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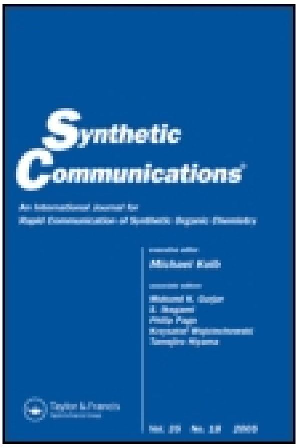

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Direct Synthesis of Nitriles from Aldehydes Using Chloramine-T/KI in Aqueous Ammonia

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DIRECT SYNTHESIS OF NITRILES FROM ALDEHYDES USING CHLORAMINE-T/KI IN AQUEOUS AMMONIA

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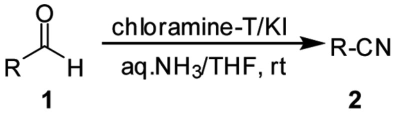
GRAPHICAL ABSTRACT



Abstract *A convenient method for direct conversion of aldehydes into nitriles has been developed using chloramine-T/KI in aqueous ammonia.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource: Full experimental and spectral details.]*

Keywords Aldehydes; aqueous ammonia; chloramine-T; nitriles; oxidation

INTRODUCTION

Nitriles are important compounds not only for their interesting biological properties but also because of their use as versatile starting materials for many important aromatic compounds, including acids, ketones, oximes, and amines.[1,2]

Various methods for the synthesis of nitriles have been reported. Among these methods, the most widely used are based on the transitionmetal–mediated displacement of aromatic halides and triflates by the cyanide ion.[3–18] On the other hand, an important alternative for the synthesis of nitriles is to use aldehydes as substrates. Generally, the conversion of aldehydes into nitriles was achieved by dehydration of the corresponding aldoximes using reagents such as $NH_2OH \cdot HCl/NEt_3$/phthalic anhydride,[19] $NH_2OH \cdot HCl$/peroxymonosulfate-alumina,[20] $NH_2OH \cdot HCl$/N-methylpyrrolidine,[21] $NH_2OH \cdot HCl$/ammonium acetate,[22] $NH_4OH/MgSO_4/MnO_2$,[23] $NH_2OH \cdot HCl$/dry-$Al_2O_3/MeSO_2Cl$,[24] $NH_2OH \cdot HCl$/HY-Zeolite,[25]

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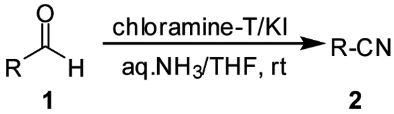


Scheme 1. Formation of nitriles from aldehydes.

$NH_2OH \cdot HCl/Graphite/MeSO_2Cl$,[26] $NH_2OH \cdot HCl/NaI/MeCN$,[27] $NH_2OH \cdot HCl/KF\text{-}Al_2O_3/DMF$,[28] $NH_2OH \cdot HCl/DBU/EtOPOCl_2/MS3\,Å$,[29] $NH_2OH \cdot HCl/KI/ZnO/CH_3CN$,[30] and furthermore, the one-pot synthesis of nitriles direct from aldehydes and ammonia water by oxidation of the aldimines, formed in situ by condensation of aldehydes and ammonia, is considered an expedient method and has been studied with $NH_3/O_2/CuCl_2 \cdot H_2O/MeONa$ in MeOH,[31] $NH_3/Pb(OAc)_4$ in dry benzene,[32] $NH_3/I_2/MeONa$ in MeOH,[33] $NH_3/S_8/NaNO_2$,[34] $NH_3/H_2O_2/CuCl$ in 2-propanol,[35] NH_3/I_2 in THF–water,[36] NH_3/ceric ammonium nitrate (CAN),[37] NH_3/N-bromosuccinimide (NBS),[38] NH_3/iodoxybenzonic (IBX) in acetonitrile–water,[39] $NH_3/NaICl_2$,[40] NH_3/trichloroisocyanuric acid (TCCA), [41] $NH_3/NaIO_4/KI$,[42] and $NH_3/H_5IO_6/KI$.[43] Some of these methods present advantages over other reaction pathways in that the reactions could be carried out at low temperatures and without the use of expensive transition metal catalysts and ligands. Herein we report a convenient method for direct transformation of aldehydes to nitriles using chloramine-T (*N*-chloro 4-methylbenzenesulfonamide, sodium salt)/KI in aqueous ammonia under mild conditions (Scheme 1).

RESULTS AND DISCUSSION

First, benzaldehyde was chosen as a model substrate. The reaction of benzaldehyde in ammonia water without chloramine-T or KI resulted in poor conversion (Table 1, entries 1–3). When chloramine-T and KI were introduced into the reaction mixture, the yield of the product was drastically increased to 90% in 1.5 h (Table 1, entry 4). Further, decreasing the amount of chloramine-T or KI led to the slightly lower conversion of benzaldehyde to benzonitrile (Table 1, entries 5 and 6). At last, we found that the optimal conditions were benzaldehyde (2 mmol), chloramine-T (1.5 equiv), KI (1.5 equiv), tetrahydrofuran (THF) (1 mL), and ammonia water (10 mL) at room temperature for 1.5 h, which provided the desired product **2a** in 90% yield.

Table 1. Evaluation of various reaction conditions[a]

Entry	Chloramine-T	KI	Yield (%)[b]
1	—	—	<1
2	3 mmol	—	<3
3	—	3 mmol	<1
4	3 mmol	3 mmol	90
5	2 mmol	3 mmol	78
6	3 mmol	2 mmol	82

[a] Reaction conditions: aldehyde (2 mmol), aqueous ammonia (10 mL), THF (1 mL), rt, 1.5 h.

[b] Isolated yields.

Table 2. Conversion of aldehydes into nitriles[a]

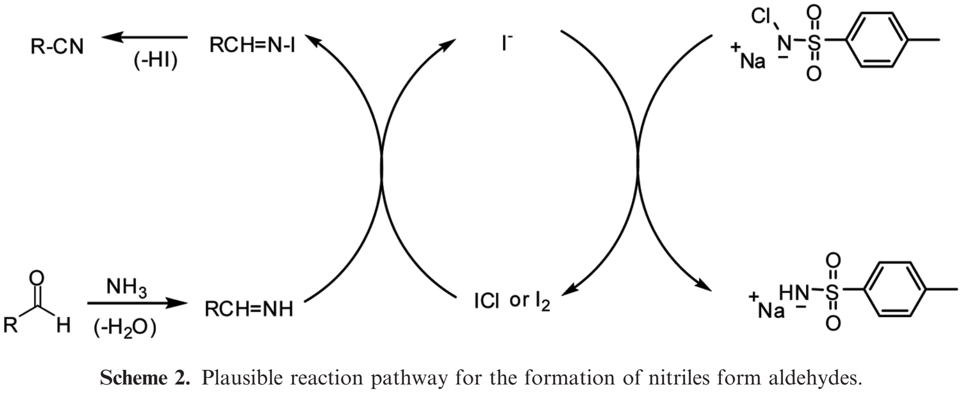
Entry	RCHO	RCN	Period (h)	Yield (%)[b]
1	C_6H_5CHO	C_6H_5CN (2a)	1.5	90
2	4-ClC_6H_4CHO	4-ClC_6H_4CN (2b)	3	91
3	3-ClC_6H_4CHO	3-ClC_6H_4CN (2c)	3	90
4	2-ClC_6H_4CHO	2-ClC_6H_4CN (2d)	4	89
5	4-$CF_3C_6H_4CHO$	4-$CF_3C_6H_4CN$ (2e)	8	82
6	4-FC_6H_4CHO	4-FC_6H_4CN (2f)	8	83
7	4-$CH_3C_6H_4CHO$	4-$CH_3C_6H_4CN$ (2 g)	5	83
8	4-$CH_3OC_6H_4CHO$	4-$CH_3OC_6H_4CN$ (2 h)	6	81
9	3-Pyridinecarboxaldehyde	3-Cyanopyridine (2i)	8	81
10	$CH_3(CH_2)_3CHO$	$CH_3(CH_2)_3CN$ (2j)	10	84
11	$CH_3(CH_2)_5CHO$	$CH_3(CH_2)_5CN$ (2k)	10	82

[a] Reaction conditions: aldehyde (2 mmol), aqueous ammonia (10 mL), THF (1 mL), chloramine-T (3 mmol), KI (3 mmol), rt.

[b] Isolated yields.

Encouraged by that result, we set out to examine a range of aldehydes (Table 2). As shown in Table 2, various aromatic, heterocyclic, and aliphatic aldehydes were efficiently transformed into their corresponding nitriles in good yields. Aryl aldehydes with electron-withdrawing groups such as chloro, fluoro, and trifluoromethyl could afford good yields, and substrate with chloro group gave the better yields (Table 2, entries 2–6). Additionally, steric effects had only a minor influence on the reaction (Table 2, entry 4). Also, aryl aldehydes having electron-donating substituents converted into the corresponding nitriles in good yields (Table 2, entries 7 and 8). Even with 3-pyridinecarboxaldehyde, a heterocyclic aldehyde, good yield was obtained (Table 2, entry 9). Aliphatic aldehydes also underwent this transformation smoothly after prolonged reaction times (Table 2, entries 10 and 11).

A plausible reaction pathway for the conversion of aldehydes into the corresponding nitriles with chloramine-T/KI is similar to that with molecular iodine suggested by Mori and Togo (Scheme 2).[44] Thus, the reaction proceeded via oxidation of aldimine with I_2 or ICl (from chloramines-T/KI) to give an N-iodo



Scheme 2. Plausible reaction pathway for the formation of nitriles form aldehydes.

aldimine intermediate, which eliminated an HI molecule by NH_3 to afford the nitrile product.

In summary, we disclosed a new and efficient one-pot reaction for the synthesis of nitriles from aldehydes through oxidation of in situ formed corresponding aldimines using chloramine-T/KI/aqueous NH_3, which offered a useful synthetic method for the preparation of nitriles because of its simplicity and good yields.

EXPERIMENTAL

A suspension of an aldehyde (2 mmol), KI (3 mmol), THF (1 mL), and ammonia water (10 mL) was stirred for 10 min at room temperature, resulting in formation of a turbid solution. Chloramine-T (3 mmol) was added slowly to this turbid solution at room temperature. Then the mixture was stirred strongly for an appropriate time (see Table 1), as indicated by thin-layer chromatography (TLC), until no more product was formed. After the reaction was completed, the mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with H_2O (2 × 15 mL). Then the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Finally, the product was isolated by flash chromatography on silica gel with EtOAc–petroleum ether as the eluent. All prepared nitriles are known compounds.

Please see the Supplemental Data, available online, for complete experimental and spectral details.

REFERENCES

1. Liu, K. C.; Howe, R. K. 3′-Arylspiro[isobenzofuran-1(3H),5′(4′H)-isoxazol]-3-ones and their conversion to 2-(3-arylisoxazol-5-yl)benzoates. *J. Org. Chem.* **1983**, *48*, 4590.
2. Harris, T. M.; Harris, C. M.; Oster, T. A.; Brown, L. E.; Lee, J. Y. C. Biomimetic syntheses of pretetramides, 2: A synthetic route based on a preformed D ring. *J. Am. Chem. Soc.* **1988**, *110*, 6180.
3. Sundermeier, M.; Zapf, A.; Beller, M. Palladium-catalyzed cyanation of aryl halides: Recent developments and perspectives. *Eur. J. Inorg. Chem.* **2003**, 3513.
4. Chidambaram, R. A robust palladium-catalyzed cyanation procedure: Beneficial effect of zinc acetate. *Tetrahedron Lett.* **2004**, *45*, 1441.
5. Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C. Y. An investigation into causes and effects of high cyanide levels in the palladium-catalyzed cyanation reaction. *Org. Lett.* **2004**, *6*, 3723.
6. Collibee, S. E.; Strivastava, R. R. Application of polymer-supported triphenyl phosphine in the palladium-catalyzed cyanation reaction under microwave conditions. *Tetrahedron Lett.* **2004**, *45*, 8895.
7. Williams, J. M.; Yang, C. Y. Palladium-catalyzed cyanation of aryl bromides promoted by low-level organotin compounds. *Org. Lett.* **2004**, *6*, 2837.
8. Stazi, F.; Palmisano, G.; Turconi, M.; Stantagostino, M. Statistical experimental design-driven discovery of room-temperature conditions for palladium-catalyzed cyanation of aryl bromides. *Tetrahedron Lett.* **2005**, *46*, 1815.
9. Hatsuda, M.; Seki, M. A practical synthesis of highly functionalized aryl nitriles through cyanation of aryl bromides employing heterogeneous Pd/C: In quest of an industrially viable process. *Tetrahedron* **2005**, *61*, 9908.

10. Hatsuda, M.; Seki, M. A practical synthesis of highly functionalized aryl nitriles through cyanation of aryl bromides employing heterogeneous Pd/C. *Tetrahedron Lett.* **2005**, *46*, 1849.
11. Jensen, R. S.; Gajare, A. S.; Toyota, K.; Yoshijuji, M.; Ozawa, F. A convenient procedure for palladium-catalyzed cyanation using a unique bidentate phosphorus ligand. *Tetrahedron Lett.* **2005**, *46*, 8645.
12. Lin, L. S.; Fors, B. P.; Chobanian, H. R. A facile microwave-assisted palladium-catalyzed cyanation of aryl chlorides. *Tetrahedron Lett.* **2006**, *47*, 3303.
13. Whittall, J.; Cormack, P. M.; Pitts, W. R. Optimisation and scale-up of microwave-assisted cyanation. *Tetrahedron* **2006**, *62*, 4705.
14. Martin, M. T.; Liu, B.; Cooley Jr, B. E.; Eaddy, J. F. Open air palladium-catalyzed cyanation—the use of PMHS to protect from oxygen. *Tetrahedron Lett.* **2007**, *48*, 2555.
15. Polshettiwar, V.; Hesemann, P.; Moreau, J. J. E. Palladium containing nanostructured silica functionalized with pyridine sites: A versatile heterogeneous catalyst for Heck, Sonogashira, and cyanation reactions. *Tetrahedron* **2007**, *63*, 6784.
16. Littke, A.; Soumeillant, M.; Kaltenbach III, R. F.; Cherney, R. J.; Tarby, C. M.; Kiau, S. Mild and general methods for the palladium-catalyzed cyanation of aryl and heteroaryl chlorides. *Org. Lett.* **2007**, *9*, 1711.
17. Nandurkar, N. S.; Bhanage, B. M. Palladium bis(2,2,6,6-tetramethyl-3,5-heptanedionate) catalyzed Suzuki, Heck, Sonogashira, and cyanation reactions. *Tetrahedron* **2008**, *64*, 3655.
18. Franz, A. W.; Popa, L. N.; Li, T.; Müller, T. J. J. First synthesis and electronic properties of cyano(oligo)phenothiazines. *Tetrahedron Lett.* **2008**, *49*, 3300.
19. Wang, E. C.; Lin, G. J. A new one-pot method for the conversion of aldehydes into nitriles using hydroxyamine and phthalic anhydride. *Tetrahedron Lett.* **1998**, *39*, 4047.
20. Bose, D. S.; Narsaiah, A. V. Efficient one-pot synthesis of nitriles from aldehydes in solid state using peroxymonosulfate on alumina. *Tetrahedron Lett.* **1998**, *39*, 6533.
21. Kumar, H. M. S.; Reddy, B. V. S.; Reddy, P. T.; Yadav, J. S. Efficient one-pot preparation of nitriles from aldehydes using N-methyl-pyrrolidone. *Synthesis* **1999**, 586.
22. Das, B.; Ramesh, C.; Madhusudhan, P. An improved one-pot conversion of aldehydes into nitriles under microwave irradiation using ammonium acetate. *Synlett* **2000**, 1599.
23. Lai, G.; Bhamare, N. K.; Anderson, W. K. A one-pot method for the efficient preparation of aromatic nitriles from aldehydes using ammonia, magnesium sulfate, and manganese dioxide. *Synlett* **2001**, 230.
24. Sharghi, H.; Sarvari, M. H. A direct synthesis of nitriles and amides from aldehydes using dry or wet alumina in solvent-free conditions. *Tetrahedron* **2002**, *58*, 10323.
25. Srinivas, K. V. N. S.; Reddy, E. B.; Das, B. Highly convenient and efficient one-pot conversions of aldehydes into nitriles and ketones into amides using HY-zeolite. *Synlett* **2002**, 625.
26. Sharghi, H.; Sarvari, M. H. Graphite as an efficient catalyst for one-step conversion of aldehydes into nitriles in dry media. *Synthesis* **2003**, 243.
27. Ballini, R.; Fiorini, D.; Plamieri, A. Highly convenient, one-pot synthesis of nitriles from aldehydes using the $NH_2OH \cdot HCl/NaI/MeCN$ system. *Synlett* **2003**, 1841.
28. Movassagh, B.; Shokri, S. An efficient and convenient KF/Al_2O_3-mediated synthesis of nitriles from aldehydes. *Tetrahedron Lett.* **2005**, *46*, 6923.
29. Zhu, J. L.; Lee, F. L.; Wu, J. D.; Kuo, C. W.; Shi, K. S. An efficient new procedure for the one-pot conversion of aldehydes into the corresponding nitriles. *Synlett* **2007**, 1317.
30. Kivrak, A.; Zora, M. Efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde using $NH_2OH \cdot HCl/KI/ZnO/CH_3CN$ system. *J. Organomet. Chem.* **2007**, *692*, 2346.
31. Brackman, W.; Smit, P. J. New synthesis of nitriles. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 757.

32. Parameswaram, K. N.; Friedman, O. M. Synthesis of nitriles from aldehydes. *Chem. Ind. (London)* **1965**, 988.
33. Misono, A.; Osa, T.; Koda, S. The synthesis of nitriles from aldehydes. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 854.
34. Sato, R.; Itoh, Y.; Itep, K.; Nihina, H.; Goto, T.; Saito, M. Novel conversion of aromatic thioamides and aldehydes into nitriles with elemental sulfur and sodium nitrite in liquid ammonia. *Chem. Lett.* **1984**, *13*, 1913.
35. Erman, M. B.; Snow, J. W.; Williams, M. J. A new efficient method for the conversion of aldehydes into nitriles using ammonia and hydrogen peroxide. *Tetrahedron Lett.* **2000**, *41*, 6749.
36. Talukdar, S.; Hsu, J. L.; Chou, T. C.; Fang, J. M. Direct transformation of aldehydes to nitriles using iodine in ammonia water. *Tetrahedron Lett.* **2001**, *42*, 1103.
37. Bandgar, B. P.; Makone, S. S. Organic reactions in water: Highly rapid CAN-mediated one-pot synthesis of nitriles from aldehydes under mild conditions. *Synlett* **2003**, 262.
38. Bandgar, B. P.; Makone, S. S. Organic reactions in water: Transformation of aldehydes to nitriles using NBS under mild conditions. *Synth. Commun.* **2006**, *36*, 1347.
39. Arote, N. D.; Bhalerao, D. S.; Akamanchi, K. G. Direct oxidative conversion of aldehydes to nitriles using IBX in aqueous ammonia. *Tetrahedron Lett.* **2007**, *48*, 3651.
40. Telvekar, V. N.; Patel, K. N.; Kundaikar, H. S.; Chaudhari, H. K. A novel system for the synthesis of nitriles from aldehydes using aqueous ammonia and sodium dichloroiodate. *Tetrahedron Lett.* **2008**, *49*, 2213.
41. Veisi, H. Direct oxidative conversion of alcohols, amines, aldehydes, and benzyl halides into the corresponding nitriles with trichloroisocyanuric acid in aqueous ammonia. *Synthesis* **2010**, 2631.
42. Zolfigol, M. A.; Hajjami, M.; Ghorbani-Choghamarani, A. A simple and one-pot oxidative conversion of alcohols or aldehydes to the nitriles using $NaIO_4/KI$ in aqueous NH_3. *Bull. Korean Chem. Soc.* **2011**, *32*, 4191.
43. Ghorbani-Choghamarani, A.; Zolfigol, M. A.; Hajjami, M.; Sardari, S. Direct synthesis of nitriles from alcohols or aldehydes using H_5IO_6/KI in aqueous ammonia. *Synth. Commun.* **2013**, *43*, 52.
44. Mori, N.; Togo, H. Direct oxidative conversion of primary alcohols to nitriles using molecular iodine in ammonia water. *Synlett* **2005**, 1456.
45. Manjula, K.; Pasha, M. A. Rapid method of converting primary amides to nitriles and nitriles to primary amides by $ZnCl_2$ using microwaves under different reaction conditions. *Synth. Commun.* **2007**, *37*, 1545.
46. Online data from product catalog (2009), Sigma-Aldrich: http://www.sigmaaldrich.com/technical-service-home/product-catalog.html.