A Reexamination of the Mechanism of the Biginelli Dihydropyrimidine Synthesis. Support for an *N*-Acyliminium Ion Intermediate[1]

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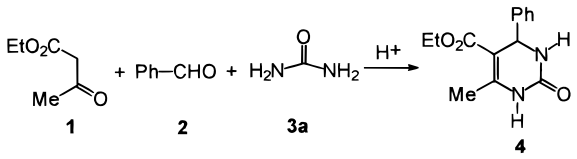
The mechansim of the three-component Biginelli dihydropyrimidine synthesis was reinvestigated using ^{1}H and ^{13}C NMR spectroscopy. Condensation of benzaldehyde, ethyl acetoacetate, and urea (or *N*-methylurea) in CD_3OH according to the procedure described by Biginelli produced the expected 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylates. According to NMR measurements, there is no evidence that the first step in the Biginelli reaction is an acid-catalyzed aldol reaction of ethyl acetoacetate and benzaldehyde leading to a carbenium ion intermediate, as has been suggested previously. In contrast, all experimental evidence points to a mechanism involving an *N*-acyliminium ion as the key intermediate, formed by acid-catalyzed condensation of benzaldehyde and urea (or *N*-methylurea). Interception of this iminium ion by ethyl acetoacetate produces open-chain ureides which subsequently cyclize to the Biginelli dihydropyrimidines.

In 1893 Biginelli reported the first synthesis of dihydropyrimidines of type **4** by a simple one-pot condensation reaction of ethyl acetoacetate (**1**), benzaldehyde (**2**), and urea (**3a**).[2] In the following decades the original cyclocondensation reaction has been extended widely to include variations in all three components, allowing access to a large number of multifunctionalized dihydropyrimidine derivatives.[3] Largely ignored for many years, the Biginelli reaction has recently attracted a great deal of attention, and several improved procedures for the preparation of dihydropyrimidines of type **4** have been reported within the past few years.[3−5] Various solid-phase modifications of the Biginelli reaction suitable for combinatorial chemistry have also been described.[6]



1 **2** **3a** **4**

The present interest in "Biginelli compounds" **4** is mainly due to their close structural relationship to the clinically important dihydropyridine calcium channel modulators of the nifedipine-type.[7] Properly functionalized dihydropyrimidines of type **4** show a very similar pharmacological profile to classical dihydropyridine drugs and several lead compounds with excellent calcium channel modulatory activity have been identified.[8] In addition, several marine alkaloids with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have been isolated.[9−11] Most notably among these are the crambine[9] and batzelladine alkaloids[10] and the more complex pentacyclic alkaloid ptilomycalin A,[11] which was recently synthesized employing a "tethered Biginelli condensation" as one of the key steps.[12]

Despite the importance and current interest in dihydropyrimidines of type **4,** the mechanism of the classical three-component Biginelli condensation has not been elucidated with certainty and remains disputed.[3] Early work by Folkers and Johnson suggested that *N*,*N*″-benzylidenebisurea (**15a**, see below), *i.e.* the primary bimolecular condensation product of benzaldehyde (**2**) and urea (**3a**), is the first intermediate in this reaction.[13] Later, Sweet and Fissekis have proposed a different mechanism postulating that carbenium ion **6** (see below), produced by an acid-catalyzed aldol reaction of benzaldehyde (**2**) with ethyl acetoacetate (**1**), is the key intermediate and is formed in the first and limiting step of the Biginelli reaction.[14] To decide which of the two fundamentally different mechanistic proposals is correct

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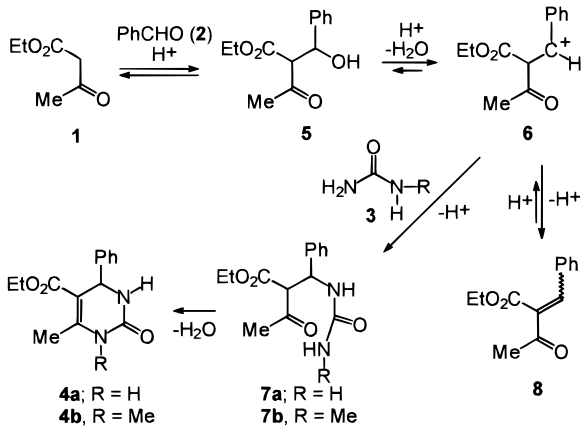
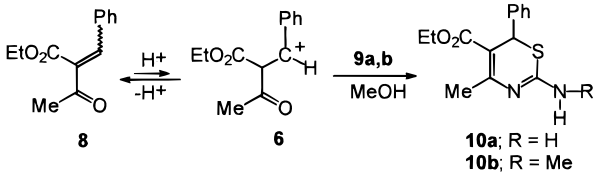
we have carried out a detailed reinvestigation of the mechanism of the Biginelli condensation using ^{1}H and ^{13}C NMR spectroscopy to identify possible intermediates. To be able to monitor all reactions by ^{1}H and ^{13}C NMR spectroscopy, CD_3OH was used as solvent in the NMR experiments which were carried out at room temperature in the presence of a catalytic amount of HCl (see Supporting Information).[13,15] As already suggested by Folkers and Johnson,[13] it is very likely that this three-component condensation proceeds via one of the three possible bimolecular reaction pathways from the urea/aldehyde/acetoacetate system. We have reinvestigated these pathways, which are discussed below.

The "carbenium ion mechanism" was proposed by Sweet and Fissekis,[14] who investigated the reaction in 1973 and suggested that an acid-catalyzed aldol condensation is the first and limiting step of the Biginelli condensation. It was proposed that under acid catalysis benzaldehyde (**2**) and ethyl acetoacetate (**1**) would react in an aldol-type fashion to produce the corresponding aldol **5**, which dehydrates in the presence of acid to the resonance-stabilized carbenium ion **6**.[14,16] Interception of cation **6** by urea (**3a**) or *N*-methylurea (**3b**) then produces ureides **7,** which ultimately cyclize to the Biginelli products **4**.[14] The main argument for the proposed mechanism made by the authors[14] relates to the fact that acid-catalyzed treatment of independently prepared enone **8** with *N*-methylurea (**3b**) also produced pyrimidine **4b**, albeit in moderate yield.[14] According to Sweet and Fissekis, protonation of enone **8** regenerates the carbenium ion intermediate **6,**[16] which then can react with urea (**3a**) or *N*-methylurea (**3b**) as described above (**6** → **7** → **4**).[14] It was also considered important that in the reaction of enone **8** with *N*-methylurea (**3b**) only the *N*1-methyl derivative **4b** was produced and not the *N*3-substituted isomer **12b** (see below), which corresponds to the regiochemical outcome observed in the three-component Biginelli reaction of ethyl acetoacetate (**1**), benzaldehyde (**2**), and *N*-methylurea (**3b**).[3,17]



According to the experimental data described herein, a mechanism involving carbenium ion **6** as the key intermediate in the Biginelli reaction seems unlikely. We have attempted to observe the acid-catalyzed aldol reaction of benzaldehyde (**2**) with ethyl acetoacetate (**1**) proposed by Sweet and Fissekis[14] under typical Biginelli reaction conditions. Although aldol reactions are most often catalyzed by base, the possibility of an acid-catalyzed aldol reaction of benzaldehyde with a 1,3-dicarbonyl component such as ethyl acetoacetate can not be a priori excluded.[18] However, it is well-known that in the case of acid catalysis the reaction products of the aldol reaction are in most cases the α,β-unsaturated carbonyl compounds (*i.e.* **8**) and not the β-hydroxycarbonyl (aldol) products (*i.e.* **5**).[18] Upon monitoring the reaction of benzaldehyde (**2**) and ethyl acetoacetate (**1**) in CD_3OH/HCl by ^{1}H and ^{13}C NMR spectroscopy, no evidence for an aldol reaction or any other reaction between the two components at room temperature could be obtained (see Supporting Information). The fact that benzaldehyde (**2**) and ethyl acetoacetate (**1**) do not react under conditions where the Biginelli condensation itself proceeds smoothly (see below) rules out the carbenium ion mechanism, where such a reaction is proposed to be the first step.

The possibility of a carbenium ion intermediate of type **6** in the Biginelli condensation seems even more unlikely if one considers the case where thiourea is substituted for urea. Both thiourea (**9a**)[17] and *N*-methylthiourea (**9b**)[19] are known to produce the expected dihydropyrimidine-2-thiones ("Biginelli compounds") when reacted with benzaldehyde (**2**) and ethyl acetoacetate (**1**) under standard Biginelli conditions.[3,17,19] In contrast, treatment of enone **8** with thiourea (**9a**) or *N*-methylthiourea (**9b**) under acid catalysis, *i.e.* under conditions where according to Sweet and Fissekis carbenium ion **6** is generated,[14] furnished exclusively the isomeric 2-amino-1,3-thiazines **10a**,**b** in excellent yields.



The structures of thiazines **10** were established by spectroscopic methods (see the Experimental Section) and, for **10a**, by comparison with authentic material.[19,20] In contrast to the reaction of enone **8** with *N*-methylurea,[14] where reaction times of 2 weeks and only moderate yields of pyrimidine **4b** have been encountered, the reaction times with thioureas **9** are much shorter (3−5 h), which can be rationalized by the considerable higher nucleophilicity of sulfur. The fact that in the three-component Biginelli reaction using thioureas the thiazine products **10** are not observed makes a carbenium ion intermediate of type **6** unlikely.

The so-called "ureidocrotonate mechanism" was already considered by Folkers and Johnson[13] but was ruled out as a mechanistic pathway since the bimolecular condensation product of ethyl acetoacetate (**1**) and urea (**3a**), *i.e.* ureidocrotonate **11a**,[21] was shown to rapidly

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(16) A more modern description of the carbenium ion intermediate would be the tautomeric *O*-protonated enone.[18]

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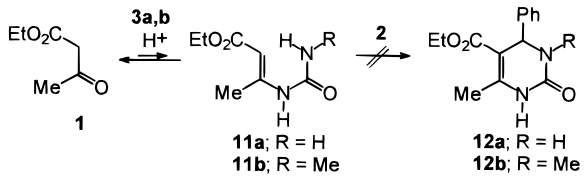
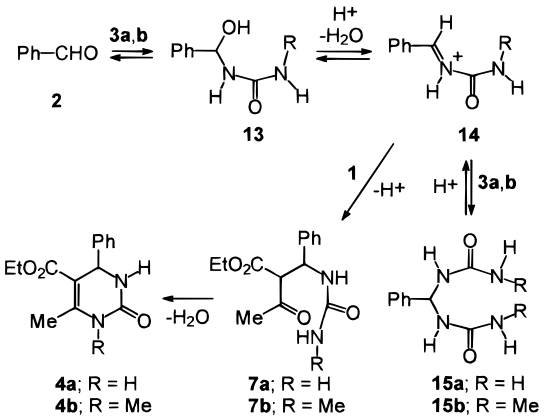
hydrolyze under the typical Biginelli reaction conditions (EtOH, HCl).[13] Since the fact that ureidocrotonate **11a** is sensitive to hydrolysis does not exclude this intermediate for the Biginelli reaction, we have reinvestigated this pathway (including the *N*-methyl analogue **11b**[22]). The independently prepared[21,22] enamides **11a**,**b** were shown to rapidly hydrolize in CD_3OH when catalytic amounts of acid (and water) were present (see the Supporting Information). While ureidocrotonates **11a**,**b** can be prepared from **1** and **3a**,**b** under strictly anhydrous conditions, *i.e.* by allowing a mixture of **1** and **3** to react in a desiccator over concentrated H_2SO_4 for several days,[21,22] it is evident that under Biginelli reaction conditions the equilibrium is far on the acetoacetate/urea side.



Another argument against the involvment of an ureidocrotonate intermediate relates to the fact that *N*-methylurea (**3b**) reacts with ethyl acetoacetate (**1**) to furnish exclusively regioisomer **11b** bearing the *N*-methyl substituent at the terminal amino group.[22] The formation of a Biginelli dihydropyrimidine in a 5 + 1 cyclocondensation manner from **11b** and benzaldehyde would be expected to lead to the *N*3-substituted Biginelli product **12b**,[19] which is observed neither in the three-component Biginelli reaction (see above)[3,14,17] nor from the reaction of ureide **11b** with benzaldehyde under Biginelli conditions. In both cases the isomeric dihydropyrimidine **4b** is formed as the exclusive regioisomer, which further supports Folkers and Johnson's[13] proposition that the Biginelli reaction does not proceed through an ureidocrotonate intermediate of type **11** and that immediate hydrolysis of **11** takes place if the reaction is started from such ureidocrotonates.

Finally, we have considered the original mechanistic proposal made by Folkers and Johnson,[13] who suggested that the first step in the three-component Biginelli condensation is the reaction of benzaldehyde (**2**) with urea (**3a**). When benzaldehyde (**2**) and urea (**3a**, 2 mol equiv) were reacted under typical Biginelli conditions (CH_3OH/HCl) at room temperature, the anticipated condensation product bisureide **15a**[23] started to precipitate from the solution within 15−20 min. Bisureide **15a** was also formed when equimolar amounts of the two components were employed, and the analogous condensation product (**15b**)[24] was produced when *N*-methylurea (**3b**) was used instead of urea (**3a**). However, when these reactions were carried out *in the presence of ethyl acetoacetate (1)* under otherwise identical reaction conditions, bisureides **15a**,**b** were not formed, but dihydropyrimidines **4a**,**b** started to precipitate slowly from the reaction mixture within 1−2 h (complete conversion took 2−3 days).



On the basis of these experimental results, we propose the following mechanistic concept. Addition of ureas **3a** or **3b** to benzaldehyde (**2**) leads to *N*-(1-hydroxybenzyl)-ureas of type **13** via standard nucleophilic addition. Although this is likely to be an equilibrium reaction, "hemiaminals" **13** are expected to undergo rapid dehydration in the presence of acid to a carbenium ion which may be formulated as a highly reactive *N*-acyliminium species, *i.e.* **14**. In the absence of the 1,3-dicarbonyl compound a second equivalent of urea **3a,b** is added to furnish bisureides **15a**,**b,** which due to their low solubility[23,24] precipitate from the reaction mixture. However, if ethyl acetoacetate (**1**) is present in the reaction medium, iminium ion **14** is intercepted by the 1,3-dicarbonyl compound, possibly through its enol tautomer, to furnish intermediates **7a**,**b,** which then cyclize to the Biginelli compounds **4a**,**b**. Monitoring the formation of bisureides **15a**,**b** from **2** and **3a**,**b** by ^{1}H NMR (CD_3OH, HCl) did not allow the observation of any intermediates, *e.g.* **13**, in this process. We assume that the first addition step (**2** → **13**) is the rate-determining (slow) step and that both the subsequent acid-catalyzed dehydration (**13** → **14**) and the addition of a second equivalent of urea to the iminium ion (**14** → **15**) are fast steps, therefore not allowing **13** to accumulate. This seems also to be true for the Biginelli reaction itself: under typical Biginelli conditions, no intermediates in the reaction of ethyl acetoacetate (**1**), benzaldehyde (**2**), and *N*-methylurea (**3b**) could be observed by ^{1}H or ^{13}C NMR spectroscopy. After about 30 min, signals due to the final product (**4b**) started to appear in the ^{1}H NMR that were easily identified, as these signals are nicely separated from the peaks due to starting materials (see Table S1 in the Supporting Information). As the reaction proceeded, these peaks became more prominent and after *ca.* 18 h 50% conversion was achieved. At this point **4b** started to precipitate from the NMR solution and the experiment was terminated.

In conclusion, we have shown that the original mechanistic proposal put forward by Folkers and Johnson in 1933,[13] involving an aldehyde−urea condensation product as key intermediate in the Biginelli condensation is essentially correct. The first step in this mechanism evidently involves the acid-catalyzed formation of an *N*-acyliminium ion precursor of type **14** from an aldehyde and urea component. In the case of amides and carbamates, this reaction pathway is well-established,[25] and at least one example exists for ureas.[26] The second step (**14** → **7**) can be regarded as an addition of a π-nucleophile, *i.e.* the enol tautomer of acetoacetate **1** to the electron-deficient *N*-acyliminium species **14**. Additions of π-nucleophiles to iminium species are very well-known and

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have proven to be valuable synthetic transformations in target-oriented synthesis.[25] Importantly, several examples of this type of reaction involving 1,3-dicarbonyl compounds and urea-derived *N*-acyliminium ions yielding dihydropyrimidines of type **4** are reported in the literature,[26] providing additional support for this mechanism.

Experimental Section

General Methods. Consult ref 4. Details of all NMR measurements are presented in the Supporting Information along with Tables S1 and S2.

Reagents. Benzaldehyde (**2**) and ethyl acetoacetate (**1**) were freshly distilled under vacuo and stored under argon. The following compounds were prepared according to literature procedures: enone **8**,[14] ureidocrotonate **11a**,**b**,[21,22] and bisureides **15a**,**b**.[23,24] The preparation of **15a**,**b** is given in the Supporting Information).

Ethyl 2-Amino-4-methyl-6-phenyl-6*H*-1,3-thiazine-5-carboxylate (10a). A solution of enone **8** (2.18 g, 10 mmol) and thiourea **9a** (0.76 g, 10 mmol) in MeOH (10 mL) containing concentrated HCl (1 mL) was heated at reflux for 3−5 h. After all starting material had been consumed (TLC), the mixture was concentrated in vacuo. The crude product (**10a**·HCl) was dissolved in H_2O (30 mL) and treated with ice-cold 2 N NaOH (6 mL) to yield 2.31 g (84%) of thiazine **10a** as a colorless solid, mp 120−122 °C ($CHCl_3$/hexane) (lit.[23] mp 120−122 °C). This product was identical (TLC, IR, ^{1}H NMR) with an authentic sample prepared according to ref 19

Ethyl 4-Methyl-2-(methylamino)-6-phenyl-6*H*-1,3-thiazine-5-carboxylate (10b). This compound was prepared in an analogous fashion as decribed above for **10**a, using *N*-methylthiourea (**9b**) instead of thiourea (**9a**) to yield 2.29 g (79%) of **10b** as colorless solid: mp 128−131 °C; IR (KBr) 3340, 3220, 1690, 1670 cm-1; ^{1}H NMR (DMSO-d_6) δ 1.14 (t, J = 7.0 Hz, 3H), 2.45 (s, 3H), 2.82 (3H), 4.04 (q, J = 7.0 Hz, 2H), 5.33 (s, 1H), 7.15−7.27 (m, 5H), 7.84 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.2, 24.5, 28.8, 41.6, 59.5, 101.1, 126.5, 127.1, 128.4, 142.7, 153.5, 158.6, 166.5. Anal. Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 62.14; H, 6.34; N, 9.58.

Ethyl 1,6-Dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b) from Ureidocrotonate 11b. A mixture of ureidocrotonate **11b** (1.86 g, 10 mmol) and benzaldehyde (**2**) (1.06 g, 10 mmol) in MeOH (40 mL) containing 1 drop of concentrated HCl was heated under reflux for 3 h. The solution was kept at −20 °C for several hours to yield 1.97 g (72%) of pyrimidine **4b**, mp 176−178 °C (lit.[14,17] mp 176−178 °C). The crude ^{1}H NMR spectrum of the concentrated reaction mixture showed no evidence for the presence of the isomeric pyrimidine **12b**.[19] For ^{1}H and ^{13}C NMR data, see Tables S1 and S2.

Ethyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a). A mixture of ethyl acetoacetate (**1**) (1.30 g, 10 mmol), benzaldehyde (**2**) (1.06 g, 10 mmol), urea (**3a**) (0.60 g, 10 mmol), and MeOH (5 mL) containing 1−2 drops of concentrated HCl was stirred at rt. After 2 h product began to precipitate from the solution, and after 3 d of stirring at rt the precipitated solid was filtrated to yield 1.98 g (76%) of pyrimidine **4a**: mp 206−207 °C (lit.[15] mp 202−204 °C, lit.[14] mp 207−208 °C); ^{1}H NMR (DMSO-d_6) δ 1.14 (t, J = 7.0 Hz, 3H), 2.26 (s, 3H), 3.91 (q, J = 7.0 Hz, 2H), 5.12 (d, J = 4.5 Hz, 1H), 7.30 (s, 5H), 7.67 (d, J = 4.5 Hz, 1H), 9.09 (br s, 1H).

Ethyl 1,6-Dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b). This pyrimidine was prepared in an analogous fashion as decribed above for **4a**, using *N*-methylurea (**3b**) instead of urea (**3a**) to yield 2.05 g (79%) of **4b** as colorless solid, mp 176−178 °C. This material was identical (mp, IR, ^{1}H NMR) with a sample prepared from **11b** and **2** described above.

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Supporting Information Available: Experimental procedures for **15a**,**b**, details of ^{1}H and ^{13}C NMR measurements, Tables S1 and S2 (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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