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Steric effects in high pressure Knoevenagel reactions

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Abstract—The pressure effect in Knoevenagel condensations involving ketones and ethyl cyanoacetate is studied. The reactions are diversely affected. For cyclic ketones there is a small effect on the reaction yield. However, in the case of acyclic ketones, the sensitivity of the reaction to pressure increases with increasing steric congestion of the ketone. Such a result highlights the synthetic utility of high pressure for the preparation of hindered functionalized alkenes. © 2000 Elsevier Science Ltd. All rights reserved.

Within the frame of a program directed toward high pressure synthesis of hindered functionalized compounds we have turned to the Knoevenagel reaction between carbonyl compounds and an active methylene group affording olefins. The reaction involving ethyl cyanoacetate occurs easily with aldehydes or unhindered ketones in the presence of a weak base such as piperidine.¹ When R and R' are made bulkier, the reaction is slowed down or even fails utterly.² Taking into account the possible beneficial effect of high pressure in sterically demanding reactions³ we have been prompted to examine the Knoevenagel condensation under pressure.



The Knoevenagel reaction is a multistep process consisting of a base-catalyzed enolate formation followed by water elimination.¹ The rate-determining step can be a nucleophilic $S_N 2$ attack on the electrophilic β -position of the ketone acceptor yielding the intermediate **I**. Alternatively, it was earlier proposed that ionization of the carbon–hydrogen bond of the active methylene group was rate-determining.⁴ Dehydration follows via a four-center transition state.¹ Recent views led to the mechanism outlined in Scheme 1 taking into account an additional intermediate step consisting in the formation of **II** undergoing E1cb elimination.⁵

The pressure effect was studied a long time ago in the condensation between cycloalkanones and ethyl

cyanoacetate.⁶ From a piezokinetic point of view, according to a previous investigation concerning the Henry (nitroaldol) reaction, the S_N2 process (step 2) is moderately pressure sensitive with an activation volume $\Delta V^{\neq} \sim -20$ to -25 cm³ mol⁻¹.⁷

Pressure may intervene in Scheme 1 in several ways. It can: (i) assist ionogenesis in step 1. For example, the basic ionization constant of piperidine in methanol was found to be increased by a factor of 1107 at 318 K when pressure was varied from ambient to 1200 MPa;⁸ (ii) favor formation of I in the bimolecular step 2; and



(iii) retard dehydration in the last step (E1cB eliminations are decelerated by pressure⁹). In addition, the reaction proceeds in a closed system hindering water escape. To illustrate the last possibility, nitroaldol reactions consisting in the base-catalyzed addition of nitroalkanes to ketones usually stop at the nitroalcohol stage, particularly under pressure.⁷ However, pressure may have puzzling effects as it was observed in sequential Henry–Knoevenagel reactions between aromatic aldehydes and nitromethane.¹⁰

The present investigation concerns the pressure effect on piperidine-catalyzed Knoevenagel condensations of hindered aldehydes and various ketones of increasing steric complexity (Table 1).¹¹ At first sight, the results are puzzling and deserve obvious interest. The pressure effect on final yields is intimately connected with the structure of the keto compound. As expected, aldehydes show high reactivity (entries 1-3), including pi-

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Scheme 1.

valaldehyde. Pressure has apparently no effect. Cyclic ketones are also very reactive. Under our standard conditions the yields of the corresponding alkenes are nearly quantitative. The yield of the resulting alkene in the cyclopentanone reaction is slightly decreased by pressure (entry 4). Condensation of the cyanoester with cyclohexanone is little affected by pressure (entry 5). This observation is in contrast with the result reported in Ref. 6, Newitt et al. found that the effect could be considerable when piperidine was present whereas a slow reaction took place at pressures above 320 MPa in the absence of the basic catalyst. The last result might be explained by pressure induced formation of ionic charges as in step 1 in Scheme 1.

Further inspection of the results in Table 1 reveals that in the case of acyclic ketones the pressure effect on the olefin yield is clearly dependent on the size of R_1 and R_2 . As inferred by our results, the Knoevenagel condensation is actually highly sensitive to the steric environment of the ketone. This pressure sensitivity is exalted with increasing bulkiness of R_1 and R_2 . This is particularly highlighted in entries 6, 7, 9, 11, 12, reporting reactions where R_1 is identical whereas R_2 is made gradually bulkier. β (ratio of yields obtained, respectively, at ambient and 300 MPa pressure under identical experimental conditions) varies from 1.6 to>11. We believe this result to be of the utmost interest for theoretical and synthetic purposes since sterically hin-

Table	1.	Effect	of	pressure	on	condensations	of	`aliphatic	ketones	and	ethyl	cyanoacetate ^a
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Entry	R	R′		0.1 MPa		β	
			Yield (%)	Isomer ratio	Yield (%)	Isomer ratio	
1	Н	iPr	91.4	100:0	No run		_
2	Н	sec-Bu	82.2	100:0	81.8	100:0	1
3	Н	t Bu	61.6	100:0	60.2	100:0	1
4	-(0	$(H_2)_4$ -	100	_	87	_	0.9
5	-(0	CH ₂) ₅ -	88.2	_	96.7	_	1.1
6 ^b	Me	Me	38.0	_	59.0	_	1.6
7	Me	Et	28.1	58:42	99.0	57:43	3.6
8	Et	Et	6.3	_	29.5	_	4.7
9	Me	iPr	6.9	Nd ^c	35.9	64:36	5.2
10	Me	nBu	20.8	57:43	66	58:42	3.2
11	Me	iBu	4.9	55:45	54.6	52:48	11.1
12	Me	CH ₂ -tBu	0.6	Nd ^c	7.1	64:36	11.9
13 ^d	Me	tBu	0	_	0	_	_
14	Et	nPr	0	-	1.5	54:46	Nd ^c

^a Ethyl cyanoacetate (1.9 mmol), piperidine (0.2 mmol), keto compound (excess, see Ref. 11), 23°C, 2 h.

^b Reaction time (1.25 h).

^c Not determined.

^d Reaction time (24 h).

R	R′	Pressure (MPa)	<i>T</i> (°C)	Time (h)	Yield (%)	Isomer ratio
Et	nPr	600	60	16.5	51.9	50:50
Et	nBu	600	60	16.5	45.7	50:50
Me	sec-Bu	850	65	24	47.5	67:33
Me	t Bu	850	65	24	2.3 ^b	Nd
Et	iPr	900	65	24	85.6	50:50
nPr	nPr	600	50	3	12.7	_
nPr	nPr	900	65	24	32.6 ^b	_

Table 2. High pressure synthesis of hindered functionalized alkenes^a

^a Ethyl cyanoacetate (1.9 mmol), piperidine (0.35 mmol), ketone (1 mL). There was no reaction at ambient pressure.

^b We suspect a possible solidification of the medium.

dered alkenes are difficult to prepare.¹² In addition, the Knoevenagel reaction reported here is an example of a reaction of a similar type, which is diversely affected by pressure. To our knowledge this finding has precedence only in the elimination reactions studied by Brower referring to alternate or mixed mechanisms.⁹

For dissymmetrical ketones, two isomers may be produced. Interestingly, the isomer ratio is not altered by pressure.

At the present stage it is difficult to venture a rational explanation for these results. The yields seem to depend on: (i) the pressure effect on equilibria shifts shown in Scheme 1 toward a privileged direction¹³ and (ii) the general pressure effect in sterically hindered reaction.³

Despite the beneficial effect of a 300 MPa pressure, hindered ketones such as pinacolone (entry 13) did not react (at variance we observed a nearly quantitative yield in the condensation of pinacolone with malononitrile at that pressure). In order to synthesize olefins which could not be prepared at low pressures, we carried out experiments at higher pressures. However, as neat conditions were required,14 it was not possible to secure liquid state of the medium at the experiment pressure (the freezing point of liquids is raised by pressure).¹⁵ It was, therefore, necessary to simultaneously limit pressure and increase temperature. Operating under such conditions, we were gratified by the fair to good results listed in Table 2. Clearly, application of pressure is of high value for the preparation of sterically hindered olefins via Knoevenagel condensations. We are pursuing such studies highlighting the correlation between pressure and steric congestion on both theoretical and synthetic levels.

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- 11. Standard runs (Table 1): Ester (1.9 mmol), piperidine (0.2 mmol) and 1,2,3-trimethoxybenzene (internal standard about 0.12 mmol) were placed in a flexible 2.5 mL PTFE tube. The volume was adjusted with the keto compound. The tube was shaken and rapidly introduced into the high pressure vessel. After release of pressure the volatile compounds were removed in vacuo. The residue was directly analyzed by ¹H NMR and the yield determined from relative intensities of characteristic protons versus methoxy groups of the internal standard.
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- 13. We tested possible reversal of step 4 in Scheme 1 by submitting the alkenes synthesized in entries 6 and 11 in the presence of water (1.5 equiv.) and piperidine (0.1 equiv.) at 23°C (2 h) at 0.1 and 300 MPa, respectively. No hydrolysis was however observed and the alkenes were recovered quantitatively.
- 14. Operation in dichloromethane solution drastically reduced the yield of alkenes.
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