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Convenient and rapid synthesis of α-aminonitriles starting directly from nitro compounds in water ☆

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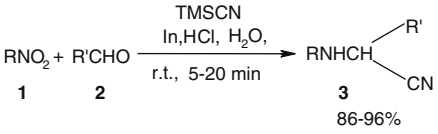
ABSTRACT

A distinct approach for the synthesis of α-aminonitriles has been discovered by three-component reaction of nitroarenes, aldehydes, and TMSCN using indium in dilute aqueous HCl at room temperature. The products were formed in high yields (86–96%) within a short period of time (5–20 min). This one-pot conversion consists of the following steps: (i) reduction of nitro compounds to amines, (ii) formation of imines from amines and aldehydes and (iii) addition of cyanide anion to the imines.

α-Aminonitriles are useful intermediates for the preparation of α-aminoacids and different nitrogen-containing heterocycles such as imidazoles and thiadiazoles.[1] The most important route for the synthesis of α-aminonitriles is the Strecker reaction.[2] In the classical Strecker reaction carbonyl compounds are treated with alkaline cyanides and salts of amines in aqueous medium. The experimental procedure of this reaction is tedious and thus, various modified protocols have been developed using different cyanide reagents (such as diethyl phosphorocyanidate, tri-*n*-butyltin cyanide, diethylaluminium cyanide, trimethylsilyl cyanide (TMSCN, etc.)[3] as well as catalysts (such as $Sc(OTf)_3$, $Pr(OTf)_3$, $Vo(OTf)_3$, $La(NO_3)_3{\cdot}6H_2O$ and $GdCl_3{\cdot}6H_2O$).[4] However, many of these protocols are associated with several drawbacks such as long reaction times, unsatisfactory yields, application of expensive reagents and harsh reaction conditions. Herein we report a distinct approach for the synthesis of α-aminonitriles directly from nitroarenes.

In continuation of our work[5] on the development of useful synthetic methodologies we have discovered that α-aminonitriles can be synthesized conveniently through the three-component reaction of nitroarenes, aldehydes, and TMSCN using indium in dilute aqueous HCl at room temperature (Scheme 1).

A series of α-aminonitriles were easily prepared following the above method using various nitro compounds and aldehydes (Table 1). TMSCN which is a safer and more effective cyanide anion source compared to other cyanide reagents has been employed here. The conversion took place very rapidly (within 5–20 min) and the products were formed in excellent yields (86–96%). Different derivatives of nitrobenzene were used to prepare the α-aminonitriles. However, in the case of 4-nitroacetophenone the carbonyl group was also reduced (Table 1, entry o).



Scheme 1.

Aromatic and heteroaromatic aldehydes underwent the conversions smoothly. However aliphatic aldehydes required a little longer reaction time compared to the aromatic aldehydes. An acid-sensitive aldehyde such as furfuraldehyde (entry f) and a sterically hindered aldehyde such as 2-naphthaldehyde (entry e) afforded the corresponding α- aminonitriles in high yields. Even a conjugated aldehyde such as cinnamaldehyde (entry d) also furnished the desired product rapidly. The alcohols, which are reduction products of the corresponding aldehydes, were not obtained. The reaction with nitroanilines produced only mono α-aminonitriles (entry n) and with nitroalkanes furnished the products in very low yields (10–14%). In the case of nitroalkanes the major amount of the substrates, nitro compounds, and aldehydes was unreacted even after 0.5 h under the present experimental conditions. Indium, which remained unchanged in air or

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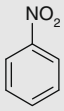
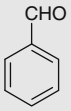
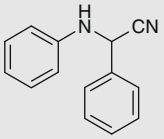
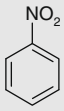
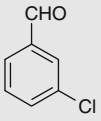
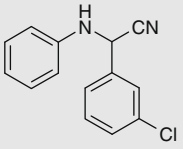
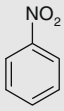
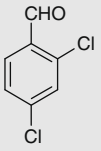
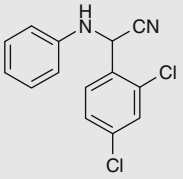
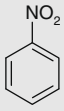
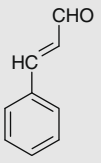
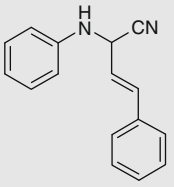
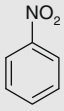
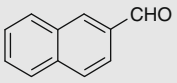
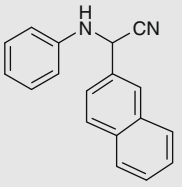
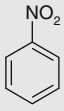
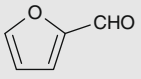
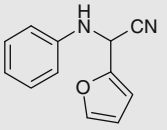
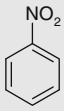
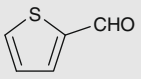
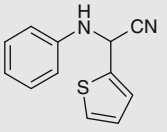
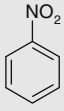
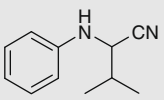
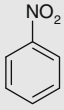
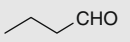
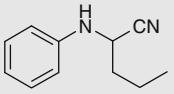
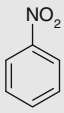
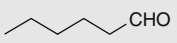
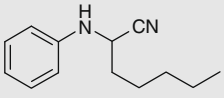
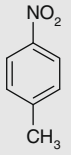
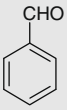
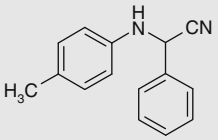
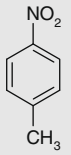
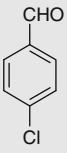
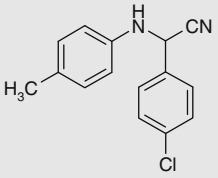
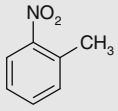
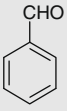
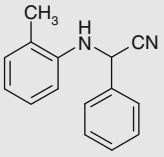
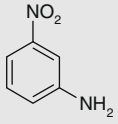
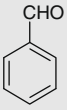
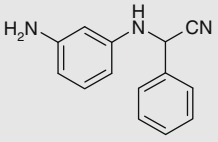
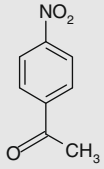
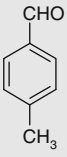
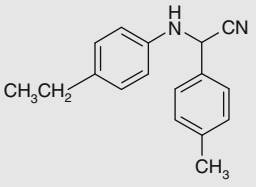
Table 1
Synthesis of α- aminonitriles using indium in dilute aqueous HCl at room temperature[a]

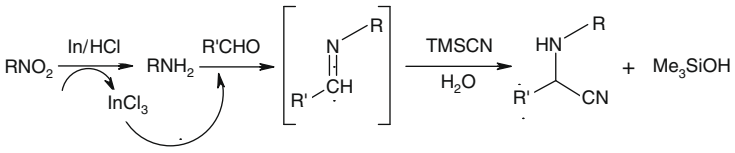
S.no.	Nitro compound **1**	Aldehyde **2**	Product **3**	Time (min)	Yield (%)
a				5	95
b				6	95
c				8	90
d				10	89
e				9	88
f				8	89
g				8	89
h				15	88
i				16	88
j				19	86

(*continued on next page*)

Table 1 (*continued*)

S.no.	Nitro compound **1**	Aldehyde **2**	Product **3**	Time (min)	Yield (%)
k				8	94
l				7	96
m				9	90
n				8	91
o				10	93

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



Scheme 2.

oxygen at room temperature and does not effect oxygen- and nitrogen-containing functionalities,[6] has been successfully applied here for the preparation of α-aminonitriles from aromatic nitro compounds in water.[7] The structures of the prepared α-aminonitriles were determined from their spectral (IR, ^{1}H and ^{13}C NMR, and MS) and analytical data.[8]

The present synthesis of α-aminonitriles involved three steps in one-pot. The nitroarenes on treatment with In/HCl reduced[6b] to anilines that reacted with aldehydes to form the corresponding imines. The addition of cyanide anion to these imines resulted in the formation of α-aminonitriles (Scheme 2). The reaction when carried out with an amine, an aldehyde, and TMSCN under the similar reaction conditions the corresponding α-aminonitrile was also formed in high yield and in short reaction time. As for an example, the treatment of aniline, benzaldehyde, and TMSCN using In/aqueous HCl at room temperature afforded the aminonitrile **3a** (Table 1) within 4 min with 95% yield.

In conclusion, we have discovered a convenient and efficient novel method for one-pot synthesis of α-aminonitriles through a three-component reaction of nitroarenes, aldehydes and TMSCN using indium in dilute aqueous HCl at room temperature. The direct application of nitroarenes, mild reaction conditions, rapid conversion (5–20 min) and impressive yields (86–96%) are the advantages of the method.

Acknowledgments

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References and notes

1. (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (b) Dyker, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 1700; (c) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1999. p 965.
2. (a) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27; (b) Groger, H. *Chem. Rev.* **2003**, *103*, 2795.
3. (a) Harusawa, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1979**, *20*, 4663; (b) Mai, K.; Patil, G. *Tetrahedron Lett.* **1984**, *25*, 4583; (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

4. (a) Heydari, A.; Fatemi, P.; Alizadeh, A.-A. *Tetrahedron Lett.* **1998**, *39*, 3049; (b) Ranu, B. C.; Dey, S. S.; Hajra, A. *Tetrahedron* **2002**, *58*, 2529; (c) Yadav, J. S.; Reddy, B. V. S.; Easwaraiah, B.; Srinivas, N. *Tetrahedron* **2004**, *60*, 1769; (d) De, S. K. *Synth. Commun.* **2005**, *35*, 653; (e) Royer, L.; De, S. K.; Gibbo, R. A. *Tetrahedron Lett.* **2005**, *46*, 4595; (f) Prakash, G. K. S.; Panja, C.; Do, C.; Mathew, T.; Olah, G. A. *Synlett* **2007**, 2395; (g) Narasimhulu, M.; Reddy, T. S.; Mahesh, K. C.; Reddy, S. M.; Reddy, A. V.; Venkateswarlu, Y. *J. Mol. Catal. A: Chem.* **2007**, *264*, 288.
5. (a) Das, B.; Krishnaiah, M.; Balasubramanyam, P.; Veeranjaneyulu, B.; Kumar, D. N. *Tetrahedron Lett.* **2008**, *49*, 2225; (b) Das, B.; Damodar, K.; Chowdary, N.; Saritha, D.; Ravikanth, B.; Krishnaiah, M. *Tetrahedron* **2008**, *64*, 9396; (c) Das, B.; Krishnaiah, M.; Laxminarayana, K.; Suneel, K.; Kumar, D. N. *Chem. Lett.* **2009**, *38*, 42.
6. (a) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347; (b) Lee, J. G.; Choi, K., Il.; Koh, H. Y.; Kang, Y.; Kim, Y.; Kang, Y.; Cho, Y. S. *Synthesis* **2001**, 81.
7. *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998.
8. *General experimental procedure*: To a mixture of a nitroarene (1 mmol), indium (325 mesh, 2 mmol) and 1 N aqueous HCl (1 mL) in water (5 mL) an aldehyde (1 mmol) was added followed by addition of TMSCN (1 mmol). The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the mixture was washed with saturated $NaHCO_3$ solution (3×5 mL) and water (3×5 mL) and subsequently extracted with EtOAc (3×5 mL). The extract was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, hexane–EtOAc) to obtain pure α- aminonitrile.
When the above reaction was carried out with 4-nitroacetophenone (1 mmol) using In (2 mmol) a mixture of products was formed. However, using excess In (6 mmol) the α- aminonitrile **3o** was obtained in high yield (93%) in 10 min.
The spectral and analytical data of the novel products are given below.

Compound **3b**: IR (KBr): 3370, 2238, 1601, 1504, 1431, 1309,1246 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.62 (1H, d, J = 2.0 Hz), 7.53 (1H, m), 7.42–7.35 (2H, m), 7.25 (2H, t, J = 8.0 Hz), 6.90 (1H, t, J = 8.0 Hz), 6.72 (2H, d, J = 8.0 Hz), 5.40 (1H, d, J = 7.0 Hz), 4.02 (1H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.2, 136.0, 135.2, 130.8, 130.0, 129.9, 127.5, 125.2, 120.9, 117.8, 114.1, 49.8; ESIMS: m/z 216 $[M-CN]^{+\cdot}$ Anal. Calcd for $C_{14}H_{11}ClN_2$: C, 69.28; H, 4.54; N, 11.55. Found: C, 69.43; H, 4.48; N, 11.62.
Compound **3c**: IR (KBr): 3368, 2247, 1601, 1503, 1473, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.71 (1H, d, J = 8.0 Hz), 7.52 (1H, d, J = 1.5 Hz), 7.35 (1H, dd, J = 8.0, 1.5 Hz), 7.29–7.20 (2H, m), 6.89 (1H, t, J = 8.0 Hz), 6.71 (2H, d, J = 8.0 Hz), 5.62 (1H, d, J = 7.0 Hz), 3.96 (1H, d, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.6, 136.8, 130.9, 130.0, 129.8, 128.1, 120.8, 114.2, 47.3; ESIMS: m/z 250, 252, 254 $[M-CN]^{+\cdot}$ Anal. Calcd for $C_{14}H_{10}Cl_2N_2$: C: 60.65; H, 3.61; N, 10.11. Found: C, 60.78; H, 3.58; N, 10.21.
Compound **3k**: IR (KBr): 3328, 2241, 1651, 1519, 1449, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.65–7.57 (2H, m), 7.49–7.38 (3H, m), 7.06 (2H, d, J = 8.0 Hz), 6.66 (1H, d, J = 8.0 Hz), 5.37 (1H, d, J = 7.0 Hz), 3.82 (1H, d, J = 7.0 Hz), 2.29 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.1, 133.9, 129.9, 129.5, 129.0, 128.8, 127.0, 118.2, 114.1, 50.2, 20.0; ESIMS: m/z 196 $[M-CN]^{+\cdot}$ Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.08; H, 6.31; N, 12.61. Found: C, 81.21; H, 6.38; N, 12.56.
Compound **3o**: IR (KBr): 3363, 2234, 1615, 1467, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.49 (2H, d, J = 8.0 Hz), 7.24 (2H, d, J = 8.0 Hz), 7.07 (2H, d, J = 8.0 Hz), 6.67 (2H, d, J = 8.0 Hz), 5.30 (1H, d, J = 7.0 Hz), 3.81 (1H, d, J = 7.0 Hz), 2.59 (2H, q, J = 7.0 Hz), 2.40 (3H, s), 1.22 (3H, t, J = 7.0 Hz) ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.8, 139.2, 135.5, 130.9, 129.4, 128.2, 127.0, 118.6, 113.8, 50.0, 27.8, 20.9, 15.2; ESIMS: m/z 224 $[M-CN]^{+\cdot}$ Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.60; H, 7.20; N, 11.20. Found: C, 81.72; H, 7.14; N, 11.28.