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Unexpected result of alkaline hydrolysis of Biginelli compounds

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Abstract: 4-Aryl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-ones are final products of transformation of ethyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates in alkaline hydrolytic conditions.

Keywords: ethyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates, Biginelli compounds, 4-aryl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-ones, alkaline hydrolysis, decarboxylation, coupling

- **Introduction**
- **Results and Discussion**
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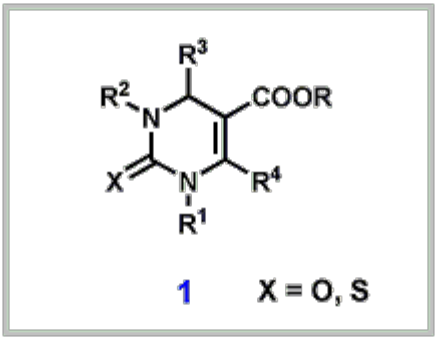
Introduction

Esters of 4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acids (**1** X = O, R_3 = aryl) (so-called "Biginelli compounds") are known already more than 111 years [1, 2]. However, these compounds and their 2-thioxo analogues received significant attention only in the last 20 years after their diverse biological activity was discovered. For example, they are active antihypertensive agents [3, 4], kinesin Eg5 inhibitors [5], α_{1a} antagonists [6], etc. Besides, owing to its versatile reactivity they were applied in the syntheses of a large variety of heterocycles [7, 8].



1 X = O, S

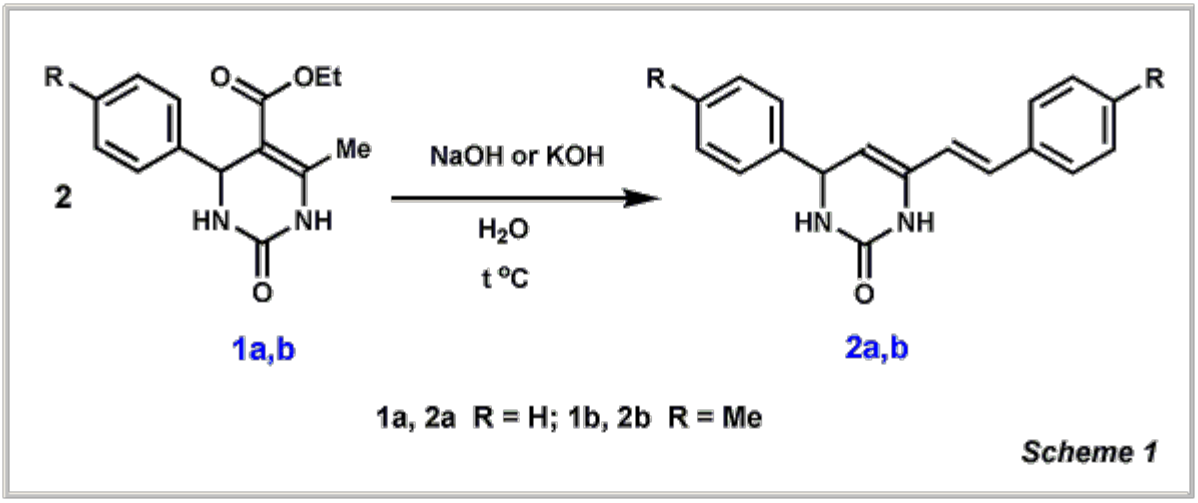
A principal feature of reactivity of Biginelli compounds is their behaviour towards hydrolytic conditions. However, up to the present, the obtained data are severely limited and contradictory. As early as 1893, Pietro Biginelli showed [2] that boiling of ethyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a** X = O, R = Et, R_1 = R_2 = H, R_3 = Ph, R_4 = Me) in water in the presence of KOH led to a deep decomposition of **1a** to result in benzaldehyde, ammonia, potassium carbonate, etc. Zigeuner [9] demonstrated that $N_{(1)}$-unsubstituted Biginelli compounds (**1** R = Et, CH_2Ph) were inactive under alkaline hydrolysis conditions (5 % alcoholic solution of KOH, reflux) whereas $N_{(1)}$-methyl substituted ones underwent easy hydrolysis to form the corresponding tetrahydropyrimidine-5-carboxylic acids. In 1993, in review [7] devoted to Biginelli compounds, rather poor reactivity of their ester group towards hydrolysis was pointed out. The author of the review attributed this effect to the strong conjugation of this group with the adjacent C=C double bond. However, it was reported in short communication [10] that $N_{(1)}$-unsubstituted Biginelli compounds (**1** R = Me), when refluxed in methanol in the presence of 1 M aqueous solution of NaOH, were subjected to hydrolysis and decarboxylation to produce mixtures of 5-unsubstituted 4-hydroxyhexahydro-, 1,2,3,4-tetrahydro- and 1,2,5,6-tetrahydropyrimidin-2-ones. It should be noted that experimental details of this investigation were lacking in the cited work.

Thus, from the aforesaid, it would be interesting to study the behaviour of Biginelli compounds towards hydrolytic conditions thoroughly. In this communication, some preliminary results of our investigation on alkaline hydrolysis of ethyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**1a,b**) are presented.

Results and Discussion

We found that on refluxing **1a** in water in the presence of 3 equivalents of NaOH, gas evolution occurs in the initial period of time to result in abundant foam formation. Gradually foaming decreases, odours of benzaldehyde and ammonia are recognized, humid pH test paper turns blue at outlet from the reflux condenser. These observations indicate that a deep decomposition of **1a** involving the ring cleavage takes place in the reaction conditions. As the reaction proceeds, water-insoluble white precipitate becomes yellowish and loose. According to TLC data, the precipitate taken in different points of time is a mixture of the starting **1a** and at least four other compounds. With time, ratio of all components of the mixture changes and the most chromatographically mobile compound accumulates. In 5-6 hours this material becomes practically single. After completion of the reaction, the pale yellow solid was isolated by

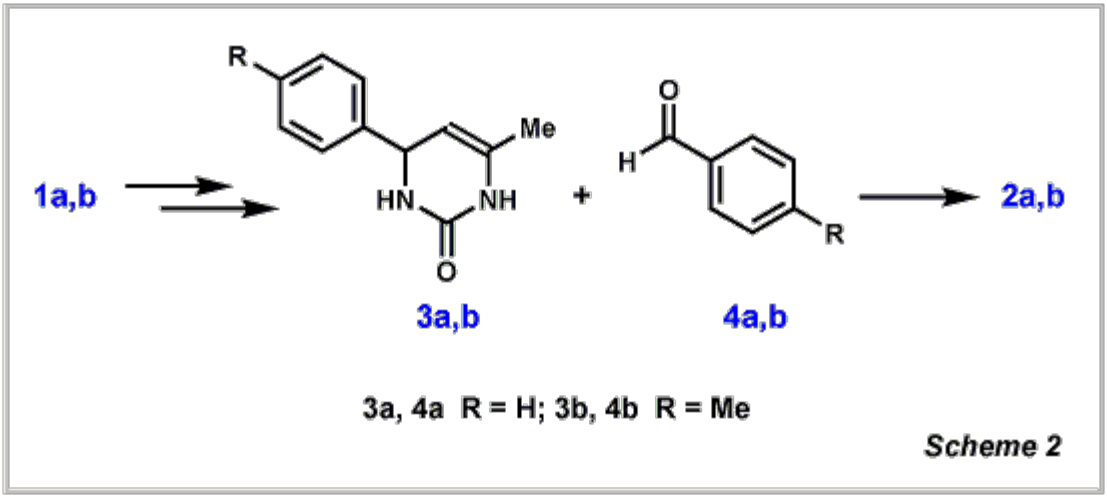
filtration and identified as 4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-one (**2a**) (*Scheme 1*). Yield of **2a** was 74 % based on 2 equiv. of **1a** (*Method A*).



Alkaline hydrolysis of **1b** (aqueous NaOH, reflux) takes place in much the same way as **1a**. However, full conversion of **1b** into the pyrimidine **2b** requires more time (about 9 h). Under these conditions, **2b** was obtained in 67 % yield in practically pure form (*Method A*).

The application of potassium hydroxide instead of sodium hydroxide proved to be less effective for the synthesis of **2a,b** from **1a,b**. Indeed, heating of **1a** in refluxing aqueous solution of KOH (3 equiv.) for 6 h gives pure **2a** in only 46 % yield. Under the same conditions, transformation of **1b** into **2b** is not completed and the product isolated after 9 h is a mixture of **1b** and **2b** in a 25:75 molar ratio correspondingly (1H NMR data).

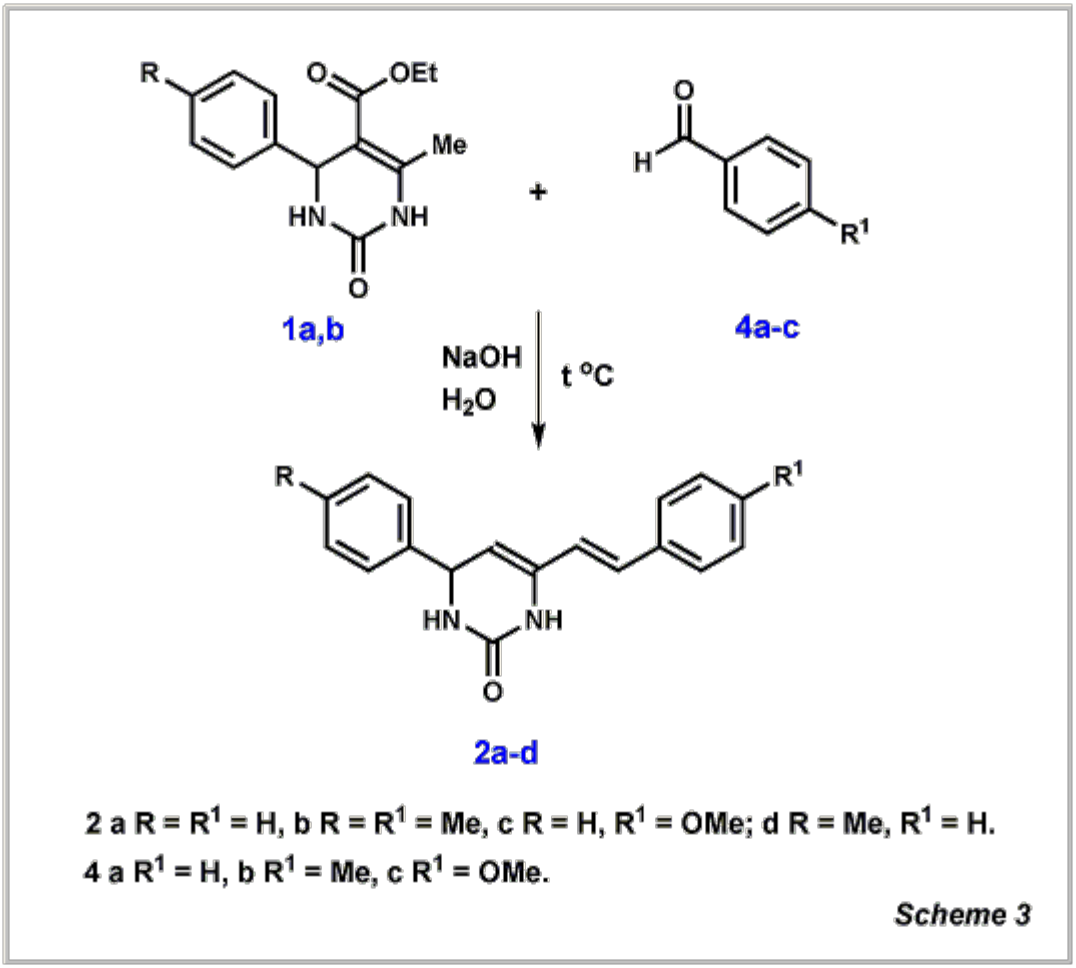
The formation of **2a,b** in the above reactions can probably be explained by the coupling of the corresponding 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-ones (**3a,b**) and aromatic aldehydes (**4a,b**) which are produced as intermediates in result of a deep destruction of Biginelli compounds under the conditions applied (*Scheme 2*).



Surprisingly, though the process is obviously multistage, **2a,b** are formed in rather good yields (67-74 %). It seems to depend on a number of various factors, in particular, on high hydrolytic

stability of **2a,b** due to the presence of the conjugated aryldiene system in their molecules.

We supposed that addition of the corresponding aldehydes **4a,b** to the reactions of **1a,b** described above could trap the intermediate **3a,b** to give hydrolytically stable **2a,b**. It would increase degree of utilization of the starting pyrimidines **1a,b** and yields of **2a,b**. In fact, refluxing of **1a** in water in the presence of NaOH (3 equiv.) and benzaldehyde (**4a**) (1 equiv.) for 5 h 40 min provides **2a** in high yield (79 % based on 1 equiv. of **1a**) (*Scheme 3*) (*Method B*). Under the same conditions, the reaction of **1b** with 4-methylbenzaldehyde (**4b**) for 9 h leads to **2b** in 71 % yield.



The developed approach can be also used in the synthesis of other 4-aryl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-ones (**2**) including "asymmetric" ones (**2** R≠R1). Thus, the reaction of **1a** with anisic aldehyde (**4c**) (1.5 equiv.) in the presence of NaOH (3 equiv.) in water (reflux, 7 h) gives **2c** in 79 % yield, and the treatment of **1b** with benzaldehyde (1.5 equiv.) in similar conditions (NaOH, water, reflux, 9 h) results in **2d** in 81 % yield (*Scheme 3*).

The structures of **2a-d** were determined by IR, 1H and 13C NMR spectroscopic methods as well as elemental analytical data. It should be noted that all the obtained compounds were stereo homogeneous with (*E*)-configuration of the styryl fragment.

Conclusion

In summary we have found that Biginelli compounds show rather high reactivity towards water-alkali solutions by heating. For the first time it was demonstrated that the resulting products of transformation of these compounds in the studied conditions were 4-aryl-6-styryl-1,2,3,4-tetrahydropyrimidin-2-ones. We have also developed a general convenient synthesis of the last pyrimidines based on reaction of Biginelli compounds with aromatic aldehydes in the presence of alkali by heating in water.

References

1. P. Biginelli, *Ber*., 1891, **24**, 1317.

2. P. Biginelli, *Gazz. Chim. Ital*., 1893, **23**, 360.

3. K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg, B. C. O'Reilly, *J. Med. Chem*., 1991, **34**, 806.

4. G. J. Grover, S. Dzwonczyk, D. M. McMullen, D. E. Normandin, C. S. Parham, P. G. Sleph, S. Moreland, *J. Cardiovasc. Pharmacol.*, 1995, **26**, 289.

5. S. J. Haggarty, T. U. Mayer, D. T. Miyamoto, R. Fathi, R. W. King, T. J. Mitchison, S. L. Schreiber, *Chem. Biol*., 2000, 7, 275.

6. D. Nagarathnam, S. W. Miao, B. Lagu, G. Chiu, J. Fang, T. G. M. Dhar, J. Zhang, S. Tyagarajan, M. R. Marzabadi, F. Q. Zhang, W. C. Wong, W. Y. Sun, D. Tian, J. M. Wetzel, C. Forray, R. S. L. Chang, T. P. Broten, R. W. Ransom, T. W. Schorn, T. B. Chen, S. O'Malley, P. Kling, K. Schneck, R. Benedesky, C. M. Harrell, K.P. Vyas, C. Gluchowski, *J. Med. Chem*., 1999, **42**, 4764.

7. C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937.

8. C. O. Kappe, *Acc. Chem. Res*., 2000, **33**, 879.

9. G. Zigeuner, C. Knopp, H. Blaschke, *Monatsh. Chem*., 1976, **107**, 587.

10. T. G. Steele, C. A. Coburn, M. A. Patane, M.G. Bock, *Tetrahedron Lett*., 1998, **39**, 9315.