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Effect of high pressure on Biginelli reactions. Steric hindrance and mechanistic considerations

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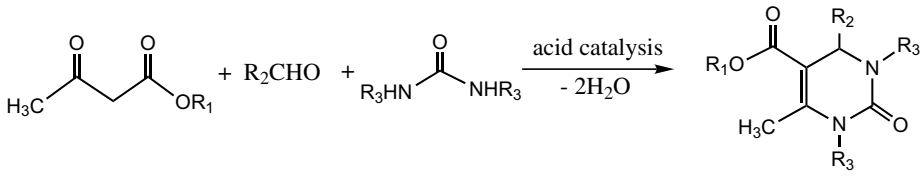
Abstract—The effect of high pressure is examined in 3-CC Biginelli reactions. This effect is small when moderately hindered aldehydes or ureas are involved. However, particularly in the case of bulky aldehydes, the sensitivity of the reaction to pressure increases with increasing steric congestion in line with earlier studies described in the reference list. The results also provide insights into the mechanism. Such a result highlights the synthetic utility of high pressure activation for the preparation of hindered Biginelli products.

One-pot multicomponent reactions (M-CC) are attracting considerable interest for various reasons.[1] They are particularly adapted for the elaboration of combinatorial libraries which may, eventually, lead to the discovery of biologically active compounds.[2] M-CC condensations involve three or four compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials. The Biginelli reaction is a 3-CC multicomponent reaction involving an α-ketoester, an urea, and an aldehyde yielding 3,4-dihydro-2(1*H*)-pyrimidinones (Eq. 1).[3] Such compounds are prone to develop interesting bioactivity and could be used as channel blockers, antihypertensive, antiviral, antibacterial, antiinflammatory, and antitumor agents.[4–6] A variant of the Biginelli condensation has been recently described for its application to the total synthesis of bioactive guanidine alkaloids.[7]

The Biginelli reaction suffered in former times from the need of harsh conditions to afford acceptable yields. Recently, the development of mild Lewis acid[4–6,8,9] and heteropolyacid[10] catalysts has considerably improved the outcome of the reaction. In presence of such catalysts, the reaction is relatively facile, leading to high yields of dihydropyrimidinones. This is true, however, insofar as unhindered ureas and aldehydes are involved. In our long lasting concern at investigating the effect of steric hindrance in high pressure reactions,[11] we examined recently two 3-CC condensations under pressure. We found that Passerini reactions could be deeply affected by pressure when hindered substrates (ketones or isocyanides) were reacted.[12] The same observation held true in Strecker condensations.[13] We have found this interesting as to whether this unexpected phenomenon could be further extended to other multicomponent reactions such as Biginelli condensations, keeping



(1)

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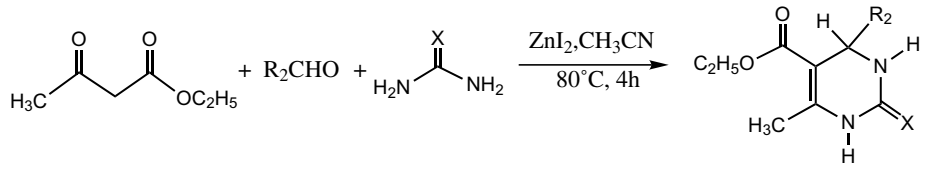

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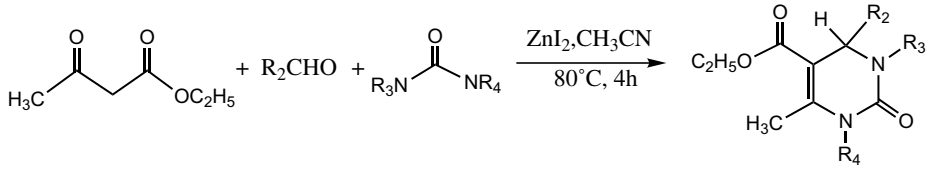


(3)

in mind the possible correlation between bioactivity and steric parameters.[14]

In a first step, we submitted an acetonitrile solution of ethyl acetoacetate, urea or thiourea, and an aliphatic aldehyde in the presence of the Lewis acid ZnI_2 to ambient and 300 MPa pressure (Eq. 2). The experimental conditions were intentionally chosen so as to limit the yields of dihydropyrimidinones resulting from unhindered aldehydes to reasonable values at 0.1 MPa in order to be able to appreciate the pressure effect.[15]

In most cases, the reaction proceeded cleanly and afforded the desired dihydropyrimidinone as unique product. The results are listed in Table 1. β_{300} is the expression of the pressure effect on the yields. Inspection of the results reveals

(i) a modest pressure effect in reactions involving unhindered aldehydes (entries 1, 2, 7),
(ii) an enhanced pressure sensitivity in Biginelli condensations with aldehydes of higher steric congestion (entries 3, 5, 6, 8). As expected from our previous studies,[12,13] the reaction involving the aldehyde with the less sterically demanding isobutyl group (entry 4) (compared to the isopropyl group) is less affected by pressure than the corresponding reaction described in entry 3.

Figure 1 provides an illustrative picture of the pressure effect in Biginelli reactions involving ethyl acetoacetate, urea, and aldehydes of increased steric complexity. Whereas β_P slowly increases in the case of valeraldehyde, the increment is higher when 2-ethylbutyraldehyde is reacted and, even more, in the reaction of pivalaldehyde.

The results depicted in Table 1 and Figure 1 are reminiscent of those relevant of the pressure effect on hindered Passerini reactions[12] and Knoevenagel condensations.[16]

Next, we studied the Biginelli condensation using urea and *N*-methyl substituted ureas with the unhindered aldehyde, propionaldehyde, and the sterically congested pivalaldehyde, respectively (Table 2, Eq. 3).

Whereas the reactivity of propionaldehyde in the Biginelli reaction involving *N*-mono or *N*,*N*-disubstituted ureas is independent of the type of urea, the *tert*-butyl group of pivalaldehyde is a compressive group leading to low or no reactivity at atmospheric pressure. Application of pressure has little influence on the yield of dihydropyrimidinones stemming from propionaldehyde. This is obviously, not the case in the pivalaldehyde reactions, which are all highly sensitive to pressure. It

Table 1. Effect of pressure on the yield of dihydropyrimidinones[a] (Eq. 2)

Entry	X	R_2	Yields (%)		β_{300}
			0.1 MPa	300 MPa	
1	O	C_2H_5	43	73	1.7
2	O	C_3H_7	21	37	1.8
3	O	$(CH_3)_2CH$	33	77	2.3
4	O	$(CH_3)_2CHCH_2$	40	55	1.4
5	O	$C_3H_7(CH_3)CH$	19	60	3.0
6	O	$(C_2H_5)_2CH$	20	77	3.0
7	S	C_3H_7	7	11	1.6
8	S	$(CH_3)_3C$	0	10	High

[a] Aldehyde (0.6 mmol), urea (0.44 mmol), ethyl acetoacetate (0.40 mmol), ZnI_2 (0.04 mmol), solvent (acetonitrile), 80 °C, reaction time (4 h). β_{300} is the ratio of yields at 300 and 0.1 MPa, respectively.

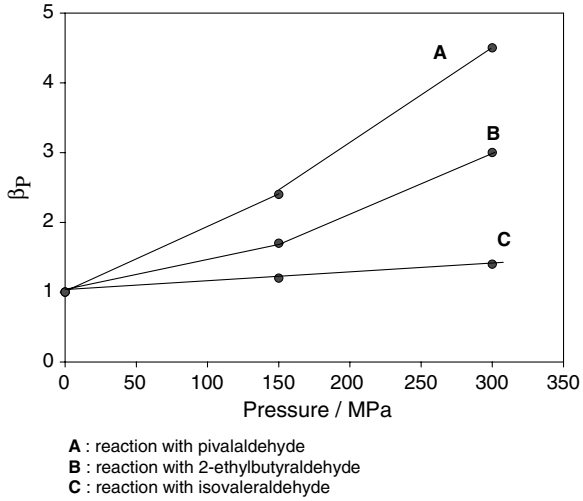
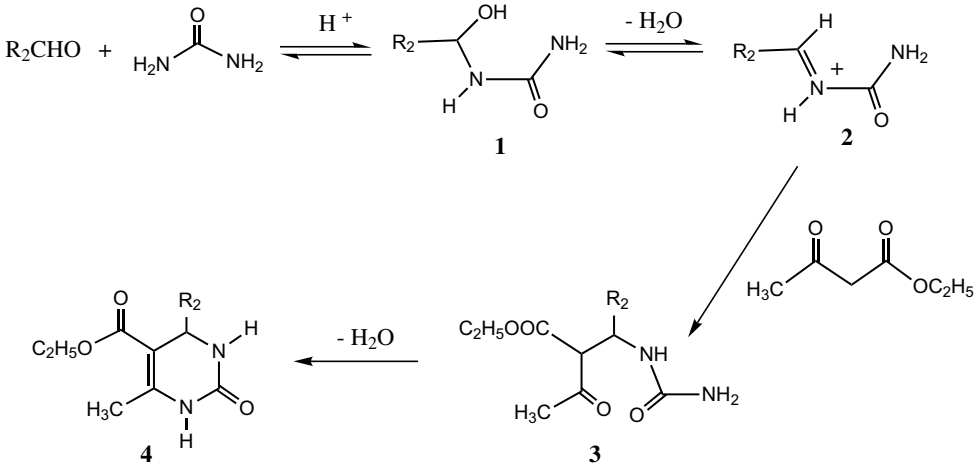


Figure 1. Effect of pressure on β_P (±0.1) in Biginelli reactions.

Table 2. Effect of pressure on the yield of dihydropyrimidinones issued from propionaldehyde and pivalaldehyde[a] (Eq. 3)

R_3	R_4	R_2	Yields (%)[a]		β_{300}
			0.1 MPa	300 MPa	
H	H	C_2H_5	43	73	1.7
		$(CH_3)_3C$	2 (6)	35 (65)	High
CH_3	H	C_2H_5	85	90	1.1
		$(CH_3)_3C$	0 (2)	15 (40)	High
CH_3	CH_3	C_2H_5	67	65	1.0
		$(CH_3)_3C$	0 (0)	8 (20)	High

[a] Conditions as in Table 1. The yields in parentheses refer to experiments carried out in excess ethyl acetoacetate in the absence of acetonitrile, other conditions being standard.



Scheme 1.

should be emphasized that the yields at 300 MPa can be noticeably increased when operating in excess ethyl acetoacetate serving as reagent and medium. These experiments play a confirmatory role to assess the correlation between pressure and steric hindrance.[11]

Recent mechanistic investigations supported the original proposal made by Folkers and Johnson.[17] Kappe[18] and Hu et al.[19] both agreed with a hierarchical scheme in which the first step consists in the nucleophilic addition of aldehyde and urea to give **1**, followed by interception of intermediate **2** by the ketoester and final cyclization of the ureide **3** to the Biginelli product **4** (Scheme 1). The first step was assumed by Kappe to be rate determining on the basis that presumed intermediates **1**, **2** could not be isolated, suggesting therefore a rapid reaction of **1** or **2** with the acetoacetate. The ureide **3** could be observed in the Biginelli reaction involving benzaldehyde, urea and a bulky β-ketoester, thus supporting Scheme 1.[19]

In order to verify the mechanistic proposal, we followed the kinetics of the Biginelli reaction involving ethyl acetoacetate, urea, and pivalaldehyde at 0.1 and 250 MPa, respectively (Fig. 2).

The formation of the dihydropyrimidinone is rapid under pressure. Both graphs show asymptotic yields culminating to 40% at 250 MPa and 11% at ambient pressure. The ^{1}H NMR spectrum of the reaction mixture at various time intervals showed the formation of **1**: 0.85 (s, 3H), 4.85 (br, 1H), 5.50 (br s, 1H), 6.10 (br s, 1H). With prolonged reaction times at 0.1 MPa or increased pressure the protons of the *tert*-butyl group shifted to 0.75 ppm (s, 3H) with a corresponding decrease in intensity of peaks at 4.85, 5.50, 6.10 ppm and appearance of peaks corresponding to the protons of **4**. Submitting 4:1 mixtures of **1** and **4** (which resulted from experiments involving either urea or *N*-methylurea at 0.1 MPa) under standard conditions (ZnI_2, 24 h, excess

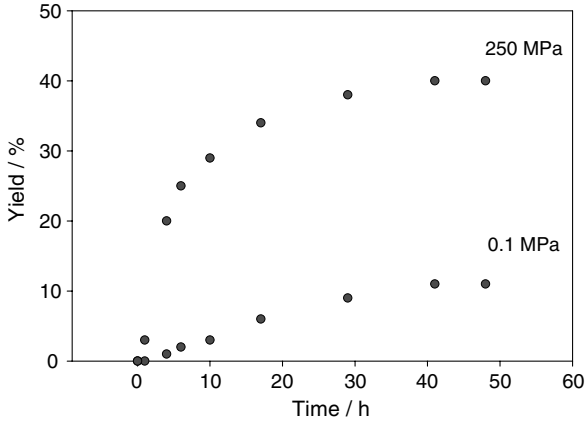


Figure 2. Kinetics of the Biginelli reaction involving pivalaldehyde, urea, and ethyl acetoacetate under standard conditions.[15]

ketoester) at either 0.1 or 300 MPa for 15–24 h showed complete transformation into **4**. The fact that pressure had no effect on the following steps leading to **3** and **4** gives support to Kappe's suggestion, the rate-determining step being apparently the formation of **1**. The major pressure effect detected in the present hindered Biginelli reactions is, therefore, a consequence of steric constraints. The result is of primary importance and stays in full harmony with those previously reported in our laboratory.[12,13,16]

Conclusion

The three-component Biginelli reaction giving access to dihydropyrimidinones is little sensitive to pressure as long as unhindered aldehydes are involved. With increasing steric congestion, however the sensitivity of the reaction to pressure is clearly enhanced. The results also support a multistep mechanism where the first step consisting of the nucleophilic addition of aldehyde to urea would be rate determining. The remarkable capacity of high pressure to relieve steric inhibition is probably in relation with an early transition state, which is shifted to product when steric constraints gain more importance. Pressure is therefore, an essential physical parameter in difficult Biginelli syntheses like microwaves, which may also have an activation effect.[20]

References and notes

1. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3168–3210.
2. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 565–600.
3. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.
4. Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270–6272.
5. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864–3868.
6. Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. *Synlett* **2001**, 863–865.
7. Aron, Z. D.; Overman, L. E. *Chem. Commun.* **2004**, 253–265.
8. Yadav, J. S.; Subba Reddy, B. V.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341–1345.
9. Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465–3468.
10. Yadav, J. S.; Subba Reddy, B. V.; Sidhar, P.; Reddy, J. S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. *Eur. J. Org. Chem.* **2004**, 552–557.
11. Jenner, G. *J. Chem. Soc., Faraday Trans. 1* **1985**, *81*, 2437–2460.
12. Jenner, G. *Tetrahedron Lett.* **2002**, *43*, 1235–1238.
13. Jenner, G.; Ben Salem, R.; Kim, J. C.; Matsumoto, K. *Tetrahedron Lett.* **2003**, *44*, 447–449.
14. Fujita, T.; Iwamura, H. *Top. Curr. Chem.* **1983**, *114*, 119–157.
15. Typical experimental procedure: A mixture of zinc iodide (25 mg, 0.08 mmol), urea (72 mg, 1.2 mmol), ethyl acetoacetate (104 mg, 0.8 mmol), and pivalaldehyde (70 mg, 0.80 mmol) was placed in a flexible 1 mL PTFE tube. The volume was adjusted with acetonitrile. Then the ampoule was closed, introduced in the vessel thermostated at 80 °C and pressurized to 300 MPa. After release of pressure the content was poured into a flask and the volatile compounds were removed in vacuo. The solid residue was weighed. Then ice-cold water was added to remove the catalyst and unreacted urea. After filtration, the white solid was dried, carefully weighed and, finally analyzed by NMR (DMSO-d_6).
    Some spectroscopic data: Dihydropyrimidinone from urea and pivalaldehyde: ^{1}H NMR: 0.75 (s, 9H), 1.19 (t, 3H), 2.16 (s, 3H), 3.88 (d, 1H), 4.08 (q, 2H), 4.90 (br, 1H), 7.36 (br, 1H); ^{13}C NMR: 167.1, 153.9, 148.1, 97.8, 59.6, 58.7, 25.6, 18.0, 14.6; Dihydropyrimidinone from *N*-methylurea and pivalaldehyde: ^{1}H NMR: 0.73 (s, 9H), 1.20 (t, 3H), 2.33 (s, 3H), 3.00 (s, 3H), 3.87 (d, 1H), 4.09 (q, 2H), 7.15 (br, 1H); ^{13}C NMR: 167.5, 154.5, 149.3, 101.6, 59.9, 57.6, 30.0, 25.4, 16.5, 14.6.
16. Jenner, G. *Tetrahedron Lett.* **2001**, *42*, 243–245.
17. Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 3784–3791.
18. Kappe, O. C. *J. Org. Chem.* **1997**, *62*, 7201–7204.
19. Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454–3457.
20. Stadler, A.; Kappe, O. C. *J. Combinatorial Chem.* **2001**, *3*, 624–630.