Solvent-Free Synthesis of Racemic α-Aminonitriles

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Abstract: A very simple one-step, environmentally friendly procedure for the synthesis of α-aminonitriles from aldehydes and ketones, using trimethylsilyl cyanide in the absence of solvent, is reported. The active catalyst of this three-component (Strecker) reaction was the amine employed in the transformation. In general, aldehydes react more rapidly than ketones and give almost quantitative yields of the corresponding α-aminonitriles in less than fifteen minutes. However, only cyclic ketones afford the corresponding α-aminonitriles in excellent chemical yields under these conditions.

Key words: addition reactions, Strecker synthesis, catalysis, aminonitriles, green chemistry, solvent-free

The Strecker reaction, which allows the synthesis of α-aminonitriles, was discovered in 1850;[1] it was the first reported multicomponent reaction.[2] The advantages of Strecker-type reactions have attracted many chemists to focus on the design of suitable asymmetric and nonracemic versions of this efficient α-amino acid (α-AA) synthesis.[3] One of the most remarkable features of this process is the easy accessibility of very important proteinogenic and nonproteinogenic α-amino acid derivatives, especially arylglycines, which are very difficult to obtain by other preparative methods. In addition, the resulting α-aminonitriles, proposed as prebiotic precursors to porphyrins, corrins, nicotinic acids, and nucleic acids by Eschenmoser,[3b] have been employed as precursors of iminium ions in the synthesis of natural products and heterocyclic compounds. The corresponding α-metalated α-aminonitriles (masked acyl anion equivalents)[4] have been used in the generation of multiple polyfunctional structures such as diamines, amino alcohols, enamines, and carbonyl compounds.

Although enantioselective processes were unknown until the mid-1990s, the popular synthesis of racemic α-aminonitriles is very well known. It is generally based on the use of preformed imines and subsequent addition of hydrogen cyanide, trimethylsilyl cyanide, or another cyanide source in the presence of a catalyst, although direct processes are also known. The latter are a more attractive route than sequential reactions, and efforts have been focused on developing easier methods to obtain α-aminonitriles. Numerous examples of two- or three-component reactions have been reported over the last few years; in all cases the use of a catalyst to achieve successful results was necessary [e.g., La(O-*i*-Pr)$_3$, Sc(OTf)$_3$, $BiCl_3$, $NiCl_2$, $RuCl_3$, Cu(OTf)$_2$, sulfonium salts, organocatalysts,[5] Lewis bases such as Et_3N,[5f] and even montmorillonite KSF[6] or iodine[7]]. To the best of our knowledge there are only two processes where the presence of the catalyst could be avoided; in both cases the solvent became crucial, acting as a catalyst.[8]

On the other hand, the absence of solvent in organic synthesis and the employment of a small excess of reagent make procedures simpler, saves energy, and prevents solvent waste, hazards, and toxicity. In this sense a solvent-free synthesis of α-aminonitriles employing excess carbonyl compound (aldehyde or ketone) was reported in 1985.[9] This reaction cannot be considered as a one-pot, three-component process because a preformed imine was used, formed by heating the reaction mixture at 100 °C, and then an excess of trimethylsilyl cyanide was required to obtain the desired nitriles after heating at 100 °C. Recently, the first effective three-component Strecker reaction in the absence of solvents has been reported, however, the presence of magnesium bromide–diethyl ether complex as a Lewis acid catalyst was also necessary.[10] Continuing our research in solvent-free organic synthesis and based on the experience in an analogous reaction for obtaining O-protected cyanohydrins,[11] here we reported a three-component Strecker reaction in the absence of solvent and catalyst, avoiding waste reagents and workup protocols.

The trial reaction was performed with freshly distilled benzaldehyde, aniline (1.05 equiv), and trimethylsilyl cyanide (1.05 equiv) (Scheme 1). The aminonitrile **1a** was obtained quantitatively after three minutes as a crude compound with >92% purity (Table 1, entry 1). Easily removable amino groups, such as 4-methoxyphenyl and benzyl, were next introduced from the corresponding amine, obtaining aminonitriles **1b** and **1c**, respectively, in excellent yields and purity and in very short reaction times (Table 1, entries 2 and 3). The same reaction occurred when allylamine was used, giving **1d** in quantitatively yield in only three minutes (Table 1, entry 4). The use of symmetrically or unsymmetrically substituted secondary amines led to a slight increase in the reaction time (Table 1, entries 6–8) without a decrease in the yield.

When 4-chlorobenzaldehyde, isobutyraldehyde, 3-phenylpropanal, or α,β-unsaturated aldehydes, such as (*E*)-cinnamaldehyde and (*E*)-oct-2-enal were allowed to react with primary amines the corresponding α-aminonitriles

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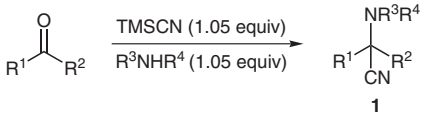

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Scheme 1 Synthesis of α-aminonitriles **1**

were obtained in high yields in short reaction times, independently of the amine employed. (Table 1, entries 9–15, 17). A lower yield and longer reaction time were observed when the secondary amine dibenzylamine reacted with isobutyraldehyde (Table 1, entry 16). In this example, the mixture of the amine and the aldehyde was allowed to react for five minutes prior to the addition of the cyanide source in order to minimize the large amount of cyanohydrin obtained when all the reagents were mixed simultaneously. Compound **1p** was only isolated in 74% yield, probably due to the slow formation of the imine and steric repulsion between bulky dibenzylamine and the α-branched aldehyde (Table 1, entry 16).

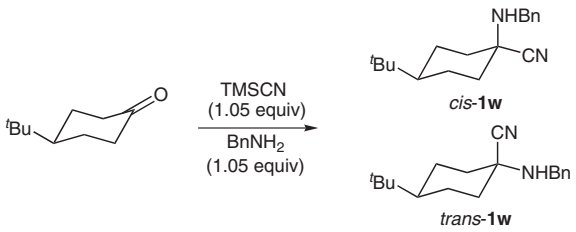
Ketones reacted very slowly with benzylamine and the reaction was incomplete despite the longer reaction times. In particular, acetophenone gave very poor yield of nitrile

Table 1 Synthesis of Racemic α-Aminonitriles **1**

Entry	R^1	R^2	NR^3R^4	Time (min)	Product	Yield[a] (%)
1	Ph	H	NHPh	3	**1a**	99
2	Ph	H	NH(C_6H_4-4-OMe)	7	**1b**	99
3	Ph	H	NHBn	3	**1c**	99
4	Ph	H	$NHCH_2CH{=}CH_2$	3	**1d**	99
5	Ph	H	$NHCHPh_2$	3	**1e**	99
6	Ph	H	NBn_2	10	**1f**	98
7	Ph	H	NMeBn	10	**1g**	95
8	Ph	H	pyrrolidin-1-yl	5	**1h**	98
9	4-ClC_6H_4	H	NHBn	5	**1i**	93[b]
10	(*E*)-CH=CHPh	H	NHPh	5	**1j**	98
11	(*E*)-CH=CHPh	H	NHBn	3	**1k**	99
12	(*E*)-CH=CHPh	H	NBn_2	12	**1l**	90
13	(*E*)-$CH{=}CH(CH_2)_4Me$	H	NHBn	5	**1m**	95
14	*i*-Pr	H	NHPh	3	**1n**	99
15	*i*-Pr	H	NHBn	3	**1o**	99
16	*i*-Pr	H	NBn_2	15	**1p**	74[b,c]
17	CH_2CH_2Ph	H	NHBn	10	**1q**	98
18	Ph	Me	NHBn	35	**1r**	21[b,c,d]
19	$CH{=}CH_2$	Me	NHBn	20	**1s**	–
20	CH=CHPh	Me	NHBn	20	**1t**	2[b,c,d]
21	Et	Et	NHBn	18	**1u**	77[b,c,d]
22	$-(CH_2)_4-$		NHBn	13	**1v**	98[b,d]
23	$-(CH_2)_2C(t\text{-Bu})(CH_2)_2-$		NHBn	12	**1w**[e]	97
24	$-(CH_2)_2O(CH_2)_2-$		NHBn	9	**1x**	99[b,d]
25	$-(CH_2)_2S(CH_2)_2-$		NHBn	11	**1y**	98[b,c,d]

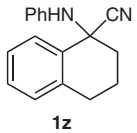
[a] Isolated crude compounds (>92% purity by ^1H NMR).
[b] Carbonyl compound and amine were allowed to react for 5 min before TMSCN was added.
[c] The corresponding cyanohydrin was also obtained.
[d] Amine (1.3 equiv) and TMSCN (1.2 equiv) were added.
[e] Obtained as a >95:5 *cis*/*trans* mixture of diastereomers.

1r (Table 1, entry 18) and reactions of α,β-unsaturated ketones failed under these reaction conditions. In the case of methyl vinyl ketone (Table 1, entry 19), Michael-type addition products of the amine to the conjugated system and unidentified products were detected by ^{1}H NMR of the crude material. In contrast, when 4-phenylbut-3-en-2-one was used, the cyanohydrin product was obtained as the major product (Table 1, entry 20). Nonaromatic acyclic and cyclic aliphatic ketones are more appropriate substrates for this solvent-free Strecker reaction, thus pentan-3-one gave the desired nitrile **1u** in 77% yield (Table 1, entry 21) and the corresponding cyanohydrin in 23% yield. Cyclopentanone and 4-*tert*-butylcyclohexanone gave excellent yields of **1v** and **1w**, respectively, in 12–13 minutes (Table 1, entries 22, 23). Heterocyclic aliphatic ketones, such as tetrahydro-4*H*-pyran-4-one and tetrahydro-4*H*-thiopyran-4-one, were used and gave the corresponding Strecker adducts **1x** and **1y** in excellent yields and in short reaction times (Table 1, entries 24, 25). The reactive ketones depicted in Table 1 (entries 21–25) reacted with trimethylsilyl cyanide (1.2 equiv) and benzylamine (1.3 equiv) and the aldehyde/benzylamine mixture was always stirred for five minutes before the addition of trimethylsilyl cyanide, except for the 4-*tert*-butylcyclohexanone, which reacted under the same reaction conditions as the aldehydes. In the latter case, the product **1w** was obtained as a >95:5 *cis*/*trans* mixture of diastereomers [by chemical shifts and NMR experiments (NOESY)] (Table 1, entry 23, and Scheme 2).



Scheme 2 Synthesis of the α-aminonitriles derived from 4-*tert*-butylcyclohexanone

The reaction using aromatic ketones and benzo-condensed cyclic ketones, such as indanone and α-tetralone, gave cyanohydrins exclusively under the reaction conditions described. For these unsuccessful examples we decided to use the conditions that used a sequential reaction by mixing the ketone and the amine at 100 °C for one minute followed by reaction of the resulting mixture with trimethylsilyl cyanide at 100 °C for 15 minutes.[9] Thus, acetophenone gave a 71% of **1r** and α-tetralone afforded α-aminonitrile **1z** (Figure 1) in 69% yield (both obtained after column chromatography).



1z

Figure 1

In order to avoid the use of hazardous trimethylsilyl cyanide, we thought it might be possible to replace it with acetone cyanohydrin (1.05 equiv) in the reaction of benzaldehyde and benzylamine (1.05 equiv). Under these new reaction conditions the corresponding α-aminonitrile **1a** was obtained after 20 minutes in 91% conversion (determined by ^{1}H NMR), unfortunately the crude mixture was not very clean and some unidentified products were observed.

Other cyanide sources such as diethyl cyanophosphonate, methyl cyanoformate, or benzoyl cyanide were also utilized instead of trimethylsilyl cyanide as cyanide source in the Strecker-type reaction of benzaldehyde and benzylamine. In these reactions neither α-aminonitriles (free base or N-protected) nor cyanohydrin products were obtained. Presumably a large amount of amine reacts with the cyanide source, causing total decomposition, which was observed by ^{1}H NMR and ^{13}C NMR analysis. The addition of potassium cyanide to benzaldehyde in presence of ammonium chloride or ammonium hydroxide to give the corresponding free α-aminonitrile was also assessed, leading in both cases to a complex mixture of products as occurred under the published reaction conditions.[9]

The presence of hydrogen cyanide in commercial trimethylsilyl cyanide, as we have already demonstrated by ^{13}C NMR in previous work,[11,12] seems to be crucial in the reaction pathway since it could activate the carbonyl compound, acting as a Brønsted acid, favoring imine formation. This was affirmed by two simultaneous ^{1}H NMR experiments performed in deuterochloroform. In the first, equimolecular amounts of benzaldehyde and benzylamine were mixed, and in the second the same components and trimethylsilyl cyanide were allowed to react. In the first and second experiments, it was observed that the imine formation and the generation of α-aminonitrile, respectively, took place in very short reaction times. It is noteworthy that in the second experiment a small proportion of cyanohydrin compound was detected as consequence of the dilution in deuterochloroform, which makes the process slower, favoring the irreversible side reaction. In addition, the amine (in very slight excess) could activate hydrogen cyanide, by formation of an ammonium salt, and increase the reaction rate.[11] On the other hand, the high proportion of cyanohydrin obtained in some cases could be explained because the amine itself catalyzes the process,[11] which is favored when the imine formation is slow as described above.

In accordance with these observations and the reactivity observed, we can conclude that new conditions for the synthesis of a-aminonitriles from aldehydes and aliphatic ketones have been developed. This environmentally friendly, one-pot reaction proceeds at room temperature, without solvent, with the minimum amounts of reagents, and avoiding the typical workup; the crude reaction product did not require any further purification. This procedure, which reduces the amount of the cyanide reagents to the minimum and proceeds under mild conditions without

the presence of a catalyst, could potentially be applied at an industrial level.

Spectroscopic and physical data for know compounds corresponded to those given in the literature: **1a**,[6] **1b**,[13] **1c**,[6] **1d**,[14] **1e**,[15] **1f**,[5a] **1g**,[5a] **1h**,[5g] **1i**,[8b] **1j**,[6] **1k**,[16] **1l**,[5a] **1n**,[8a] **1o**,[8b] **1p**,[17] **1r**,[18] and **1u**.[19] All new compounds were fully characterized.

α-Aminonitriles 1; General Procedure

The corresponding amine (0.525 mmol) and TMSCN (0.525 mmol) were added sequentially to the carbonyl compound (0.5 mmol) (in some cases, as indicated in Table 1, the amine and the carbonyl compound were allowed to react for 5 min before addition of TMSCN). The mixture was stirred until the reaction was judged to be complete. The mixture was evaporated to remove excess TMSCN (*Caution!* hazardous compound!) and the final pure α-aminonitriles were obtained either by distillation or by crystallization (hexanes). Only when crude yields were lower than 90% was purification by flash chromatography necessary to afford the pure compounds (see Table 1).

***(E)*-2-(Benzylamino)non-3-enenitrile (1m)**

Yellow sticky oil; R_f = 0.68 (*n*-hexane–EtOAc, 4:1).

IR (KBr): 3327, 2254, 1653, 1454, 1381 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.24–1.41 (m, 6 H, 3 CH_2), 2.07 (m, 2 H, CH_2CH), 3.01 (br s, 1 H, NH), 3.83, 3.99 (2 d, *J* = 12.9 Hz, 2 × 1 H, CH_2Ph), 4.15 (d, *J* = 5.2 Hz, 1 H, CHCN), 5.50 (dd, *J* = 5.2, 15.5 Hz, 1 H, C*H*CHCN), 6.04 (m, 1 H, C*H*=CHCHCN), 7.26–7.37 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.4, 28.3, 31.2, 31.9 (4 CH_2), 46.0 (*C*HCN), 51.0 (CH_2Ph), 118.5 (CN), 123.1 (*C*HCH-CN), 127.5, 128.3, 128.5, 138.2 (ArC), 136.2 (*C*H=CHCHCN).

MS (EI): *m*/*z* (%) = 215 ([M – HCN]$^+$, 5), 202 (19), 188 (65), 175 (21), 160 (32), 132 (31), 131 (22), 130 (27), 118 (59), 117 (54), 107 (19), 106 (27), 92 (24), 91 (100).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{16}H_{22}N_2$: 242.1783; found: 242.1777.

2-(Benzylamino)-4-phenylbutanenitrile (1q)

Colorless sticky oil; R_f = 0.53 (*n*-hexane–EtOAc, 4:1).

IR (KBr): 3318, 2225, 1736, 1496, 1454, 1244 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.66 (br s, 1 H, NH), 2.06 (q, *J* = 7.6 Hz, 2 H, CH_2CH), 2.82 (m, 2 H, CH_2CH_2Ph), 3.45 (t, *J* = 7.2 Hz, 1 H, CHCN), 3.78, 4.04 (2 d, *J* = 12.5 Hz, 2 × 1 H, HNCH_2Ph), 7.13–7.33 (m, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.6 (CH_2CH_2Ph), 35.0 (*C*H_2CH), 48.8 (*C*HCN), 51.6 (HN-*C*H_2Ph), 120.1 (CN), 126.3, 127.5, 128.3, 128.4, 128.5, 128.6, 138.3, 139.9 (ArC).

MS (EI): *m*/*z* (%) = 223 ([M – HCN]$^+$, 36), 132 (77), 105 (19), 91 (100).

HRMS: *m*/*z* [M – HCN]$^+$ calcd for $C_{16}H_{17}N$: 223.1361; found: 243.1355.

1-(Benzylamino)cyclopentanecarbonitrile (1v)

Colorless solid; mp 43–44 °C (hexane); R_f = 0.59 (*n*-hexane–EtOAc, 4:1).

IR (KBr): 3316, 2219, 1496, 1454 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.64 (br s, 1 H, NH), 1.81–1.90 (m, 6 H, CH_2), 2.08–2.17 (m, 2 H, CH_2), 3.88 (s, 2 H, CH_2Ph), 7.25–7.37 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5, 38.9 (2 CH_2), 50.1 (*C*H_2Ph), 61.2 (*C*CN), 122.9 (CN), 127.3, 128.3, 128.5, 139.2 (ArC).

MS (EI): *m*/*z* (%) = 173 ([M – HCN]$^+$, 41), 172 (19), 91 (100).

HRMS: *m*/*z* [M – HCN]$^+$ calcd for $C_{12}H_{15}N$: 173.1204; found: 173.1199.

1-(Benzylamino)-4-*tert*-butylcyclohexanecarbonitrile (1w)

Colorless prisms; mp 81–82 °C (hexane); R_f = 0.70 (*n*-hexane–EtOAc, 4:1).

IR (KBr): 3316, 2252, 1479, 1467, 1454 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 [s, 9 H, C(CH_3)$_3$], 1.25–1.47 (m, 4 H, CH_2), 1.52–1.63 (br m, 2 H, CH, NH), 1.83, 2.16 (2 m, 2 × 2 H, CH_2), 3.93 (s, 2 H, CH_2Ph), 7.29–7.38 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8 (CH_2), 27.5 [C(*C*H_3)$_3$], 32.3 [*C*(CH_3)$_3$], 36.7 (CH_2), 47.3 (CH), 48.8 (*C*H_2Ph), 58.1 (*C*CN), 122.0 (CN), 127.4, 128.4, 128.6, 139.4 (ArC).

MS (EI): *m*/*z* (%) = 243 ([M – HCN]$^+$, 26), 228 (48), 186 (18), 158 (18), 91 (100).

HRMS: *m*/*z* [M – HCN]$^+$ calcd for $C_{17}H_{25}N$: 243.1987; found: 243.1986.

Anal. Calcd for $C_{18}H_{26}N_2$: C, 80.0; H, 9.7; N, 10.4. Found: C, 79.6; H, 9.4; N, 10.2.

4-(Benzylamino)tetrahydro-2*H*-pyran-4-carbonitrile (1x)

White solid; mp 71–73 °C (hexane); R_f = 0.22 (*n*-hexane–EtOAc, 4:1).

IR (KBr): 3302, 2221, 1477, 1449, 1431 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (br s, 1 H, NH), 1.83, 2.04 (2 m, 2 × 2 H, 2 CH_2CCN), 3.70, 3.99 (2 m, 2 × 2 H, 2 CH_2O), 3.93 (s, 2 H, CH_2NH), 7.26–7.40 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9 (*C*H_2CCN), 48.3 (CH_2NH), 55.0 (*C*CN), 63.8 (CH_2O), 121.1 (CN), 127.5, 128.3, 128.6, 138.8 (ArC).

MS (DIP-EI): *m*/*z* (%) = 216 ([M]$^+$, 5), 157 (9), 106 (14), 91 (100).

HRMS: *m*/*z* [M – HCN]$^+$ calcd for $C_{12}H_{15}NO$: 189.1154; found: 189.1126.

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.2; H, 7.5; N, 13.0. Found: C, 72.2; H, 7.6; N, 12.8.

4-(Benzylamino)tetrahydro-2*H*-thiopyran-4-carbonitrile (1y)

Colorless prisms; mp 76–77 °C (hexane); R_f = 0.38 (*n*-hexane–EtOAc, 4:1).

IR (KBr): 3309, 2217, 1475, 1453, 1429 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 (br s, 1 H, NH), 1.98, 2.34 (2 m, 2 × 2 H, 2 CH_2CCN), 2.81 (m, 4 H, 2 CH_2O), 3.91 (s, 2 H, CH_2NH), 7.26–7.39 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (CH_2S), 36.7 (*C*H_2CCN), 48.2 (CH_2NH), 56.7 (*C*CN), 121.0 (CN), 127.5, 128.3, 128.6, 138.8 (ArC).

MS (EI): *m*/*z* (%) = 205 ([M – HCN]$^+$, 23), 177 (17), 91 (100).

HRMS: *m*/*z* [M – HCN]$^+$ calcd for $C_{12}H_{15}NS$: 205.0925; found: 205.0951.

Anal. Calcd for $C_{13}H_{16}N_2S$: C, 67.2; H, 6.9; N, 12.1; S, 13.8. Found: C, 67.6; H, 6.8; N, 12.0; S, 13.5.

1-(Benzylamino)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (1z)

Brown sticky oil; R_f = 0.43 (*n*-hexane–EtOAc, 4:1).

IR (KBr): 3314, 2221, 1494, 1453 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97–2.03 (m, 2 H, CH_2), 2.16 (br s, 1 H, NH), 2.65–2.69 (m, 2 H, CH_2), 2.83–2.86 (s, 2 H, CH_2), 4.72 (s, 2 H, CH_2Ph), 7.12 (m, 1 H, ArH), 7.25–7.46 (m, 9 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 28.2, 28.5 (3 CH_2), 49.1 (CH_2Ph), 57.7 (*C*CN), 122.0 (CN), 127.3, 128.3, 128.5, 139.2 (ArC).

MS (EI): *m*/*z* (%) = 235 ([M – HCN]$^+$, 83), 234 (100), 91 (75).

HRMS: *m*/*z* [M – HCN]$^+$ calcd for $C_{17}H_{17}N$: 235.1361; found: 235.1340.

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