A Different Role of *Meldrum*'s Acid in the *Biginelli* Reaction

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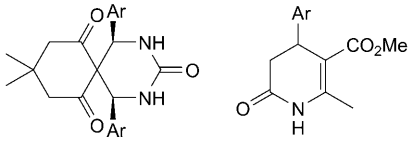
A *Biginelli*-type condensation using *Meldrum*'s acid has been accomplished in refluxing AcOH to give 6-substituted dihydropyrimidine-2,4-(1*H*,3*H*)-diones. In contrast to other aldehydes, the three-component reaction with salicylaldehyde led to an oxygen-bridged pyridine. A reaction mechanism is proposed.

Introduction. – 2,2-Dimethyl-1,3-dioxane-4,6-dione (**1**), also known under the trivial name of *Meldrum*'s acid and being formally a cyclic acylal, can be also classified as a cyclic malonate (isopropylidene malonate). The high C–H acidity (pK_a 4.83), flat ring structure, rigidness, and unique chemical properties render this compound a versatile reagent for preparative organic chemistry (see [1] for reviews). In terms of synthesis [2], **1** is referred to as an efficient precursor of a d^2-synthon. In the last decade, widespread attention has been focused on the construction of highly substituted spiro-heterocycles possessing a *Meldrum*'s acid unit. Due to their remarkable reactivity, these derivatives have proven to be attractive intermediates in the synthesis of complex organic molecules, various classes of natural products and their analogs, pharmacologically active agents, and unusual amino acids [1c–1e][3].

Recently, *Lewis* acid ($NiCl_2$, $CoCl_2$)-mediated preparation of spiro-heterocycle **2** through *Biginelli*-like condensation of *Meldrum*'s acid, aldehyde, and urea has been described [4] (*Fig. 1*). Similar use of a *Brønsted* acid additive (AcOH; 1 equiv.) led to an identical product **2** under otherwise analogous conditions (microwave-assisted synthesis without solvent) [5a]. However, the same group demonstrated later that the spiro-heterobicyclic ring system of **2** is produced even without catalyst and solvent at 80° [5b]. These findings differ from our method developed for the synthesis of pyridinecarboxylates **3** *via Hantzsch*-like reaction from *Meldrum*'s acid, methyl acetoacetate, aldehyde, and $AcONH_4$ in boiling EtOH [6]. Evidently, **1** acts in this case both as a second active CH_2 component and a C_2-reagent. Later, *Verdecia et al.*, in order to improve the yield of **3**, modified our procedure by using reflux in AcOH [7].



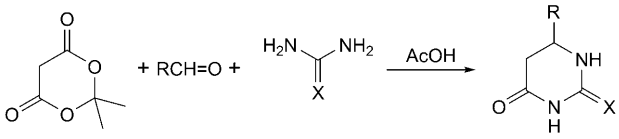
2 **3**

Fig. 1. *Structures of compounds* **2** *and* **3**

In the light of these facts, it was of interest to revisit the aforementioned unexpected *Biginelli* reaction using conventional heating technique in solution. The present study was also prompted by the recent pharmacological revival of *Biginelli* dihydropyrimidines which exhibited activity as mitotic kinesin Eg5 inhibitors [8], melanin-concentrating hormon receptor (MCH1-R) antagonists [9], chemical modulators of heat shock protein 70 (Hsp 70) [10], hepatitis B-replication inhibitors [11], and inhibitors of the fatty acid transporter [12]. In particular, a simple 4-aryldihydropyrimidine derivative was recently discovered to be a highly effective agent against a methicillin-resistant strain of *Staphylococcus aureus* (MRSA) [13]. In pursuing our work on the *Hantzsch*- and *Biginelli*-like heterocyclizations [6][14], we present here a novel practical application of *Meldrum*'s acid for the synthesis of 6-aryldihydropyrimidine-2,4-diones, the so-called 5,6-dihydrouracils.

Results and Discussion. – Since acid catalysis is required in the *Biginelli* condensation [15], we chose AcOH as both an acidic promoter and the reaction medium. Initially, a test experiment with an equivalent of benzaldehyde, *Meldrum*'s acid, and urea was conducted in AcOH at reflux for 14 h. Although the melting point of isolated compound **4a** (*Scheme 1*) was close to that reported [5] for spiro heterocycle **2** (Ar = Ph), a combustion analysis clearly ruled out this derivative. We, therefore, considered **1** to be involved as a d^2-synthon in the *Biginelli* reaction forming product **4a**. In view of the above-mentioned pyridine **3**, a substituted pyrimidine-2,4-dione **4a**, being partially related to *Biginelli* derivatives, appears to be a reasonable alternative in this case. Indeed, ^{1}H- and ^{13}C-NMR spectra are in good agreement with the proposed structure **4a**. Moreover, the structure assignment was confirmed by comparing our spectroscopic data with published values [16a].

Scheme 1



1

	R	X
4a	Ph	O
4b	4-NO_2–C_6H_4	O
4c	3-NO_2–C_6H_4	O
4d	4-Cl–C_6H_4	O
4e	4-MeO–C_6H_4	O
4f	Thiophen-2-yl	O
4g	Me_2CHCH_2	O
4h	Ph	S

To explore the scope of the three-component reaction depicted in *Scheme 1*, we have evaluated a variety of aldehyde substrates. It was found that benzaldehydes bearing electron-withdrawing substituents reacted well to give moderate yields of heterocyclic condensates, whereas those containing electron-donating groups together with a heterocycle led to only lower yields. Unfortunately, the one-pot condensation

works poorly with aliphatic aldehydes under the same conditions. Furthermore, a successful application of this method for synthesis of 2-thioxo congeners employing thiourea as reactant is exemplified by derivative **4h**.

In principle, two *Knoevenagel* conjugates, **A** and **B**, are conceivable as precursors of *Biginelli* structure **C** (*Fig. 2*). Although *N*-acylimine species was evidenced as a key intermediate in the *Biginelli* reaction [15], a pathway involving enone adduct **A** seems more probable because of the high reactivity of *Meldrum*'s acid. Also 5-benzylidene derivatives of type **A** were reported [5b] to be isolated in spirocyclizations. The bicyclic derivative **C** is further converted into desired pyrimidine-2,4-dione **4** by decarboxylative fragmentation of the 1,3-dioxane skeleton under release of CO_2 and acetone.

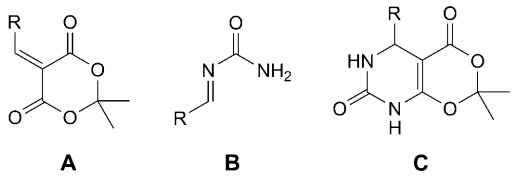


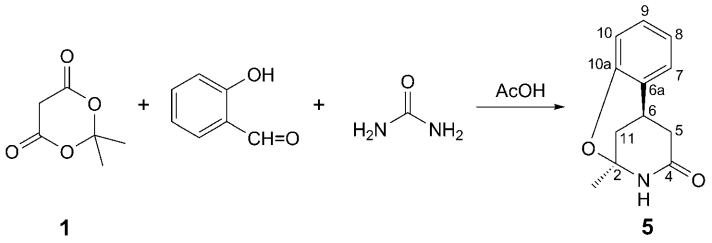
Fig. 2. *Two* Knoevenagel *conjugates,* **A** *and* **B***, are conceivable as precursors of* Biginelli *structure* **C**

Alternatively, from a mechanistic study [17] concerning the transformation of 5-acyl *Meldrum*'s acids through an α-oxo ketene R–CO–CH=C=O, one may deduce that a similar highly reactive heterocumulene R–CH=C=C=O might be involved as an intermediate. Nevertheless, this alternative is speculative and remains to be evaluated.

In the light of the above-mentioned results, we continued to examine a cyclocondensation with salicylaldehyde, a topic of our continuing interest. Surprisingly, and in spite of identical reaction conditions, an anomalous course of the three-component reaction was observed in contrast to the previous heterocyclizations. A product isolated upon treatment in AcOH and usual workup exhibited a molecular-ion (M^+) peak at *m*/*z* 203 in its mass spectrum, indicating an odd number of N-atoms [18]. It follows from this observation that only one N-atom originating from urea was built in the product. The ^{1}H-NMR spectrum indicated the presence of one Me group, two CH_2 groups, one CH group, an *ortho*-phenylene ring, and one exchangeable H-atom (most probably NH). In addition, the ^{13}C-NMR spectrum displayed a resonance at δ(C) 82.6 for an sp^3-C-atom and a low-field signal (δ(C) 170.2) attributable to a CO group. The chemical-shift value of the former matches the interval near 80 ppm which is diagnostic for a C(O)N grouping, *i.e.*, an N,O-acetal moiety [6]. In addition, 2D homo- and heteronuclear correlations (COSY and HMBC) corroborated a CH_2–CH–CH_2 linkage. This fact, together with a full NMR analysis, allowed us to ascribe formula **5** to the isolated compound (*Scheme 2*).

The structure is fully consistent with that of the heterocyclic product from the cyclocondensation of 4-(2-hydroxyphenyl)but-3-en-2-one, *Meldrum*'s acid, and $AcONH_4$ in refluxing EtOH [6]. Structure **5** was confirmed by mixed melting point with an authentic sample prepared as mentioned above [6]. The O-bridged pyridine **5** can be considered as the result of a *Hantzsch*-like reaction. Although the sole formation of the tricyclic compound **5** is rather surprising, *Hantzsch*-type by-products under *Biginelli* conditions has been described in [19]. It is assumed that urea

Scheme 2



1 **5**

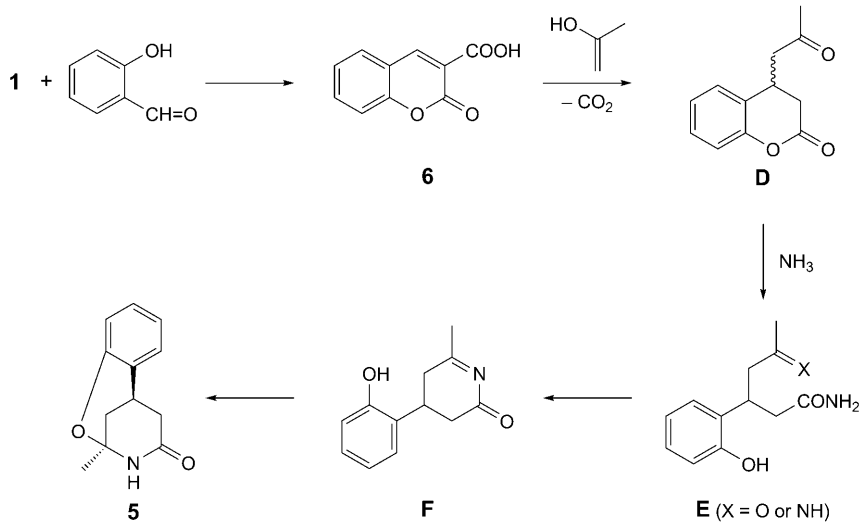
decomposes to CO_2 and NH_3, followed by the heterocyclization step. Structure **5** indicates that both *Meldrum*'s acid and acetone, together with salicylaldehyde and NH_3, take part in the formation of the pyridine ring. The involvement of acetone, generated from *Meldrum*'s acid, in a cascade mechanism clarifies certain domino processes with **1**, which have recently been proposed [3]. The transformation described here is, to our knowledge, one of a few examples where an intermediacy of acetone formed from **1** plays a key role [3][20]. A different result was obtained when treating salicylaldehyde with *Meldrum*'s acid and urea in boiling EtOH under HCl catalysis, which is the established *Biginelli* protocol. Instead of pyridine **5**, the product we isolated was coumarin-3-carboxylic acid (**6**). Afterwards, we detected traces of **6** in the mother liquor from the condensation leading to **5**. This would imply a different reaction pathway and consequently another intermediate to be considered when comparing the discussed foregoing pyrimidine route. Apparently, the OH group of the phenol part must account for the observed specific behavior. To confirm our assumption that coumarin derivative **6** might be a key intermediate in the condensation studied, acid **6** was treated with acetone and urea in hot AcOH, and indeed, the O-bridged pyridine **5** was obtained in 80% yield.

Based upon these findings, a reasonable mechanism can be formulated as shown in *Scheme 3*. Thus, coumarin-3-carboxylic acid (**6**) formed in conventional manner [21] through enone **B** undergoes *Michael* addition with acetone to provide species **D**. The loss of CO_2 may occur in parallel or consecutively. The lactone ring is cleaved by NH_3 to give intermediate amide **E**, which subsequently again cyclizes to give pyridone **F**. Finally, a nucleophilic addition of the phenolic OH group at the activated imine C-atom of the 2-aza-enone moiety forms the O-bridge in product **5** to terminate the reaction sequence. A similar mechanism has been reported for the ring transformation of 3-acetylcoumarin [22].

These results lead to a question regarding the factors that determine which of two pathways, pyrimidine or pyridine route, will be followed. One speculative explanation concerning salicylaldehyde is the assumption that the heterocyclization course of the carboxylic acid **6** proceeds also with urea, while $CONH_2$ linked to the reacting N-atom is lost during the follow-up reaction to yield pyridine **5**. Nevertheless, there is a lack of data to support this hypothesis.

In conclusion, we have demonstrated a different behavior of *Meldrum*'s acid in *Biginelli*-like condensation depending on reaction conditions. In addition to the formation of spiro-heterocycles reported by other authors, it has been shown that the

Scheme 3



three-component reaction of *Meldrum*'s acid with aldehydes and urea gives 6-substituted dihydropyrimidine-2,4(1*H*,3*H*)-diones. In contrast, salicylaldehyde unexpectedly gave an O-bridged pyridine derivative. An unusual incorporation in the tricyclic molecule of acetone released from the *Meldrum*'s acid fragment has been established. Some of the prepared compounds are evaluated for anticancer and AIDS antiviral activity at the National Cancer Institute in Bethesda.

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Experimental Part

General. M.p.: *Kofler* hot-stage microscope; not corrected. IR Spectra (KBr): *Nicolet Impact 400D* spectrometer; $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Varian Mercury 300* instrument; in (D_6)DMSO at 300 and 75 MHz, resp. δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *VG 7070E* mass spectrometer; at 70 eV; in *m*/*z*. Elemental analyses: *Carlo-Erba Elemental Analyzer 1012*.

Compounds **4**: *General Procedure.* A soln. of *Meldrum*'s acid (**1**; 1.44 g, 10 mmol), the appropriate aldehyde (10 mmol), and urea (0.6 g, 10 mmol) or thiourea (0.76 g, 10 mmol) in AcOH (20 ml) was refluxed for 14 h. After removal of the solvent, the oily residue was dissolved in EtOH and left to stand at r.t. The crystallized products **4** were collected by filtration.

*5,6-Dihydro-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione* (**4a**): Yield: 0.78 g (41%). White solid. M.p. 219–221° ([16a]: 216–218°). ^{1}H-NMR: 2.61 (*dd*, J = 16.2, 6.9, H_a–C(5)); 2.84 (*dd*, J = 16.2, 6.0, H_b–C(5)); 4.67 (*dt*, J = 6.3, 2.4, H–C(6)); 7.27–7.40 (*m*, 5 arom. H); 8.00 (*s*, H–N(1)); 10.16 (*s*, H–N(3)). ^{13}C-NMR: 38.3 (CH_2); 50.1 (CH); 126.1 (2 arom. C, C_o); 127.7 (1 arom. C, C_p); 128.7 (2 arom. C, C_m); 141.2 (1 arom. C, C_{ip}); 153.9 (C(2)=O); 169.9 (C(4)=O).

*5,6-Dihydro-6-(4-nitrophenyl)pyrimidine-2,4(1*H*,3*H*)-dione* (**4b**): Yield: 1.46 g (62%). Brownish powder. M.p. 257–259° ([16b]: 254–256°).

*5,6-Dihydro-6-(3-nitrophenyl)pyrimidine-2,4(1*H*,3*H*)-dione* (**4c**): Yield: 1.39 g (59%). Beige powder. M.p. 265–267°. IR: 3305, 3228 (NH), 1709, 1685 (CO), 1525, 1358 (NO_2), 1458 (CH_2), 803, 689

(=CH). ^{1}H-NMR: 2.72 (*dd*, *J* = 16.2, 7.2, H_a–C(5)); 2.89 (*dd*, *J* = 16.2, 5.7, H_b–C(5)); 4.87 (*ddd*, *J* = 7.2, 5.7, 2.4, H–C(6)); 7.66 – 7.72 (*m*, 1 arom. H); 7.79 – 7.82 (*m*, 1 arom. H); 8.14 (*s*, H–N(1)); 8.14 – 8.21 (*m*, 2 arom. H); 10.26 (*s*, H–N(3)). Anal. calc. for $C_{10}H_9N_3O_4$ (235.20): C 51.07, H 3.86, N 17.87; found: C 50.89, H 4.03, N 18.01.

*6-(4-Chlorophenyl)-5,6-dihydropyrimidine-2,4(1*H*,3*H*)-dione* (**4d**): Yield: 0.67 g (30%). White solid. M.p. 249 – 251° ([16c]: 251 – 253°).

*5,6-Dihydro-6-(4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione* (**4e**): Yield: 0.46 g (21%). White powder. M.p. 230 – 231° ([16d]: 228°).

*5,6-Dihydro-6-(thiophen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione* (**4f**): Yield: 0.31 g (16%). White crystals. M.p. 242 – 244° ([16a]: 243 – 245°).

*5,6-Dihydro-6-(2-methylpropyl)pyrimidine-2,4(1*H*,3*H*)-dione* (**4g**): Yield: 0.15 g (9%). White solid. M.p. 216 – 218° ([16e]: 215 – 217°).

*3,4,5,6-Tetrahydro-6-phenyl-2-thioxopyrimidin-4(1*H*)-one* (**4h**): Yield: 0.68 g (33%). White solid. M.p. 235 – 237° ([16f]: 238°).

*(±)-(2*RS*,6*SR*)-2,3,5,6-Tetrahydro-2-methyl-4*H*-2,6-methano-1,3-benzoxazocin-4-one* (**5**). *a*) This compound was prepared from salicylaldehyde (1.1 ml, 10 mmol), *Meldrum*'s acid (3.0 g, 21 mmol), and urea (0.6 g, 10 mmol) following the above protocol. Yield: 1.37 g (67%). M.p. 258 – 259° ([6]: 257 – 258°). ^{1}H-NMR: 1.60 (*s*, Me); 2.02 (*ddd*, *J* = 13.2, 1.8, 1.7, H_{eq}–C(11)); 2.14 (*dd*, *J* = 13.2, 1.8, H_{ax}–C(11)); 2.26 (br. *d*, *J* = 17.4, H_{eq}–C(5)); 2.63 (*dd*, *J* = 17.4, 4.8, H_{ax}–C(5)); 3.18 – 3.20 (*m*, H–C(6)); 6.74 (*d*, *J* = 7.8, arom. H–C(10)); 6.89 (*t*, *J* = 7.8, arom. H–C(8)); 7.13 (*t*, *J* = 7.8, arom. H–C(9)); 7.18 (*d*, *J* = 7.8, arom. H–C(7)); 8.37 (br. *s*, NH). ^{13}C-NMR: 26.9 (Me); 28.9 (C(6)); 32.1 (C(11)); 40.5 (C(5)); 82.6 (C(O)N); 116.7 (arom. C(10)); 120.7 (arom. C(8)); 125.6 (arom. C(6a)); 128.1 (arom. C(9)); 129.3 (arom. C(7)); 151.3 (arom. C(10a)); 170.2 (C(4)=O). EI-MS: 203 (M^+).

b) Alternative procedure: a mixture of *coumarin-3-carboxylic acid* (**6**; 0.6 g, 3.16 mmol), urea (0.19 g, 3.16 mmol), and acetone (3 ml) in AcOH (25 ml) was refluxed for 24 h. The solvent was evaporated, and the oily residue was triturated with EtOH. The crystalline product was filtered off. Yield: 0.52 g (80%). NMR Data are identical to those given above.

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