Catalytic Acylcyanation of Imines with Acetylcyanide

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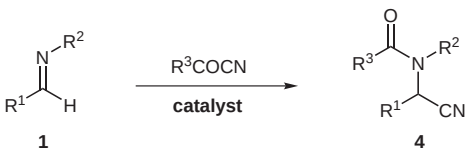
Received 15 August 2006

Abstract: Aldimines react with acetyl cyanide in the presence of a catalytic amount of a thiourea catalyst to give the corresponding N-acetylated amino nitriles in high yields. The scope of the reaction is broad and both aromatic as well as aliphatic aldimines can readily be used.

Key words: acylcyanation, α-amino nitrile, Brønsted acid catalysis, organocatalysis, acetyl cyanide

The Strecker reaction of imines with HCN provides one of the most efficient methods for the preparation of α-amino nitriles, which are useful intermediates in the synthesis of α-amino acids.[1] However, the Strecker reaction has limitations in particular due to the volatile and highly toxic nature of HCN. In this regard, trimethylsilyl cyanide (TMSCN) offers certain advantages. However, due to its high toxicity and 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 the acylcyanation of carbonyl compounds.[2] Surprisingly however, while the reaction of acetyl cyanide and analogous α-oxonitriles with aldehydes and ketones has been studied extensively in recent years, its reaction with imines has been significantly less investigated. Thus in 1958, Dornow et al. first reported the reaction of acyl cyanides with imines and later described a triethylamine-catalyzed version.[3] Survey of the literature reveals that there are no other catalytic versions of this atom-economic yet rarely used approach to α-amino nitriles.[4]

Recently, Brønsted acid and hydrogen-bonding catalysis have emerged as powerful strategies for organocatalysis.[5] Inspired by these studies and realizing the potential of the acylcyanation of imines for the synthesis of α-amino acids, we were encouraged to investigate the catalytic addition of acyl cyanides to imines (Scheme 1).



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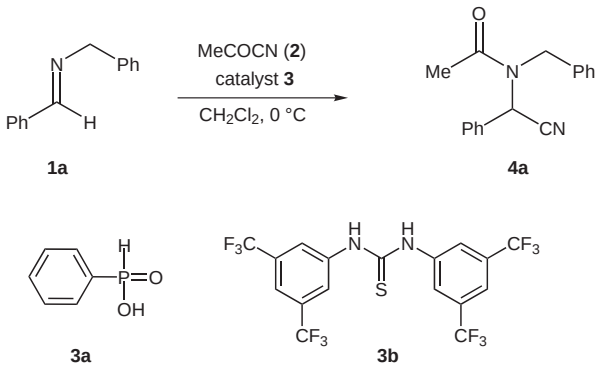
Scheme 1 Catalytic acylcyanation of imines

Initial experiments focused on the examination of different catalysts for this transformation (Table 1).[6] While the highly acidic TFA (trifluoroacetic acid) did not give any conversion in dichloromethane (entry 1), moderately acidic phenylphosphinic acid **3a** gave good conversion (entry 2). In the context of these studies we then found that the reaction cannot only be catalyzed by stronger, specific acid catalysts but also by hydrogen-bonding-type, general acid catalysts.[7]

Table 1 Catalytic Acylcyanation of Imine **1a**



1a 4a 3a 3b

Entry[a]	Catalyst	mol%	Time (h)	Conv. (%)[b]
1	TFA	20	72	0
2	**3a**	20	24	90
3	**3b**	10	24	99
4	**3b**	2	24	98
5	**3b**	1	24	93

[a] All reactions were performed using 0.1 mmol of imine **1a** and 0.15 mmol of acetyl cyanide (**2**).
[b] Determined by GC.

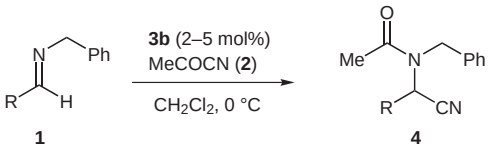
We identified Schreiner's thiourea catalyst **3b**, in particular, to be highly efficient in promoting the reaction (entry 3).[8] In each instance, the reaction was carried out with 1.5 equivalents of acetyl cyanide. Decreasing the catalyst loading from 10 mol% to 2 mol% essentially preserved the conversion (entry 4). Reducing the catalyst loading to only 1 mol% reduced the yield somewhat (entry 5).[9] Consequently, either 2 mol% or 5 mol% of catalyst **3b** was used in subsequent experiments.

Using dichloromethane as the solvent and thiourea **3b** as the catalyst (2–5 mol%), we decided to explore the scope of this reaction (Table 2). It turned out that the selected re-

SYNLETT 2006, No. 19, pp 3275–3276
Advanced online publication: 23.11.2006
DOI: 10.1055/s-2006-951543; Art ID: G27406ST

action conditions are broadly useful for a variety of different substrates. Both aromatic aldimines (entries 1–4) with electron-donating or -withdrawing substituents, as well as heteroaromatic aldimines (entries 5 and 6), can be used with similar efficiencies. Furthermore, aliphatic branched, unbranched, and unsaturated aldimines can also be employed to give moderate to good yields (entries 7–10).

Table 2 Catalytic Acylcyanation of Various Imines



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Entry[a]	R	Time (h)	Yield (%)[b]
1	Ph	24	88
2	4-$MeOC_6H_4$	24	84
3	4-ClC_6H_4	24	79
4	2-ClC_6H_4	24	83
5	2-Furyl	24	67
6	3-Pyridyl	24	96
7[c]	*i*-Pr	48	76
8[c]	*t*-Bu	48	64
9[c]	1-Cyclohexenyl	48	82
10[c]	*t*-$BuCH_2$	48	81

[a] All reactions were performed using 2 mol% of the catalyst unless otherwise stated.
[b] Yields of pure product after silica gel column chromatography.
[c] 5 mol% of the catalyst.

Mechanistically, the reaction may proceed via an initial reaction of the imine with acetyl cyanide to form an acyl iminium–cyanide ion pair. Its recombination to product **4** may be urea-catalyzed.

In summary, we have developed a new efficient and potentially useful variant of the Strecker reaction, the general Brønsted acid catalyzed acylcyanation of imines with acetyl cyanide as a new cyanide source. The operational simplicity, practicability, and mild reaction conditions render it an attractive approach for the generation of different *N*-acyl α-amino nitriles. Further studies in our laboratory aim at expanding the scope of the reaction to include ketimines and at developing an asymmetric catalytic version.[10]

Preparative Experiment for the Acylcyanation of Imines

The imine **1a** (2.0 mmol) and catalyst **3b** (2 mol%) were placed in a dry Schlenk flask. Then, dry CH_2Cl_2 (4 mL) was added to the mixture. The flask was cooled to 0 °C and stirred for 10 min. Acetyl cyanide (0.2 mL, 1.5 equiv) was added, and the mixture was stirred for 24 h at 0 °C. The mixture was directly subjected to silica gel column chromatography to give 464 mg (1.76 mmol, 88% yield) of the pure product **4a** as a colorless liquid.

Acknowledgment

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

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(6) Under our reaction conditions using triethylamine as the catalyst only 4% conversion of imine **1a** to product **4a** was achieved.
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(9) Even in the absence of catalyst, significant conversion (>30%) to the product was observed.
(10) Using the chiral phosphoric acid catalyst 3,3′-bis[(2,4,6-tris(isopropyl)phenyl]-5,5′,6,6′,7,7′,8,8′-octahydro-1,1-binaphthyl hydrogen phosphate (10 mol%) at –40 °C, product **4a** was obtained in 92% yield and 69:31 er.