Catalytic One-Pot, Three-Component Acyl-Strecker Reaction

Subhas Chandra Pan, Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany
Fax +49(208)3062999; E-mail: list@mpi-muelheim.mpg.de

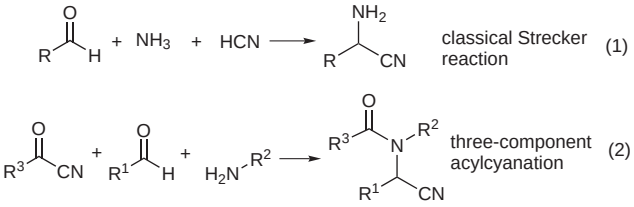
Received 20 October 2006

Abstract: Different aldehydes and amines react with acyl cyanides in the presence of a catalytic amount of the Schreiner thiourea catalyst to give the corresponding *N*-acyl amino nitriles in high yields. The scope of the reaction is broad and both aromatic and aliphatic aldehydes and amines can readily be used.

Key words: acylcyanation, α-amino nitriles, multicomponent reactions, organocatalysis, acyl cyanides

Discovered in 1850,[1] the Strecker reaction has been identified as one of the most powerful multicomponent reactions and has a central importance in organic synthesis.[2] This three-component coupling of aldehydes, amines, and hydrogen cyanide to give α-amino nitriles provides a practical method in the synthesis of α-amino acids (Scheme 1, eq. 1). Multicomponent reactions[3] such as the Strecker reaction are often useful due to their high atom economy, selectivity, environmental friendliness, and formation of low levels of by-products. However, the Strecker reaction has drawbacks in particular due to the volatile and highly toxic nature of HCN. In this regard trimethyl cyanide (TMSCN) offers certain advantages. However, due to its high toxicity and high price, access to alternative cyanation reagents is desirable. For example, acyl cyanides are not only less toxic and readily available but also have already been used in acylcyanation of carbonyl compounds.[4] In the course of our investigation of Brønsted acid catalyzed reactions of imines,[5] we recently developed a new efficient and potentially useful variant of the Strecker reaction, the Brønsted acid catalyzed acylcyanation of imines with acetyl cyanide (**1a**) as a new cyanide source.[6] After screening different Brønsted acid catalysts,[7] thio urea catalyst **5** developed earlier by Schreiner et al.[8] turned out to be a highly efficient catalyst for this rarely used and yet highly atom economic reaction.[9]

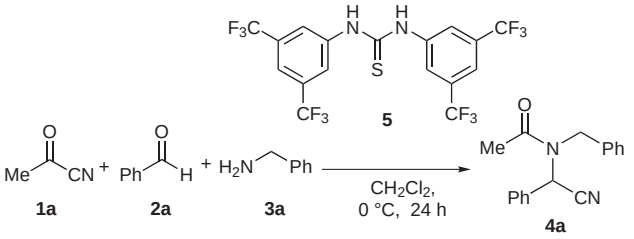
We reasoned that a useful extension of our catalytic imine acylcyanation would be avoiding the isolation of the preformed imine intermediate entirely and developing a one-pot three-component acylcyanation (or acyl-Strecker reaction) of amines, aldehydes, and acyl cyanides (Scheme 1, eq. 2). Such a reaction would not only simplify our approach towards α-amino acid derivatives but also provide a potentially useful entry towards molecular diversity if assortments of reagents were used. We were aware that the irreversible reaction of acyl cyanide and amine to give an amide would threaten our concept but hoped to avoid this side reaction by sequencing the reagent additions in a suitable order.



Scheme 1

Our initial investigations focused on finding appropriate conditions[10] for the three-component reaction of benzaldehyde (**2a**), benzyl amine (**3a**) and acetyl cyanide (**1a**, Table 1). According to our findings in the two-component version we used dichloromethane as the solvent. We were pleased to find good conversion at our initial attempt using $MgSO_4$ as the drying agent (entry 1). Interestingly, use of 5 Å MS as the drying agent further improved the

Table 1 Optimizing the Reaction Conditions for the One-Pot, Three-Component Acylcyanation



Entry[a]	Catalyst **5** (mol%)	Additive	Conversion (%)[b]
1	5	$MgSO_4$	86
2	5	5 Å MS	92
3[c]	5	5 Å MS	99
4[c]	1	5 Å MS	70
5[c]	0	5 Å MS	42

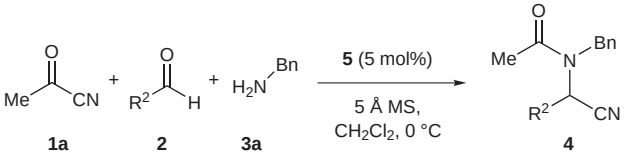
[a] Reaction condition: aldehyde **2a**, amine **3a**, additive, and catalyst **5** were stirred together at 0 °C for 2 h before acetyl cyanide **1a** (1.5 equiv) was added.
[b] Determined by GC.
[c] Aldehyde **2a**, amine **3a**, additive, and catalyst **5** were stirred together at r.t. for 2 h before acetyl cyanide (**1a**, 1.5 equiv) was added at 0 °C.

SYNLETT 2007, No. 2, pp 0318–0320
Advanced online publication: 24.01.2007
DOI: 10.1055/s-2007-968008; Art ID: G31706ST

conversion (entry 2). The best result was obtained when the mixture of aldehyde, amine, additive, and catalyst were stirred together at room temperature before the addition of acetyl cyanide at 0 °C (entry 3). Lowering the catalyst loading further resulted in lower yields and side product (*N*-benzyl acetamide) formation although a significant background reaction was observed (entries 4 and 5).

After establishing suitable reaction condition, we decided to explore the scope of this new three-component reaction. First, a variety of different aldehydes **2a–j** was examined with benzyl amine **3a** as the amine component and acetyl cyanide **1a** as the cyanide source (Table 2, entries 1–10). Both aromatic aldehydes (entries 1–4) with electron-donating or -withdrawing substituents, as well as heteroaromatic aldehydes (entries 5 and 6) can be used with similar efficiencies. Furthermore, aliphatic branched, unbranched, and unsaturated aldehydes can also be employed to give moderate to good yields (entries 7–10).

Table 2 Three-Component Acylcyanation of Different Aldehydes



1a **2** **3a** **4**

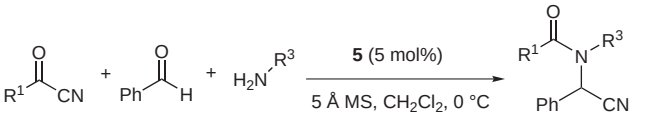
Entry[a]	R^2	Time (h)	Yield (%)[b]
1	Ph	36	80
2	4-$MeOC_6H_4$	36	82
3	4-ClC_6H_4	48	73
4	2-Naph	36	83
5	2-furyl	36	76
6	3-pyridyl	36	84
7	*i*-Pr	36	78
8	*t*-Bu	48	48
9	1-cinnamyl	36	85
10	*n*-Pent	36	82

[a] Aldehyde **2** (0.5 mmol), amine **3a** (0.5 mmol), 5 Å MS (150 mg) and catalyst (0.025 mmol) were stirred together at r.t. for 2 h before acetyl cyanide (0.75 mmol) was added at 0 °C.
[b] Isolated yield after silica gel column chromatography.

A variety of amines were studied next with benzaldehyde (**2a**) as the aldehyde component and acetyl cyanide (**1a**) as the cyanide source (Table 3, entries 1–6). It turned out that the three-component acylcyanation processes works well with several amines. Both benzyl amines with electron-rich or electron-poor phenyl group can be used with similar efficiencies (entries 2, 3). Furfuryl amine having a heteroaromatic moiety (entry 4) can also be employed. Noteworthy, the reaction also affords products with allyl amine or even with a simple alkyl amine (entries 5 and 6).

In addition to acetyl cyanide, heptanoyl cyanide as another commercially available acyl cyanide has also been used with similar reactivity (Table 3, entry 7).

Table 3 Three-Component Acylcyanation with Different Amines and Acylcyanides



1 **2a** **3** **4**

Entry[a]	R^1	R^3	Time (h)	Yield (%)[b]
1	Me	1-NaphCH_2	36	77
2	Me	4-$ClC_6H_4CH_2$	36	81
3	Me	4-$MeOC_6H_4CH_2$	36	78
4	Me	furfuryl	48	76
5	Me	allyl	48	68
6	Me	*n*-Pent	36	75
7	*n*-Hex	Bn	36	72

[a] Aldehyde **2a** (0.5 mmol), amine **3** (0.5 mmol), 5 Å MS (150 mg), and catalyst **5** (0.025 mmol) were stirred together at r.t. for 2 h before the acyl cyanide **1** (0.75 mmol) was added at 0 °C.
[b] Isolated yield after silica gel column chromatography.

In summary, we have developed a new efficient and potentially useful variant of the three-component one-pot Strecker reaction using acyl cyanides as cyanide source. Its rather broad scope, operational simplicity, practicability, and mild reaction conditions render it an attractive approach for the generation of diverse assortments of α-amido nitriles. Besides the use of our reaction in the preparation of α-amino acids, it may find place in medicinal chemistry due to its potential diversity. Further studies in our laboratory aim at expanding the scope of the reaction to include ketones and at developing an asymmetric catalytic version.

General Procedure for the One-Pot Three-Component Acylcyanation

The aldehyde **2** (0.5 mmol), amine **3** (0.5 mmol), 5 Å MS (150 mg) and catalyst **5** (5 mol%) was taken in a dry Schlenk flask. Then 2 mL dry CH_2Cl_2 was added to the mixture and stirred at r.t. for 2 h. The flask was cooled to 0 °C and stirred for 10 min. Then 50 μL of acetyl cyanide **1a** (0.75 mmol) was added to the mixture and stirred for 36–48 h at 0 °C. The mixture was directly subjected to silica gel column chromatography to give the pure corresponding product. All compounds were fully characterized on the basis of ^1H NMR, ^{13}C NMR and HRMS. Compound **4a**: colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.38 (m, 5 H), 7.31–7.24 (m, 3 H), 7.14–7.07 (m, 3 H), 4.58 (d, *J* = 17.6 Hz, 1 H), 4.49 (d, *J* = 12.9 Hz, 1 H), 2.14 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 135.3, 131.9, 129.1, 128.8, 128.4, 127.4, 125.9, 116.1, 49.2, 48.3, 21.7. HRMS (EI): *m*/*z* calcd for $[MH]^+$ 264.126062; found: 264.126260.

Acknowledgment

We thank Degussa, Merck, Saltigo, and Wacker for the donation of chemicals and Novartis for a Young Investigator award to BL. Our work was supported by the Max-Planck-Gesellschaft, the Deutsche Forschungsgemeinschaft (Priority Program 1179 *Organocatalysis*), and the Fonds der Chemischen Industrie.

References and Notes

(1) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
(2) For reviews, see: (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (b) Yet, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 875. (c) Spino, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 1764. (d) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.
(3) For reviews on multicomponent reactions, see: (a) Ugi, I.; Dömling, A.; Ebert, B. *Comb. Chem. High Throughput Screening* **1999**, 125. (b) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. (c) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (d) Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.
(4) (a) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3636. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021. (c) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413. (d) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6295. (e) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197. (f) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505. (g) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592. (h) Belokon, Y. N.; Ishibashi, E.; Nombra, H.; North, M. *Chem. Commun.* **2006**, *16*, 1775.
(5) (a) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424. (b) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (c) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.
(6) Pan, S. C.; Zhou, J.; List, B. *Synlett* **2006**, 3275.
(7) For reviews, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (d) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (e) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062. (f) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909. (g) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.
(8) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.
(9) (a) Dornow, A.; Lüpfert, S. *Chem. Ber.* **1956**, *89*, 2718. (b) Dornow, A.; Lüpfert, S. *Chem. Ber.* **1957**, *90*, 1780. (c) Dornow, A.; Lüpfert, S. US 2849477, **1958**. (d) Gardent, M. J.; Delépine, M. M. *C. R. Acad. Sci.* **1958**, *247*, 2153. (e) Rai, M.; Krishan, K.; Singh, A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1978**, *16*, 834. (f) Sakamoto, M.; Akiyama, Y.; Furumi, N.; Ishii, K.; Tomimatsu, Y.; Date, T. *Chem. Pharm. Bull.* **1983**, *31*, 2623.
(10) On mixing aldehyde, amine, catalyst, additive, and acetyl cyanide together at 0 °C, the product was obtained with poor yield due to considerable side product formation.