Amberlyst-15 catalysed synthesis of N-tosyl-α-aminonitriles through Strecker reaction

Dega Sudhakar, Vallabhaneni Madhava Rao, Maddila Suresh and Chunduri Venkata Rao*

Department of Chemistry, Sri Venkateswara University, Tirupati- 517 502, India

N-Tosyl-α-aminonitriles have been synthesised by a Strecker reaction of various *N*-tosyl aldimines with trimethylsilyl cyanide in the presence of catalytic amount of Amberlyst-15 polymer at room temperature under heterogeneous conditions.

Keywords: *N*-tosyl-α-amino nitriles, trimethylsilyl cyanide, amberlyst-15, Strecker reaction

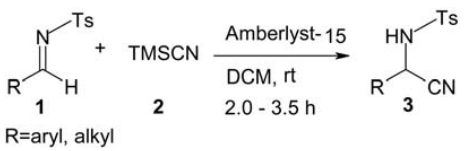
α-Aminonitriles are important precursors for the synthesis of α-amino acids[1] and various nitrogen and sulfur heterocycles such as imadazoles and thiadiazoles.[2] α-Amino acids are versatile compounds in biology as valuable building blocks.[3,4] Although several methods for their synthesis[5–7] have been reported in the literature, the Strecker reaction is widely used. The Strecker reaction involves the nucleophilic addition of cyanide ion to the imines. Various catalysts such as Lewis acids and bases,[8,9] metal complexes and metal-salen complexes have been used.[10] Recently ionic liquids in water instead of regular organic solvents have also been used in Strecker reaction.[11] A number of cyanide reagents such as diethyl phosphorocyanidate, trimethylsilyl cyanide[12,13] (TMSCN) have been used in Strecker reaction. Among these TMSCN was the safer reagent to handle. In recent years, sulfonyl and sulfinyl imines have played important role in the synthesis of many organic compounds.[14,15] These sulfonyl, sulfinyl groups are good activators of the C=N bond for nucleophilic addition reactions. Therefore the addition of TMSCN to sulfonyl imines may be a good method for obtaining α-aminonitriles.

To our knowledge there are only few reports on the Strecker reaction of sulfonyl imines using *N*-heterocyclic carbene (NHC).[16] Feng's bifunctional *N,N′*-dioxide,[17] Lewis acids and bases[18,19] and NAP-MgO.[20] However, many of these methods suffer from draw backs such as long reactions time, difficult reaction conditions, costly reagents and unsatisfactory yields.

The continuation of our work[21] on the development of new synthetic methodologies we have synthesised *N*-tosyl-α-aminonitriles by the reaction of aldimines with TMSCN in the presence of Amberlyst-15 at room temperature under heterogeneous conditions in good yield (Scheme 1).

The catalyst Amberlyst-15[22] works under heterogeneous conditions and is less expensive, reusable and commercially available. It can be easily recovered and reused for three times with limited variation in the product yields.

To establish the optimal conditions we have carried out the reaction at room temperature with *N*-tosyl benzaldimine as model substrate and TMSCN in the presence of catalytic amount of Amberlyst-15 with different solvents like CH_3CN, $PhCH_3$, DCM, THF and DMF (Table 1). Among these solvents the reaction was fast in DCM and 95% yield of *N*-tosyl-α-aminonitriles were obtained (Table 2). To test the general



Scheme 1

* Correspondent. E-mail: cvrsvu@gmail.com

Table 1 Effect of solvents in the synthesis of *N*-tosyl-α-amino nitriles

Entry	Solvent	Time /h[b]	Yield[a] /%
1	CH_3CN	4.5 h	50
2	DMF	5 h	45
3	THF	5 h	54
4	$PhCH_3$	7 h	10
5	DCM	2 h	95

[a] All yields refer to isolated product.
[b] All reactions carried out at room temperature.

scope and versatility of this method in the synthesis of variety of *N*-tosyl-α-aminonitriles, we have examined a number of differently substituted *N*-tosyl aldimines derived[14,23] from various aromatic, aliphatic and heteroaromatic aldehydes, using TMSCN in the presence of Amberlyst-15 at room temperature. The conversion was completed within 2.0–3.5 h and *N*-tosyl-α-aminonitriles were formed in high yields. The structures of the products were characterised from their spectral data. The *N*-tosyl groups of the products can easily deprotected[24] to furnish the corresponding α-aminonitriles which can be used to explore their biological applications.

In conclusion, we have developed a simple and an efficient method for the synthesis of *N*-tosyl-α-aminonitriles from *N*-tosyl aldimines and TMSCN using Amberlyst-15 as a catalyst. Operational simplicity, mild reaction conditions, short reaction time and excellent yields are the notable advantages of this method.

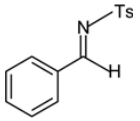
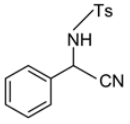
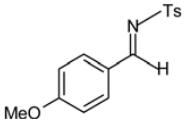
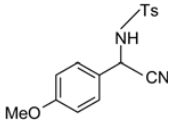
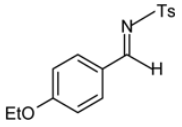
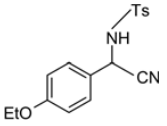
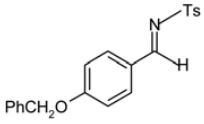
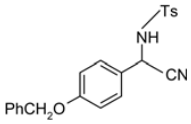
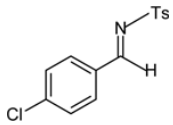
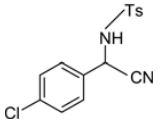
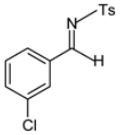
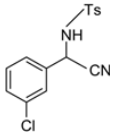
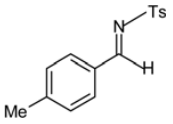
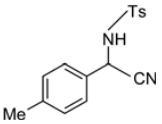
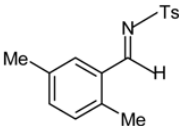
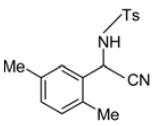
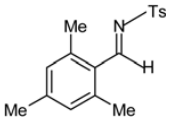
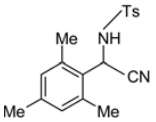
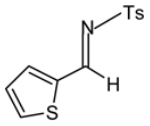
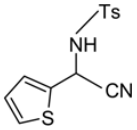
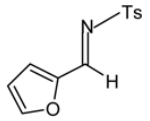
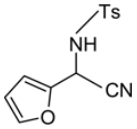
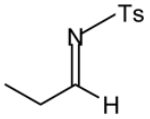
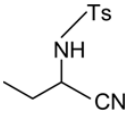
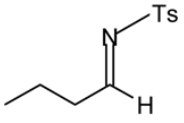
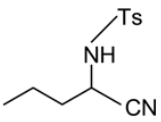
Experimental

Melting points were recorded on a Mel-Temp melting point apparatus, in open capillaries and are uncorrected. IR spectra were recorded on a Perkin–Elmer BX1 FT IR spectrophotometer and ^{1}H NMR (200 MHz), spectra were recorded on a Bruker AMX 200 MHz NMR spectrometer using TMS as internal standard and the values for chemical shifts (δ) being given in ppm and coupling constants (J) in Hertz (Hz). Mass spectra were recorded on an Agilent1100 LC/MSD. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively.

General experimental procedure for the synthesis of α-aminonitriles
N-Tosylimine (1 mmol) was dissolved in CH_2Cl_2 (2 mL) and a catalytic amount of Amberlyst −15 (40 mg) was added. To this mixture trimethylsilyl cyanide (1.3 mmol) was added dropwise. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion of the reaction the solvent was evaporated, and the reaction mass was diluted with EtOAC. The catalyst was separated by filtration and washed with EtOAC. The filtrate was evaporated, and crude product was subjected to column chromatography (silica gel, hexane-EtOAC) to obtain pure *N*-tosyl-α-aminonitrile. The spectral (IR, ^{1}H and ^{13}C NMR and MS) and analytical data of the unknown products are given below.

N-(Cyano-(4-ethoxyphenyl)methyl)-4-methylbenzenesulfonamide **(3c):** M.p. 111–113 °C. IR: 3276, 2245, 1617, 1519, 1346, 1263 cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.74 (2H, d, J = 8.0 Hz), 7.29 (2H, d,

Table 2 Amberlyst-15 catalysed synthesis of *N*-tosyl-α-aminonitriles from *N*-tosyl aldimines

Entry	*N*-tosyl aldimine (**1**)	*N*-tosyl-α-aminonitrile (**3**)[a]	Time/h	Yield[b]/%
3a			2.5	95
3b			3.5	89
3c			3.5	85
3d			3.5	86
3e			2	94
3f			2	92
3g			3	90
3h			3	90
3i			3.5	89
3j			3.5	89
3k			3.5	86
3l			2	92
3m			2	94

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

J = 8.0 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 6.85 (2H, d, *J* = 8.0 Hz), 5.63 (1H, brs), 5.39 (1H, d, *J* = 8.0 Hz), 4.05 (2H, q, *J* = 7.0 Hz), 2.46 (3H, s), 1.43 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 160.1, 145.0, 136.5, 130.1, 128.7, 127.3, 123.8, 116.7, 115.2, 63.9, 47.9, 21.6, 14.6; LCMS: *m/z* 353 $[M+Na]^+$; Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.82; H, 5.45; N, 8.48. Found: C, 61.92; H, 5.51; N, 8.56%.

N-[(4-Benzyloxyphenyl)(cyano)methyl]-4-methylbenzenesulfonamide **(3d):** M.p. 165–167 °C., IR: 3265, 2245, 1616, 1518, 1335, 1253 cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* = 8.0 Hz), 7.44–7.30 (9H, m), 6.95 (2H, d, *J* = 8.0 Hz), 5.40 (1H, d, *J* = 10.0 Hz), 5.16 (1H, d, *J* = 10.0 Hz), 5.00 (2H, s), 2.43 (3H, s); ^{13}C NMR (200 MHz, $CDCl_3$): δ 158.6, 145.7, 136.0, 130.3, 130.6, 130.0, 127.4, 124.5, 115.7, 70.0, 48.1, 21.8; LCMS: *m/z* 415 $[M+Na]^+$; Anal. Calcd for $C_{22}H_{20}N_2O_3S$: C, 67.35; H, 5.10; N, 7.14. Found: C, 67.49; H, 5.05; N, 7.25%.

N-[(3-Chlorophenyl)cyanomethyl]-4-methylbenzenesulfonamide **(3f):** M.p. 101–103 °C., IR: 3270, 2243, 1590, 1445, 1353, 1166 cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.0 Hz), 7.38–7.30 (6H, m), 5.62 (1H, d, *J* = 10.0 Hz), 5.35 (1H, d, *J* = 10.0 Hz), 2.46 (3H, s); ^{13}C NMR (200 MHz, $CDCl_3$): δ 144.8, 135.6, 135.5, 133.6, 130.6, 129.5, 130.0, 127.2, 124.8, 116.0, 47.5, 21.9; LCMS: *m/z* 343 $[M+Na]^+$; Anal. Calcd for $C_{15}H_{13}ClN_2O_2S$: C, 56.25; H, 4.06; N, 8.75. Found: C, 56.35; H, 4.11; N, 8.64%.

N-[Cyano(2,5-dimethylphenyl)methyl]-4-methylbenzenesulfonamide **(3h):** M.p. 135–137 °C. IR: 3259, 2230, 1585, 1340, 1160 cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.85 (2H, d, *J* = 8.0 Hz), 7.45 (2H, d, *J* = 8.0 Hz), 7.25 (1H, dd, *J* = 8.0, 2.0 Hz), 7.10 (2H, brs), 5.55 (1H, d, *J* = 10.0 Hz), 4.93 (1H, d, *J* = 10.0 Hz), 2.50 (3H, s), 2.32 (3H, s), 2.34 (3H, s); ^{13}C NMR (200 MHz, $CDCl_3$): δ 144.6, 136.6, 136.4, 133.3, 131.4, 130.5, 129.6, 128.0, 127.5, 116.9, 46.0, 21.3, 21.0, 18.4; LCMS: *m/z* 337 $[M+Na]^+$; Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.97; H, 5.73; N, 8.91. Found: C, 64.81; H, 5.79; N, 8.82%.

N-[Cyano(2,4,6-trimethylphenyl)methyl]-4-methylbenzenesulfonamide **(3i):** M.p. 139–141 °C. IR: 3270, 1611, 1420, 1330, 1165 cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.78 (2H, d, *J* = 8.0 Hz), 7.25 (2H, d, *J* = 8.0 Hz), 6.85 (2H, s), 5.68 (1H, d, *J* = 8.0 Hz), 5.55 (1H, brs), 2.45 (3H, s), 2.35 (6H, s); 2.26 (3H, s); ^{13}C NMR (200 MHz, $CDCl_3$): δ 144.6, 139.5, 136.9, 136.2, 130.3, 130.0, 127.0, 126.1, 116.6, 42.6, 21.4, 20.7, 19.9; LCMS: *m/z* 351 $[M+Na]^+$; Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.85; H, 6.10; N, 8.54. Found: C, 65.75; H, 6.20; N, 8.61%.

N-[Cyano(thiophene-2-yl)methyl]-4-methylbenzenesulfonamide **(3j):** M.p. 112–113 °C. IR: 3241, 2222, 1607, 1335 cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.83 (2H, d, *J* = 8.0 Hz), 7.38–7.30 (3H, m), 7.24 (1H, m), 6.95 (1H, m), 5.81 (1H, d, *J* = 10.0 Hz), 5.68 (1H, d, *J* = 10.0 Hz), 2.48 (3H, s); ^{13}C NMR (200 MHz, $CDCl_3$): δ 145.1, 136.4, 134.7, 130.3, 130.2, 128.4, 128.0, 127.1, 127.4, 126.2, 115.6, 43.7, 21.4; LCMS: *m/z* 315 $[M+Na]^+$; Anal. Calcd for $C_{13}H_{12}N_2O_2S_2$: C, 53.42; H, 4.11; N, 9.59. Found: C, 53.54; H, 4.19; N, 9.47%.

N-(1-Cyanopropyl)-4-methylbenzenesulfonamide **(3l):** M.p. 79–82 °C. IR: 3274, 2253, 1604, 1448, 1345, 1173 cm^{-1}; ^{1}H NMR (200 MHz, CDCl3): δ 7.82 (2H, d, *J* = 8.0 Hz), 7.38 (2H, d, *J* = 8.0 Hz), 5.85 (1H, brs), 4.20 (1H, q, *J* = 7.0 Hz), 2.43 (3H, s), 1.86–1.74 (2H, m), 1.03 (3H, t, *J* = 7.0 Hz); ^{13}C NMR(50 MHz, $CDCl_3$): δ 144.3, 136.3, 130.3, 127.5, 117.3, 45.4, 27.6, 21.4, 9.9; LCMS: *m/z* 261 $[M+Na]^+$; Anal. Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.46; H, 5.88; N, 11.76. Found: C, 55.36; H, 5.97; N, 11.85%.

N-(1-Cyanobutyl)-4-methylbenzenesulfonamide **(3m):** M.p. 84–86 °C. IR: 3288, 2236, 1600, 1430, 1340, 1156 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.0 Hz), 7.40 (2H, d, *J* = 8.0 Hz), 5.72 (1H, brs), 4.24 (1H, q, *J* = 7.0 Hz), 2.50 (3H, s), 1.80–1.69 (2H, m), 1.49–1.40 (2H, m), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.3, 136.2, 130.0, 127.1, 117.4, 44.0, 35.7, 21.5, 18.6, 13.0; LCMS: *m/z* 275 $[M+Na]^+$; Anal. Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.14; H, 6.35; N, 11.11. Found: C, 57.23; H, 6.44; N, 11.05%.

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