell, G F Hennion *J. Am. Chem. Soc*. **60** 718 (1938)
88. A Rosowsky, R Foorsch, J Uren, M Wick, A A Kumar, J H Freisheim *J. Med. Chem*. **26** 1719 (1983)
89. R Akue-Gedu, H El-Hafidi, B Rigo, D Couturier *J. Heterocycl. Chem*. **43** 365 (2006)
90. J Obaza, F X Smith *Synth. Commun*. **12** 19 (1982)
91. E Haulotte, P Laurent, J-C Braekman *Eur. J. Org. Chem*. 1907 (2012)
92. M Smrcina, P Maler, E Majerov, T A Guerassina, M A Eissenstat *Tetrahedron* **53** 12867 (1997)
93. J R Casimir, C Didierjean, A Aubry, M Rodriguez, J-P Briand, G Guichard *Org. Lett*. **2** 895 (2000)
94. H Kim, M Kim, J Lee, H Yu, J-M Hah *Bioorg. Med. Chem*. **19** 6760 (2011)
95. L F Tietze, A Steinmetz, F Balkenhohl *Bioorg. Med. Chem. Lett*. **7** 1303 (1997)
96. L F Tietze, A Steinmetz *Angew. Chem., Int. Ed. Engl*. **35** 651 (1996)
97. J Hausler *Liebigs Ann. Chem*. 982 (1983)
98. L Lermer, E G Neeland, J P Ounsworth, R J Sims, S A Tischler, L Weiler *Can. J. Chem*. **70** 1427 (1992)
99. J Kang, Y H Kim, M Park, C H Lee, W-J Kim *Synth. Commun*. **14** 265 (1984)
100. I P Lokot, F S Pashkovsky, F A Lakhvich *Tetrahedron* **55** 4783 (1999)
101. Y Oikawa, T Yoshioka, K Sugano, O Yonemitsu *Org. Synth*. **63** 198 (1985)
102. Y Yamamoto, S Ohnishi, Y Azuma *Chem. Pharm. Bull*. **30** 3505 (1982)
103. M T Huggins, P S Barber, D Florian, W Howton *Synth. Commun*. **38** 4226 (2008)
104. K Mhori, Y Oikawa, K I Hiaro, O Yonemitsu *Heterocycles* **19** 515 (1982)
105. P Jouin, B Castro, D J Nisato *J. Chem. Soc., Perkin Trans 1* 1177 (1987)
106. S J Wittenberger, W R Baker, B G Donner, C W Hutchins *Tetrahedron Lett*. **32** 7655 (1991)
107. K H Altmann, S M Freier, U Pieles, T Winider *Angew. Chem., Int. Ed. Engl*. **33** 1654 (1994)
108. J Jiang, W Li, R M Przeslawski, M M Joullie *Tetrahedron Lett*. **34** 6705 (1993)
109. J-A Fehrentz, E Bourdel, J-C Califano, O Chaloin, C Devin, P Garrouste, A-C Lima-Leite, M Llinares, F Rieunier, J Vizavonna, F Winternitz, A Loffet, J Martinez *Tetrahedron Lett*. **35** 1557 (1994)
110. Z Liu, X Ruan, X Huang *Bioorg. Med. Chem. Lett*. **13** 2505 (2003)
111. T T Romoff, L Ma, Y Wang, D A Campbell *Synlett* 1341 (1998)
112. P Orsini, A Maccario, N Colombo *Synthesis* 3185 (2007)
113. J M Knapp, J C Fettinger, M J Kurth *Org. Lett*. **13** 4732 (2011)
114. H Emtenäs, G Soto, S J Hultgren, G R Marshall, F Almqvist *Org. Lett*. **2** 2065 (2000)
115. N Pemberton, H Emtenäs, D Boström, P J Domaille, W A Greenberg, M D Levin, Z Zhu, F Almqvist *Org. Lett*. **7** 1019 (2005)
116. H Emtenäs, M Carlsson, J S Pinkner, S J Hultgren, F Almqvist *Org. Biomol. Chem*. **1** 1308 (2003)
117. E Chorell, C Bengtsson, T S L Banchelin, P Das, H Uvell, A K Sinha, J S Pinkner, S J Hultgren, F Almqvist *Eur. J. Med. Chem*. **46** 1103 (2011)
118. N Pemberton, J S Pinkner, S Edvinsson, S J Hultgren, F Almqvist *Tetrahedron* **64** 9368 (2008)
119. V Aberg, P Das, E Chorell, M Hedenstroem, J S Pinkner, S J Hultgren, F Almqvist *Bioorg. Med. Chem. Lett*. **18** 3536 (2008)
120. V Aaberg, F Norman, E Chorell, A Westermark, A Olofsson, A E Sauer-Eriksson, F Almqvist *Org. Biomol. Chem*. **3** 2817 (2005)
121. H Emtenäs, K Åhlin, J S Pinkner, S J Hultgren, F Almqvist *J. Comb. Chem*. **4** 630 (2002)
122. H Emtenäs, C Taflin, F Almqvist *Mol. Divers*. **7** 165 (2003)
123. M Sato, H Ogasawara, E Yoshizumi, T Kato *Chem. Pharm. Bull*. **31** 1902 (1983)
124. N Pemberton, L Jakobsson, F Almqvist *Org. Lett*. **8** 935 (2006)
125. D B Rubinov, I L Rubinova, F A Lakhvich *Russ. J. Org. Chem*. **47** 277 (2011) [*Zh. Org. Khim*. **47** 284 (2011)]
126. M T Crimmins, D G Washburn, F J Zawacki *Org. Synth*. **77** 114 (2000)
127. M Sato, F Uehara, K Sato, M Yamaguchi, C Kabuto *J. Am. Chem. Soc*. **121** 8270 (1999)
128. A Habibi, K Eskandari, A Abdolali *Phosphorus, Sulfur, Silicon Relat. Elem*. **187** 1109 (2012)
129. M Sato, K Takayama, Y Are, T Furuya, N Inukai, C Kaneko *Chem. Pharm. Bull*. **38** 336 (1990)
130. E Fillion, D Fishlock, A Wilsily, J M Goll *J. Org. Chem*. **70** 1316 (2005)
131. E Fillion, A Wilsily *J. Am. Chem. Soc*. **128** 2774 (2006)
132. E Fillion, A Wilsily, A E T Liao *Tetrahedron: Asymmetry* **17** 2957 (2006)
133. A M Dumas, E Fillion *Org. Lett*. **11** 1919 (2009)
134. A Wilsily, E Fillion *J. Org. Chem*. **74** 8583 (2009)

[a] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*