A Mild and Efficient Catalytic Strecker Reaction of *N*-Alkoxycarbonylamino Sulfones with Trimethylsilyl Cyanide Using Indium(III) Chloride: A Facile Synthesis of α-Aminonitriles[1]

Biswanath Das,* Kongara Damodar, Boddu Shashikanth, Yallamalla Srinivas, Itikala Kalavathi

Organic Chemistry Division – I, Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax +91(40)7160512; E-mail: biswanathdas@yahoo.com

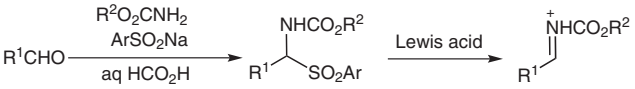
Received 6 August 2008

Abstract: The Strecker reaction of *N*-alkoxycarbonylamino sulfones with trimethylsilyl cyanide in the presence of catalytic amount of indium(III) chloride at room temperature produces the corresponding protected α-aminonitriles in high yields.

Key words: Strecker reaction, *N*-alkoxycarbonylamino sulfones, trimethylsilyl cyanide, protected α-aminonitrile, indium(III) chloride

α-Aminonitriles are versatile intermediates for the preparation of α-amino acids[2] and various nitrogen-containing heterocycles such as imidazoles and thiadiazoles.[3] α-Amino acids, in turn, are of great importance in chemistry and biology and as valuable building blocks.[4] The classical Strecker reaction for the synthesis of these compounds involves the treatment of carbonyl compounds with alkaline cyanides and salts of amines in aqueous medium.[5] The experimental procedure of this reaction is tedious and several modified methods have been subsequently developed using different cyanide reagents [such as diethyl phosphorocyanidate, α-trimethylsiloxy nitrile, tri-*n*-butyltin cyanide, acetone cyanohydrin, diethylaluminium cyanide, trimethylsilyl cyanide (TMSCN) etc.].[6] Among these cyanide ion equivalents, TMSCN is more efficient and safer in handling. The synthetic procedures to α-aminonitriles using TMSCN are of two types: (1) the reaction of imines to TMSCN[7] and (2) the reaction of aldehydes, amines, and TMSCN in one pot.[8] However, imines in general tend to be unstable during purification and so the first method has limited utility. The second one, that is, the three-component Strecker-type reaction has been studied by using various Lewis acids,[9] Lewis bases,[10] N-heterocyclic carbenes,[11] metal complexes and metal-salen complexes.[12] In recent years, a number of asymmetric Strecker reactions using highly effective catalysts have been reported.[6d,13] Herrera et al. described[6d] an efficient chiral phase-transfer-catalyzed enantioselective Strecker reaction of protected α-amino sulfones with cyanohydrins as well as KCN and TMSCN. α-Aminonitriles have also been synthesized by Strecker methodologies using ionic liquids and water instead of regular organic solvents.[14] However, many of these methods suffer from different drawbacks such as requirement of longer reaction times, application of costly reagents, harsh reaction conditions, and unsatisfactory yields. Moreover, some of the catalysts such as boron halides used for the preparation of α-aminonitriles are deactivated or decomposed by amines and water produced during imine formation. Here, we have utilized the Strecker reaction of *N*-alkoxycarbonylamino sulfones for an efficient synthesis of α-aminonitriles.

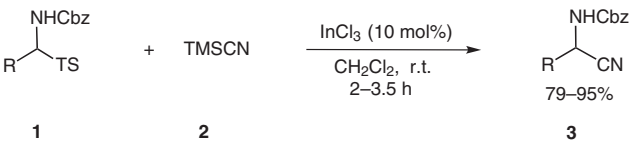
It is known that the *N*-alkoxycarbonylamino sulfones, generally referred as α-amido sulfones, can be conveniently prepared[15] from aldehydes, sodium *p*-toluenesulfinate or sodium benzenesulfinate, and suitable carbamates. Most of the *N*-alkoxycarbonylamino sulfones are stable solids and can be stored for prolonged times. They are converted into the corresponding *N*-alkoxycarbonyl imine derivatives on treatment with a Lewis acid[16] (Scheme 1). These derivatives possess a superior electrophilic character because of the presence of positively charged nitrogen atom and are highly suitable for nucleophilic reactions.[17] Thus the Strecker reaction of these sulfones with trimethylsilyl cyanide in the presence of a suitable Lewis acid constitutes an important method for the synthesis of α-aminonitriles.



R^1, R^2 = alkyl, aryl

Scheme 1

In continuation of our studies[18] we have observed that a catalytic amount of $InCl_3$ is highly effective for the reaction of *N*-alkoxycarbonylamino sulfones with trimethylsilyl cyanide to afford the corresponding protected α-aminonitriles at room temperature (Scheme 2).



1 2 3

Scheme 2

SYNLETT 2008, No. 20, pp 3133–3136
Advanced online publication: 26.11.2008
DOI: 10.1055/s-0028-1087277; Art ID: D29608ST

Initially, we carried out the reaction of *N*-alkoxycarbonylamino sulfone **1a** (R = Ph) with trimethylsilyl cyanide in the presence of various Lewis acids (Table 1).

Table 1 Cyanation of *N*-Alkoxycabonylamino Sulfone **1a** (R = Ph) Using Different Lewis Acids at Room Temperature (Scheme 2)[a]

Entry	Lewis acid	x (mol%)	Time (h)	Isolated yield (%)[b]
1	$CeCl_3 \cdot 7H_2O$	10	2.5	15
2	$CeCl_3 \cdot 7H_2O$	10	9	30
3	$ZnCl_2$	10	2.5	10
4	$ZnCl_2$	10	9	25
5	$ZrCl_4$	10	2.5	25
6	$ZrCl_4$	10	9	40
7	VCl_3	10	2.5	20
8	VCl_3	10	9	35
9	$CuBr_2$	10	2.5	30
10	$CuBr_2$	10	9	50
11	$InCl_3$	5	2.5	40
12	$InCl_3$	5	9	85
13	$InCl_3$	10	2.5	88
14	$InCl_3$	10	9	90

[a] Reaction conditions: *N*-alkoxycabonylamino sulfone **1a** (1 mmol), trimethylsilyl cyanide **2** (1.2 mmol), Lewis acid (x mol%).
[b] Yields of pure isolated products after column chromatography.

Considering the amount of the catalyst, reaction time, and yield, $InCl_3$ (10 mol%) was found to be most effective. Subsequently, this catalyst was utilized for the preparation of a series of protected α-aminonitriles (Table 2).

The reactions were completed within 2–3.5 hours. The products were formed at room temperature and in high yields.[19]

N-Alkoxycarbonylamino sulfones derived from various aldehydes (aromatic, heterocyclic, and aliphatic) underwent the present conversion smoothly. Aromatic aldehydes containing both electron-donating and electron-withdrawing groups were used to prepare the sulfones. Various functional groups such as ether, halogen, and nitro remained intact. The sulfones derived from an acid-sensitive aldehyde such as furfuraldehyde (Table 2, entry 13) and a sterically hindered aldehyde such as 2-naphthaldehyde (entry 12) also formed the corresponding protected α-aminonitriles in good yields. The structures of the products were established from their spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, FABMS, and HRMS) data.[19]

N-Alkoxycarbonylamino sulfones were also previously used for the preparation of protected α-aminonitriles but some of the reactions were carried out with toxic KCN, yields of several products were low, and some of the conversions required low temperature.[20] Herrera et al. demonstrated the use of cyanohydrins as well as KCN and TMSCN as cyanide reagents but they utilized the sulfones derived from aliphatic aldehydes only.[6d]

Table 2 $InCl_3$-Catalyzed Cyanation of *N*-Alkoxycabonylamino Sulfone **1** with Trimethylsilyl Cyanide (**2**, Scheme 2)[a]

Entry	R in **1** and **3**	Time (h)	Yield (%)[b]	Mp (°C)
1	Ph	2.0	88	107–109
2	Tol	2.0	91	111–113
3	4-*i*-PrC_6H_4	2.0	93	82–84
4	4-FC_6H_4	2.5	87	92–94
5	4-BrC_6H_4	2.5	89	106–108
6	2,4-$Cl_2C_6H_3$	2.5	88	93–95
7	PMP	2.0	95	113–115
8	3,4,5-$(MeO)_3C_6H_2$	2.0	93	151–154
9	3-MeO-4-HOC_6H_3	2.5	88	88–90
10	3-$O_2NC_6H_4$	3.5	82	112–114
11	4-$O_2NC_6H_4$	3.5	79	127–129
12	2-indenyl	3.0	85	133–135
13	2-furyl	2.5	87	104–106
14	Bn	2.5	87	110–112
15	$(CH_2)_2$Ph	2.5	90	82–84
16	Et	2.5	83	oil
17	Pr	2.5	86	oil
18	*i*-Pr	2.5	84	oil
19	$(CH_2)_4$Me	2.5	88	oil
20	$(CH_2)_6$Me	2.5	89	oil

[a] The structures of the products were established from their spectral (IR, ^{1}H NMR, ^{13}C NMR, and MS) and analytical data.

In conclusion, we have developed a mild, efficient, and novel protocol for the synthesis of protected α-aminonitriles at room temperature and in high yields by applying the Strecker reaction of *N*-alkoxycabonylamino sulfones (generated from both aromatic and aliphatic aldehydes) with TMSCN in the presence of a catalytic amount of indium(III) chloride.

Acknowledgment

The authors thank CSIR, New Delhi for financial assistance. They are also thankful to NMR, Mass, and IR Divisions of IICT for recording the spectra.

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(19) **General Procedure for the Synthesis of α-Aminonitriles**
Trimethylsilyl cyanide (**2**, 120 mg, 1.2 mmol) was added dropwise to a solution of an *N*-alkoxycabonylamino sulfone **1** (1 mmol) and $InCl_3$ (22.1 mg, 10 mol%) in CH_2Cl_2 (5 mL) under nitrogen. The mixture was stirred, and the reaction was monitored by TLC. After completion, the reaction was quenched with distilled H_2O (5 mL) and the mixture was extracted with EtOAc (3 ×10 mL). The combined organic portions were washed with H_2O (2 × 10 mL) and sat. aq NH_4Cl solution (2 × 10 mL), dried over anhyd Na_2SO_4, and concentrated under vacuum. The crude product was subjected to column chromatography (silica gel, hexane–EtOAc = 85:15 to 90:10) to obtain pure protected α-aminonitrile.

Spectroscopic Data of some Representative Products

2-(Benzyloxycarbonylamino)-2-(phenyl)acetonitrile (3a)
White solid; mp 107–109 °C. IR (KBr): 3278, 3031, 1694, 1521, 1451 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.55–7.24 (10 H, m), 5.80 (1 H, br d, *J* = 8.7 Hz), 5.37 (1 H, br d, *J* = 8.7 Hz), 5.12 (2H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.2, 135.7, 133.3, 129.9, 129.6, 128.9, 128.7, 128.5, 127.1, 117.6, 68.2, 46.8. MS–FAB: *m/z* = 267 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{16}H_{14}N_2O_2Na$ $[M + Na]^+$: 289.0952; found: 289.0951.

2-(Benzyloxycarbonylamino)-2-(4-methoxyphenyl)-acetonitrile (3g)
White solid; mp 113–115 °C. IR (KBr): 3296, 1688, 1612, 1519, 1253 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.43 (2 H, d, *J* = 8.0 Hz), 7.40–7.31 (5 H, m), 6.92 (2 H, d, *J* = 8.0 Hz), 5.76 (1 H, d, *J* = 8.0 Hz), 5.22 (1 H, d, *J* = 8.0 Hz), 5.18 (2 H, s), 3.82 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.7, 155.2, 135.7, 128.8, 128.7, 128.6, 128.5, 125.2, 117.8, 114.9, 68.1, 55.6, 46.3. ESI–MS: *m/z* = 297 $[M + H]^+$, 319 $[M+Na]^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{16}N_2O_3Na$ $[M + Na]^+$: 319.1058; found: 319.1069.

2-(Benzyloxycarbonylamino)-2-(3-nitrophenyl)aceto-nitrile (3j)
White solid; mp 112–114 °C. IR (KBr): 3280, 3057, 1692, 1532 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.37 (1 H, t, *J* = 7.0 Hz), 8.33 (1 H, dd, *J* = 8.0, 2.0 Hz), 7.83 (1 H, dd, *J* = 8.0, 2.0 Hz), 7.62 (1 H, t, *J* = 8.0 Hz), 7.35 (5 H, br s), 5.95 (1 H, br d, *J* = 8.0 Hz), 5.52 (1 H, d, *J* = 8.0 Hz), 5.17 (2 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.2, 148.9, 135.6, 135.3, 133.0, 130.7, 128.7, 128.5, 124.7, 122.2, 116.6, 68.5, 46.0. MS–FAB: *m/z* = 311 $[M]^+$. ESI-HRMS: *m/z* calcd for $C_{16}H_{13}N_3O_4Na$ $[M + Na]^+$: 334.0803; found: 334.0820.

2-(Benzyloxycarbonylamino)-2-(2-naphthyl)aceto-nitrile (3l)
White solid; mp 133–135 °C. IR(neat): 3283, 1690, 1517, 1289 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.98 (1 H, d, *J* = 2.0 Hz), 7.90–7.79 (3 H, m), 7.58–7.45 (3 H, m), 7.38–7.27 (5 H, m), 5.99 (1 H, d, *J* = 8.0 Hz), 5.39 (1 H, d, *J* = 8.0

Hz), 5.18 (2 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.1, 135.5, 133.5, 133.0, 130.2, 129.6, 128.7, 128.6, 128.3, 128.2, 127.8, 127.3, 127.1, 126.5, 123.9, 117.5, 68.0, 46.8. ESI-MS: *m/z* = 317 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{20}H_{16}N_2O_2Na$ $[M + Na]^+$: 339.1109; found: 339.1125.

2-(Benzyloxycarbonylamino)-2-(2-furyl)acetonitrile (3m)

Pale grey solid; mp 104–106 °C. IR(neat): 3270, 1694, 1532, 1255 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42 (1 H, d, *J* = 1.5 Hz), 7.39–7.22 (5 H, m), 6.52 (1 H, d, *J* = 3.0 Hz), 6.38 (1 H, dd, *J* = 3.0, 1.5 Hz), 5.89 (1 H, d, *J* = 8.0 Hz), 5.45 (1 H, d, *J* = 8.0 Hz), 5.14 (2 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.8, 145.0, 144.1, 135.3, 128.6, 128.5, 128.2, 115.6, 110.9, 109.8, 68.0, 40.5. ESI-MS: *m/z* = 257 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{14}H_{12}N_2O_3Na$ $[M + Na]^+$: 279.0745; found: 279.0742.

2-(Benzyloxycarbonylamino)-3-methylbutyronitrile (3r)

Colorless oil. IR(neat): 3324, 3035, 1706, 1527, 1266, 1237 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.26 (5 H, br s), 5.16 (1 H, br d, *J* = 8.0 Hz), 5.12 (2 H, s), 4.50 (1 H, t, *J* = 8.0 Hz), 2.03 (1 H, m), 1.11 (3 H, d, *J* = 7.0 Hz), 1.07 (3 H, d, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.5, 135.8, 128.8, 128.7, 127.0, 117.9, 67.8, 49.0, 31.8, 18.9, 18.2. MS–FAB: *m/z* 233 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{13}H_{16}N_2O_2Na$ $[M + Na]^+$: 255.1109; found: 255.1102.

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