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High pressure mediated three component Strecker synthesis of α-aminonitriles from ketones, aromatic amines and trimethylsilyl cyanide†

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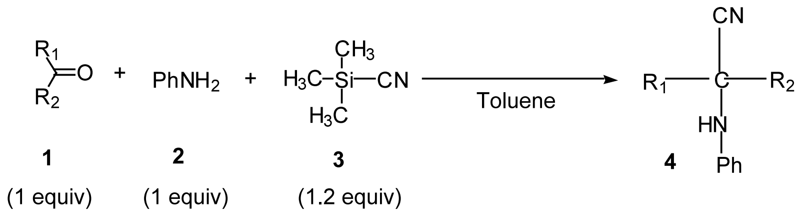
Abstract—High pressure (600 MPa) reaction conditions, in the absence of a catalyst, have proved to be a powerful way to stimulate the three component Strecker reaction synthesis of α-aminonitriles in high yields. Examples of two types of double Strecker reactions were also described. © 2002 Elsevier Science Ltd. All rights reserved.

Among the organic syntheses, multicomponent reactions as a special case of a domino process are fascinating, environmentally friendly, and recently have been extensively investigated in connection with combinatorial chemistry since the desired product can be obtained in a one-pot process from simple building blocks.[1] However, such reactions under high pressure have hardly been investigated.[2] α-Aminonitriles are very important intermediates, particularly in the preparation of α-amino acids and other biologically useful molecules.[3] Thus, an asymmetric version of this reaction has been also extensively as well as intensively studied.[4] The preferred synthetic route remains well established Strecker reaction associating an aldehyde, an amine and a cyanide source.[5] However, all these methods have focused on reactions involving aldehydes as the carbonyl compound and amines as aliphatic amines. The Strecker synthesis applied to ketones and aromatic amines remains a difficult reaction, except when NH_4Cl is used.[6] Only simple cyclic ketones are reactive yielding α-aminonitriles under catalytic conditions.[7] It appears, therefore, that the high pressure promoted one-pot Strecker reaction of a ketone, an aromatic amine and TMSCN (trimethylsilyl cyanide) is an interesting challenge.

In a first step, we examined the Strecker reaction with aniline and various ketones at a fairly high pressure (600 MPa) in the absence of a catalyst. The preliminary results are summarized in Table 1 (Scheme 1).[8] For example, at 600 MPa, acetone underwent reaction with aniline **2** and TMSCN (entry 2) to give **4a** in quantitative yield, although the same reaction at atmospheric pressure took place only in low yield (entry 1). Specifically, acetophenone **1d** with **2** did not afford the corresponding product **4d** at 0.1 MPa (entry 5),[9] whereas at



Scheme 1.

Keywords: Strecker reaction; high pressure; α-aminonitriles; trimethylsilyl cyanide.

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Table 1. Pressure promoted Strecker synthesis with ketones, aniline and TMSCN in toluene for 24 h

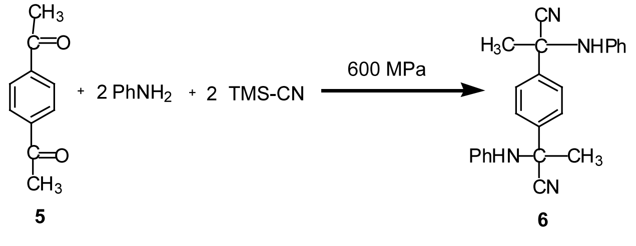
Entry	R^1	R^2	Pressure (MPa)	Temp (°C)	Product	Yield[a] (%)
1	Me	Me	0.1	30	**4a**	22
2	Me	Me	600	30	**4a**	99
3	Me	Et	600	30	**4b**	98
4	Et	Et	600	30	**4c**	95
5	Me	Ph	0.1	30	**4d**	0
6	Me	Ph	600	30	**4d**	88
7	Me	4-MePh	600	30	**4e**	82
8	Me	1′-Naphthyl	600	30	**4f**	68
9	Me	2′-Naphthyl	600	30	**4g**	96
10	Ph	Ph	600	30	–	Trace
11		$-(CH_2)_6-$	600	30	**4h**	97
12		$-(CH_2)_{12}-$	600	30	**4i**	94[b]

[a] Isolated yield based on ketones.

[b] For 48 h.

600 MPa, an 88% yield of the anticipated product **4d** was obtained (entry 6). The reactions under high pressure were dependent on the substituent of ketone. When the chain length of ketones increased, the yield was slightly reduced (entries 2, 3, 4, 11 and 12) presumably because of steric hindrance. When an aromatic substituent replaced an aliphatic substituent (entries 2, 6), the yield was slightly reduced, probably due to the same reason as well as the stabilization of the acyl carbon through delocalization by the phenyl group. Acetonaphthones also gave good yields (entries 8, 9). On comparison of 1′- and 2′-acetonaphthone, the low yield of **4f**, in comparison with that of **4g**, is likely to be due to the *peri*-hydrogen effect of the 1′-isomer (steric hindrance). Only diphenylketone could not be reacted owing probably to the prohibitive bulk of the two phenyl groups (entry 10).

The present high pressure strategy is also amenable to the double Strecker reaction. For example, 1,4-diacetylbenzene **5** with 2 molar amounts of aniline and TMSCN gave the corresponding product **6** (Scheme 2, Table 2). In this event, the choice of solvent was crucial for an efficient reaction. Among the solvents examined thus far, acetonitrile gave the best result. However, in the cases of single Strecker reactions (Scheme 1), a comparable yield of product was obtained in acetonitrile. It is speculated that the solubility of **5** at 600 MPa might be responsible for the solvent effect, the exact reason is not clear at present and will be a subject of future communications.



Scheme 2.

Table 2. The effect of solvent on double Strecker reaction

Entry	Pressure (MPa)	Temp (°C)	Time (h)	Solv.	Yield (%)
1	0.1	rt	72	CH_3CN	5
2	600	30	24	Toluene	0
3	600	30	48	Toluene	0
4	600	30	24	CH_2Cl_2	48
5	600	30	24	CH_3CN	93

Conversely, 1,4-diaminobenzene **7** smoothly underwent another type of double Strecker reaction to give **8** in 77% of an isolated yield (Scheme 3).

In this study we have successfully extended Strecker reaction to give high yields of aminonitriles by using high pressure reaction conditions.[10,11]

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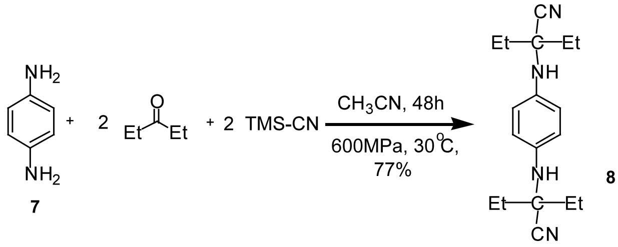

Scheme 3.

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