Pergamon

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Tetrahedron Letters 44 (2003) 447–449

TETRAHEDRON LETTERS

Effect of pressure on the Strecker synthesis of hindered α-aminonitriles from ketones and aromatic amines

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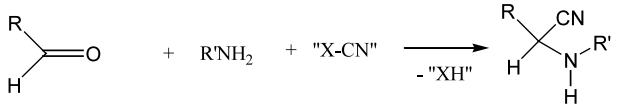
Received 4 November 2002; accepted 15 November 2002

Abstract—The effect of high pressure is examined in Strecker reactions involving ketones, amines and trimethylsilyl cyanide. This effect is small when moderately hindered reactants are involved. However, in the case of aniline and *N*-methylaniline, the sensitivity of the reaction to pressure increases with increasing steric bulk of the alkyl groups of the ketone. The results confirm the merit of pressure activation as sterically demanding reactions are subject to higher pressure acceleration than their unhindered analogs.

Alpha-aminonitriles are very important intermediates, particularly in the preparation of α-aminoacids and other biologically useful molecules. The preferred synthetic route remains the venerable Strecker reaction associating an aldehyde, an amine and a cyanide source[1,2] (Eq. (1)).



(1)

The efficiency of the reaction has been increased by the use of catalysts[3] and reactive organic cyanides such as TMSCN,[4] Bu_3SnCN[5] and bis(dialkylamino)cyanoboranes.[6] Asymmetric versions have been recently proposed in view of the need for optically active α-aminoacids.[7] The quasi totality of Strecker reactions examined hitherto makes use of aldehydes as the carbonyl compound. Unhindered cyclic ketones show low reactivity. When the size of the adjacent groups of the carbonyl bond increases, the reaction becomes forbiddingly difficult. Substituting an alkyl or an aromatic group for the aldehydic proton could result in attractive α-aminonitriles whose steric requirements could be determining for their bioactivity.[8]

Physical activation of aminocyanation of a perhydroquinolizinone by ultrasound has been reported.[9] The reaction time could be strongly reduced from days to hours. Prompted by our latest results regarding different reactions involving ketones[10] we decided to apply another physical activation mode by submitting the Strecker reagents to high pressure.[11]

(2)

In a first step, we investigated the multicomponent reaction with three aromatic amines differing by the steric environment of the amino group (benzylamine, aniline, *N*-methylaniline) and ketones substituted by alkyl groups of increasing bulkiness at two pressures (atmospheric and 300 MPa) (Eq. (2), Table 1).

The data in Table 1 are highly instructive:

– About reaction conditions, the reaction involving benzylamine could be carried out in toluene (conditions A), whereas the two other amines could not be reacted in this solvent even at 300 MPa except with acetone (low yield) (entry 7). This may be in relation with the difference in steric constants, the benzyl group having less steric demand than the phenyl group.[12]

– Whatever the amine, yields decrease ***at ambient pressure*** with increasing complexity of the ketone. If R_3 and R_4 are made very bulky, the Strecker reaction

Keywords: Strecker reaction; α-aminonitriles; steric effects; pressure.
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0040-4039/03/$ - see front matter
PII: S0040-4039(02)02598-4

Table 1. Effect of pressure on the Strecker reaction with aromatic amines

Entry	R_1	R_2	R_3	R_4	Conditions[a]	Yields (%)		β[b]
						0.1 MPa	300 MPa	
1	$PhCH_2$	H	Me	Me	A	63	62	1.0
2				nPr		34	71	2.1
3				nBu		31	54	1.7
4				iPr		17	41	2.4
5				iBu		13	31	2.4
6				*tert*-Bu		2	5	2.5
7	Ph	H	Me	Me	B	11	49	4.5
8				Et		6	25	4.2
9				nBu		4	32	8
10				iPr		7	37	5.3
11				iBu		5	23	4.6
12				*sec*-Bu		4	24	6
13				*tert*-Bu		2	13	6.5
14			nPr	nPr		1	9	9
15	Ph	Me	Me	Me	B	0	10	–
16				Et		0	17	–
17				iPr		0	6	–

[a] Conditions A: amine (0.73 mmol), ketone (0.95 mmol), TMSCN (0.9 mmol), toluene, 50°C, 24 h. Conditions B: amine (1.1 mmol), TMSCN (1.4 mmol), ketone (solvent), 30°C, 16 h.

[b] β: ratio of yields obtained at 300 MPa and ambient pressure, respectively.

occurs with difficulty (entries 6, 13, 14) or fails utterly with *N*-methylaniline (entries 15–17).

– The pressure effect is no existent when the amine and the ketone are both uncrowded (entry 1) meaning that sterically unhindered Strecker reactions are little sensitive to pressure. With benzylamine, β values are low, ranging from 1.5 to 2.5, and depend hardly on the bulk of R_4.

– In contrast, the reactions become more pressure dependent in the case of aniline. Although the correlation between the size of R_4 and the yield at 300 MPa is somewhat irregular, β values increase with the involvement of more crowded ketones, especially in entry 14 ($R_3 = R_4 = nPr$).

– With the more congested *N*-methylaniline, the pressure effect is evident as application of pressure is necessary to induce reactivity.

– The yields listed in Table 1 are modest. Prolonged reaction times improve them only slightly (75% for entry 7 and 41% for entry 12 after 4 days at 300 MPa). It means that yields are essentially determined by the applied pressure.

In order to illustrate the steric effect under pressure, we selected aniline reactions involving ketones with variable bulkiness of R_3 and R_4 (Fig. 1). With the two most congested ketones (graphics G_1 and G_2) the pressure effect is considerable with β values over 30 at 600 MPa compared to more modest values for less sterically congested ketones (graphics G_3 and G_4), thus confirming that unhindered Strecker reactions are little pressure dependent.

The simultaneous temperature and pressure effects are portrayed in Figure 2 for the Strecker combination of *N*-methylaniline with two methylketones of different bulkiness (ketone 1 with $R_3 = Me$, $R_4 = Et$ and ketone 2 with $R_3 = Me$, $R_4 = iPr$).

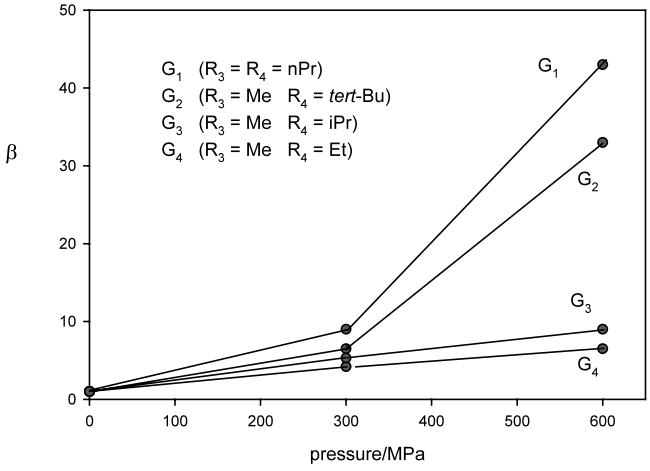

Figure 1. Effect of pressure in Strecker reactions of aniline and ketones (conditions B in Table 1).

Again, it is clear that the Strecker reaction of the hindered *N*-methylaniline with ketone 2 ($R_4 = iPr$) is more pressure-accelerated than the corresponding reaction with ketone 1 ($R_4 = Et$) for the two temperatures examined.

Although the three amines differ in their basicities, which might partly explain the difference in reactivity, the yields reported in Table 1 and Figures 1 and 2 are best rationalized by the pressure effect on steric hindrance in reactions featured by early transition states.

Conclusion

The three-component Strecker reaction giving access to α-aminonitriles is little sensitive to pressure, when unhindered keto- and amino-compounds are involved.

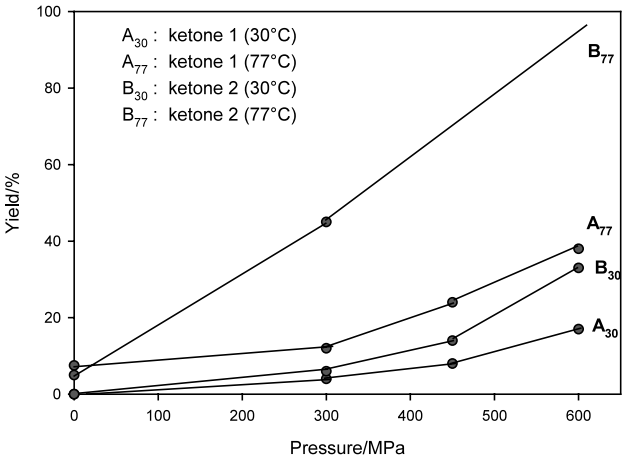

Figure 2. Effect of temperature and pressure on the yields in Strecker reactions involving *N*-methylaniline and 2-butanone (ketone 1) or 3-methyl-2-butanone (ketone 2) (conditions B in Table 1 except time = 23 h).

The result may be rationalized by supposing an early transition state for the Strecker reaction. However, with increasing size of the alkyl groups on the carbonyl bond and the steric demand of the aromatic amine, the effect of pressure becomes significant. The sensitivity to pressure increases clearly with higher steric hindrance.

The results obtained for the Strecker reactions reported remain in harmony with the correlation between pressure and steric congestion described in our previous papers for various reactions.[10,13] We feel these results of utmost importance as pressure activation of sterically congested reactions is thus shown to be a powerful tool to overcome steric hindrance. We are pursuing the ramifications of this specific pressure effect by exploring the limits of the method and its actual nature.

Acknowledgements

G. Jenner thanks The Kyoto University Foundation for Cooperative Work for a stay in Japan in 2001. J. C. Kim thanks the Korea Science and Engineering Foundation for support during his participation in this project. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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11. Experimental procedure. The weighed amine (0.9–1.0 mmol) and the internal standard (1,2,3-trimethoxybenzene) are placed in a flexible 1 mL PTFE tube. About 1 mmol ketone is added before introduction of TMSCN (1.2 mmol). The volume is adjusted with the ketone or toluene depending on run. Then, the ampoule is introduced in the vessel and submitted to the desired pressure. After release of pressure the volatile compounds are removed in vacuo. The residue is analyzed by ^{1}H NMR and the yield determined from relative intensities of characteristic protons versus methoxy protons of the internal standard. For preparative purposes, the mixture recovered from the run is washed with a 2N HCl solution, an aqueous $NaHCO_3$ solution and water successively. After extraction with ethyl acetate, the residual solid is chromatographed on silicagel.
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