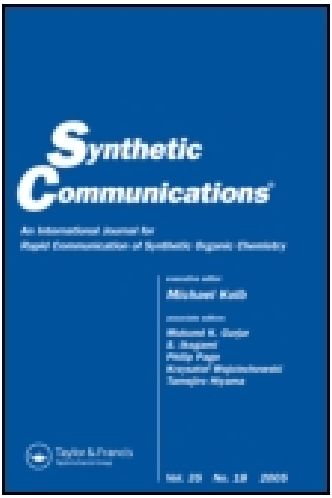

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# Development of a New α-Aminonitrile Synthesis

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# Development of a New α-Aminonitrile Synthesis

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## ABSTRACT

α-Aminonitriles are prepared upon reaction of aryl carboxaldehydes with LiHMDS and acetone cyanohydrin. This new method provides a general route to the synthesis of various substituted α-amino-arylacetonitriles in high yield and purity, and avoids the use of the highly toxic cyanide salts.

*Key Words:* α-Aminonitriles; α-Amino-arylacetonitriles; Strecker synthesis; N-Trimethylsilylimines.

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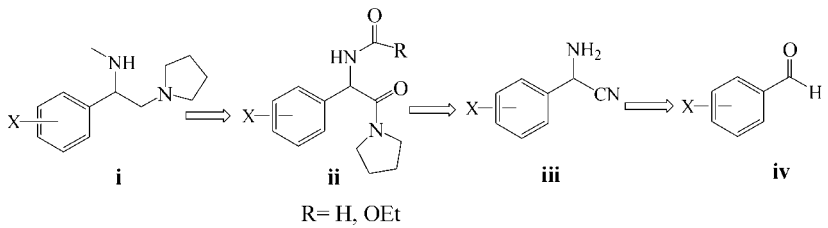
As part of our *kappa* opioid receptor agonist discovery program, we required various substituted diamines with the general structure **i** as key building blocks (Sch. 1). Diamines **i** are derived from the LAH reduction of diamides **ii**, which in turn are generated from the corresponding $\alpha$-aminonitriles **iii**, Strecker reaction products.[1] The classical Strecker synthesis of $\alpha$-aminonitriles involves treating aldehydes **iv** with $NaCN/NH_4Cl$ or $KCN/NH_4Cl$, and although widely used, it often gives unsatisfactory results.[2–5] Recently, a modified version of the Strecker reaction using $Me_3SiCN/NH_3$ was reported to circumvent the limitations of the classical reaction.[6] However, during our synthesis, both the classical and modified Strecker reaction gave unsatisfactory results for several substituted benzaldehydes **iv** of interest. Because we required various $\alpha$-aminonitriles **iii** for the preparation of a diverse set of diamines **i**, and of the general importance of **iii** as intermediates in the preparation of $\alpha$-amino acids, nitrogen-containing heterocycles, and other biologically active compounds,[7,8] we sought to develop a robust preparation of $\alpha$-aminonitriles. We describe here a new, high yield method for the conversion of aryl carboxaldehydes to $\alpha$-amino-arylacetonitriles via N-trimethylsilyl imines that can be performed on a large scale and avoids the use of the highly toxic cyanide salts.[9]

N-Trimethylsilylimines (N-TMS imines) first appeared in the literature in the 1960s.[10] In the early 1980s, Hart and coworkers reported their elegant work on the application of N-TMS imines, derived from the reaction of LiHMDS with nonenolizable aldehydes, in the total synthesis of natural products.[11] The N-TMS imines were shown to undergo facile 1,2-addition of carbon nucleophiles, including Grignard reagents and ester enolates, to give benzylamines and $\beta$-lactams, respectively. In the intervening years, other researchers prepared N-TMS imines from enolizable aldehydes and have likewise demonstrated analogous reactivity with organometallic reagents.[12] Given this precedent, the addition of cyanide ($CN^-$) to N-TMS imines was investigated as a potential route to $\alpha$-aminonitriles.

In our first attempt, a solution of (3-benzyloxy)benzaldehyde in THF was treated with LiHMDS (1.2 equiv.) to form the corresponding N-TMS imine,




***Scheme 1.***

followed by treatment with acetone cyanohydrin (2.0 equiv.), an in situ source of $CN^-$.[13] Upon aqueous work-up, the corresponding α-aminonitrile was obtained in 89% isolated yield. By comparison, the same benzaldehyde substrate under Strecker conditions was previously reported to give a 43% yield of product,[2] while a 55% yield was obtained using the modified Strecker reaction (unpublished results). To the best of our knowledge, this is the first application of N-TMS imines in the synthesis of α-amino-arylacetonitriles.

The reaction was then conducted with a variety of substituted benzaldehydes with equally satisfying results (Table 1). Substrates containing either electron-withdrawing or electron-donating groups with differing substitution patterns (*ortho*, *meta*, *para*- substituted) afforded α-amino-arylacetonitriles in good yield (entries 1–15). The yields using the new methodology were consistently superior to those previously reported for the corresponding Strecker synthesis (entries 1, 3, 4, 5, 7–10, 12, and 13). This was particularly true for benzaldehydes containing electron-withdrawing groups where the Strecker synthesis gave quite poor results. One limitation of this new method is that it did not perform well with heteroaromatic carboxaldehydes, in particular, nitrogen-containing heteroaromatic carboxaldehydes (entries 17 and 18). These substrates afforded α-aminonitriles in moderate-to-low yield.

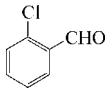
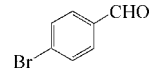
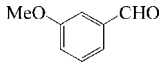
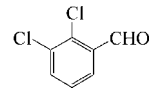
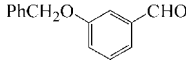
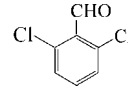
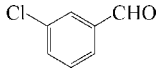
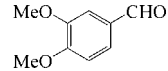
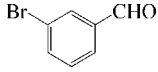
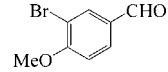
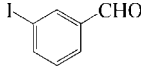
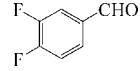
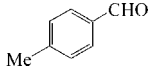
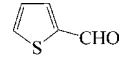
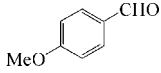
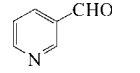
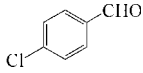
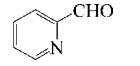
Finally, this new approach is suitable for large-scale synthesis. For example, 50 g of α-amino-(3-benzyloxyphenyl)acetonitrile (compound **iii**, X = 3-$PhCH_2O$; entry 3) was efficiently prepared by this method without attenuation in yield (89%).

In conclusion, a new α-aminonitrile synthesis has been developed based on the addition of $CN^-$ to N-TMS imines. The reaction is a general and efficient method for preparing various substituted α-amino-arylacetonitriles, complementing the classical Strecker reaction. This chemistry extends the utility of N-TMS imines in synthesis.

## General Procedure

Substituted benzaldehyde **iv** (10 mmol) was dissolved in anhydrous THF (40 mL) and cooled to −40°C. To this solution was added dropwise lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M solution in THF, 12 mL, 12 mmol). The reaction mixture was warmed to 25°C and stirred for 4 h. Acetone cyanohydrin (1.83 mL, 20 mmol) was then added and the reaction mixture stirred at 25°C for 12 h, and then quenched with water or saturated aqueous $NaHCO_3$ (40 mL). The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by flash chromatography

***Table 1.*** Preparation of $\alpha$-amino-arylacetonitriles.

| Entry | Substrates[a] | Yield %[b], ( )[c] | Entry | Substrates[a] | Yield %[b], ( )[c] |
|---|---|---|---|---|---|
| 1 |  | 92 (24)[2] | 10 |  | 82 (27)[2] |
| 2 |  | 88[6] | 11 |  | 87 |
| 3 |  | 89 (43)[2] | 12 |  | 85 (27)[2] |
| 4 |  | 81 (9)[2] | 13 |  | 87 (30)[2] |
| 5 |  | 81 (15)[3] | 14 |  | 88 |
| 6 |  | 90 | 15 |  | 80[14] |
| 7 |  | 91 (47)[4] | 16 |  | 70[6] |
| 8 |  | 88 (62)[5] | 17 |  | 28[15] |
| 9 |  | 86 (16)[2] | 18 |  | 18[16] |

[a]The aldehydes, lithium bis(trimethylsilyl)amide (1.0 M solution in THF), acetone cyanohydrin, and anhydrous THF were purchased from Aldrich and used directly without further purification.

[b]Yields refer to pure isolated $\alpha$-amino-arylacetonitriles. The compounds known from the literature were characterized by comparison of their physical and spectroscopic data with the reported data. All the new compounds (entry 6, 11, and 14) exhibited spectroscopic data ($^1$HNMR, $^{13}$CNMR, MS) in agreement with the structures indicated, and gave satisfactory elemental analysis results.

[c]Values in parentheses are the classic Strecker reaction yields reported in the literature.

on silica gel using ethyl acetate-hexane (1 : 2–2 : 1) as eluent, furnishing the corresponding α-aminonitrile **iii**. The physical and spectroscopic data of those compounds known from the literature were compared and identical with the reported data. All the new compounds (entry 6, 11, and 14) were fully characterized by $^1$HNMR, $^{13}$CNMR, and MS, and both the free base and the HCl salt gave satisfactory elemental analysis results.

The $^1$HNMR spectra data of those known compounds, and the $^1$HNMR, $^{13}$CNMR, and MS spectra data and CHN analysis result of the new compounds are given below:

**Product of entry 1**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.05 (brs, 2H), 5.22 (s, 1H), 7.40–7.32 (m, 3H), 7.63 (d, 1H).

**Product of entry 2**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.0 (brs, 2H), 3.88 (s, 3H), 4.91(s, 1H), 6.96 (d, 1H), 7.12 (m, 2H), 7.38 (t, 1H).

**Product of entry 3**: $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.50–7.35 (m, 6H), 7.20 (m, 1H), 7.10 (d, 1H), 7.02 (dd, 1H), 5.12 (s, 2H), 5.02 (s, 1H), 2.83 (brs, 2H).

**Product of entry 4**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.0 (brs, 2H), 4.90 (s, 1H), 7.42–7.35 (m, 3H), 7.55 (s, 1H).

**Product of entry 5**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.98 (brs, 2H), 4.90 (s, 1H), 7.50–7.30 (m, 3H), 7.70 (s, 1H).

**Product of entry 6, α-amino-(3-iodophenyl)acetonitrile**: mp of the free base: 61.5–62.5°C, mp of the HCl salt: 177.5–179°C dec.; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.96 (brs, 2H), 4.88 (s, 1H), 7.18 (t, 1H), 7.52 (d, 1H), 7.72 (d, 1H), 7.90 (s, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 138.28, 138.15, 135.63, 130.69, 125.94, 120.32, 94.66, 46.50; MS m/z: 259 $[M+1]^+$, 242 $[M\text{-}NH_2]^+$; Analysis calculated for $C_8H_7IN_2$ of the free base: C, 37.23; H, 2.73; N, 10.86 Found: C, 37.12; H, 2.66; N, 10.78; Analysis calculated for $C_8H_8ClIN_2$ of the HCl salt: C, 32.63; H, 2.74; N, 9.51 Found: C, 32.44; H, 2.66; N, 9.31.

**Product of entry 7**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.90 (brs, 2H), 2.38 (s, 3H), 4.88 (s, 1H), 7.21 (d, 2H), 7.40 (d, 2H).

**Product of entry 8**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.96 (brs, 2H), 3.86 (s, 3H), 4.89 (s, 1H), 6.98 (d, 2H), 7.48 (d, 2H).

**Product of entry 9**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.92 (brs, 2H), 4.90 (s, 1H), 7.40 (d, 2H), 7.50 (d, 2H).

**Product of entry 10**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.94 (brs, 2H), 4.89 (s, 1H), 4.41(d, 2H), 7.54 (d, 2H).

**Product of entry 11, α-amino-(2,3-dichlorophenyl)acetonitrile**: mp of the free base: 115.5–116.5°C, mp of the HCl salt: 173.5–174.5°C dec.; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.04 (brd, 2H), 5.28 (t, 1H), 7.35 (t, 1H), 7.51 (d, 1H), 7.60 (d, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 136.55, 134.19, 131.29, 131.21, 128.10, 126.23, 119.50, 45.71; MS m/z: 205 $[M+4+1]^+$, 203 $[M+2+1]^+$, 201 $[M+1]^+$, 188 $[M\text{-}NH_2+4]^+$, 186 $[M\text{-}NH_2+2]^+$,

184 [M-$NH_2$]$^+$; Analysis calculated for $C_8H_6Cl_2N_2$ of the free base: C, 47.79; H, 3.01; N 13.93 Found: C, 47.96; H, 3.07; N, 13.94; Analysis calculated for $C_8H_7Cl_3N_2$ of the HCl salt: C, 40.46; H, 2.97; N 11.79 Found: C, 40.47; H, 2.97; N, 11.76.

**Product of entry 12**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.32 (brs, 2H), 5.70 (s, 1H), 7.26 (t, 1H), 7.40 (d, 2H).

**Product of entry 13**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.98 (brs, 2H), 3.91 (s, 3H), 3.95 (s, 3H), 4.90 (s, 1H), 6.90 (d, 1H), 7.05 (d, 1H), 7.10 (dd, 1H).

**Product of entry 14, α-Amino-(3-bromo-4-methoxy-phenyl)acetonitrile**: mp of the free base: 108.5–109.5°C, mp of the HCl salt: 174–176°C dec.; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.93 (brs, 2H), 3.91 (s, 3H), 4.87 (s, 1H), 6.92 (d, 1H), 7.44 (dd, 1H), 7.73 (d, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 156.37, 131.70, 129.68, 126.89, 120.66, 112.17, 111.96, 56.39, 46.17; MS m/z: 226 [M-$NH_2$ + 2]$^+$, 224 [M-$NH_2$]$^+$; Analysis calculated for $C_9H_9BrN_2O$ of the free base: C, 44.84; H, 3.76; N 11.62 Found: C, 44.60; H, 3.70; N, 11.49; Analysis calculated for $C_9H_{10}BrClN_2O$ of the HCl salt: C, 38.95; H, 3.63; N 10.09 Found: C, 38.73; H, 3.55; N, 9.92.

**Product of entry 15**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.0 (brs, 2H), 4.90 (s, 1H), 7.28 (m, 2H), 7.42 (dd, 1H).

**Product of entry 16**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.10 (brs, 2H), 5.10 (s, 1H), 7.0 (m, 1H), 7.23 (d, 1H), 7.33 (d, 1H).

**Product of entry 17**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.0 (brs, 2H), 4.98 (s, 1H), 7.35 (m, 1H), 7.88 (m, 1H), 8.62 (m, 1H), 8.77 (d, 1H).

**Product of entry 18**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.22 (brs, 2H), 5.03 (s, 1H), 7.30 (m, 1H), 7.52 (d, 1H), 7.79 (m, 1H), 8.69 (d, 1H).

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