A Selective and Mild Oxidation of Primary Amines to Nitriles with Trichloroisocyanuric Acid

Fen-Er Chen,* Yun-Yan Kuang, Hui-Fang Dai, Liang Lu, Ming Huo

Department of Chemistry, Fudan University, Shanghai, 200433, P. R. China
Fax +86(21)65642021; E-mail: rfchen@fudan.edu.cn

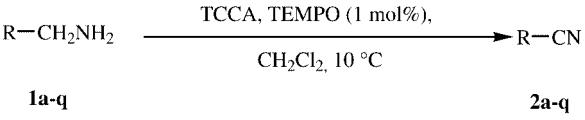
Received 4 August 2003; revised 8 September 2003

Abstract: An efficient and highly selective method for the oxidative conversion of primary amines to the corresponding nitriles using trichloroisocyanuric acid in the presence of catalytic TEMPO under mild reaction conditions is described. Other functional groups such as C,C-double bonds, benzyloxy etc. were found to be unaffected under the reaction conditions. This procedure provides a new entry to the synthesis of various aliphatic, aromatic and heterocyclic nitriles in excellent yield.

Key words: trichloroisocyanuric acid, primary amines, nitriles, oxidation

The oxidation of primary amines into the corresponding nitriles constitutes a very useful functional group transformation in organic synthesis, and the plethora of oxidizing agents for such a transformation documented in literature directly demonstrates the importance with which the functional group transformation has been addressed.[1] However, a lot of drawbacks may be encountered in using some of these reagents such as low yields, harsh reaction conditions, tedious work-up procedures, and some limitations. In addition, some of them are corrosive, toxic, expensive, or commercially unavailable. Consequently, there is a need for the development of protocols using readily available and safe reagents, which lead to high yield of nitriles from primary amines.

Trichloroisocyanuric acid (TCCA) is a stable and inexpensive reagent frequently used for swimming-pool disinfection. Some recent application of the utilization of TCCA in organic synthesis include thioacetalization of carbonyl compound,[2] conversion of alcohols to halides,[3] carboxylic acids to acid chlorides,[3] alkenes to β-chloroethers[4], N-nitrosation of *N*,*N*-dialkylamines,[5] selective mononitration of phenols[6], and oxidation of alcohols to carbonyl compounds,[7] aldehydes to methyl esters,[8] aldoximes to nitrile oxides,[9] thiols to disulfides,[10] selenols to diselenides[11] and sulfides to sulfoxides,[12] etc.[13] To the best of our knowledge, however, there is no indication in the literature on the utilization of TCCA as an oxidant for the conversion of primary amines into nitriles. Herein, we wish to report a new, simple and extremely efficient procedure for the preparation of nitriles from primary amines utilizing TCCA in the presence of catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO) under mild reaction conditions as outlined in Scheme 1.



Scheme 1

Our preliminary studies were carried out with benzylamine (**1d**) as a model substrate in order to establish the best reaction conditions. At the outset, the influence of solvent on this oxidation was investigated. In Et_2O, dioxane, and THF, only low yield of benzonitrile (**2d**) was obtained (Table 1, entries 1–3); a dramatic increase in the yield, however, was obtained in CH_2Cl_2 (Table 1, entry 4), which was therefore used as the solvent in all further experiments. Next, the effect of temperature was examined. Enhancing the temperature from 0 to 10 °C resulted in a considerable increase in the yield (49 to 88%, Table 1, entries 5,6). A somewhat higher temperature (10 °C instead of 5 °C) led to shorter reaction time, but also resulted in a significant decrease in the yield (Table 1, entry 7).

Table 1 Optimization of the Reaction Conditions for the TCCA-Mediated Oxidation of Benzylamine (**1d**) to the Benzonitrile (**2d**)[a]

Entry	Solvent	Temp (°C)	**1d**/TCCA (mole ratio)	Time (h)	Yield[b] (%)
1	Et_2O	5	1:1.2	4	70
2	dioxane	5	1:1.2	5	71
3	THF	5	1:1.2	5	62
4	CH_2Cl_2	5	1:1.2	3	85
5	CH_2Cl_2	0	1:1.2	6	49
6	CH_2Cl_2	10	1:1.2	3	88
7	CH_2Cl_2	10	1:1.2	1	69
8	CH_2Cl_2	5	1:0.5	5	45
9	CH_2Cl_2	5	1:0.8	3	72
10	CH_2Cl_2	5	1:1.3	2	90
11	CH_2Cl_2	5	1:1.5	2	90

[a] All reactions were carried out according to the typical procedure.
[b] Yield of isolated pure product.

SYNTHESIS 2003, No. 17, pp 2629–2631
Advanced online publication: 14.10.2003
DOI: 10.1055/s-2003-42431; Art ID: F06403SS

The following experiments were therefore carried out at 5 °C. Finally, the oxidation was carried out by varying the molar ratio of **1d** to TCCA from 1:0.5 to 1:1.5. It was observed that an increase in the **1d**/TCCA molar ratio increased the yield of **2d**, while further increase in the amount of TCCA was not effective and gave only comparable yields. When 1 equivalent of **1d** was used with 1.3 equivalents of TCCA, 90% yield of **2d** was achieved (entry 10). Thus, a ratio of 1:1.3 was found to be the most suitable for this reaction.

Guided by the above experiments with benzylamine (**1d**), a standard procedure was employed for the oxidation of other aliphatic, aromatic and heterocyclic primary amines with TCCA, and the results are summarized in Table 2. The results illustrated in the Table 2 indicate that this oxidation is very successful for a variety of primary amines. Moreover, benzyloxy (entry 11), C,C-double bonds (entry 9), hydroxy (entry 12), *N*,*N*-dimethlylamino (entry 8) groups present in the molecule were found to be resistant under the reaction conditions employed, which were also described in the oxidation of alcohol to carbonyl compounds.[7] It is interesting to note that benzylic amines were oxidized more readily with a higher yield than their aliphatic counterparts, just as reported in the dehydrogenation procedure of amines to nitriles using $NiSO_4/K_2S_2O_8$ system.[1e] At the same time, it is noteworthy that the presence of catalytic TEMPO was essential for the dehydrogenation of amines to nitriles. No desirable nitriles were formed in its absence and the reaction did not go to completion when lesser catalytic amounts of TEMPO was used.

In conclusion, we have developed an efficient method for oxidative conversion of the primary amines to nitriles employing trichloroisocyanuric acid. Prominent advantages of this new method are its mild reaction conditions, operational simplicity, and high yields.

Oxidation of Benzylamine (1d) to Benzonitrile (2d); Typical Procedure

Trichloroisocyanuric acid (30.23 g, 130 mmol) was slowly added to a solution of benzylamine (**1d**; 10.7 g, 100 mmol) in CH_2Cl_2 (200 mL), followed by addition of TEMPO (0.195 g, 1.3 mmol). The reaction mixture was then stirred for 2 h at 10 °C and then quenched with H_2O (150 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed successively with 0.5 N aq $NaHSO_3$

Table 2 Oxidation of Primary Amines **1a**–**q** into Nitriles **2a**–**q** with TCCA

Entry	R	Time (h)	Prod-uct[a]	Yield[b] (%)	Mp (°C) or Bp (°C)/Torr	
					Found	Reported
1	C_3H_7	4	**2a**	80	115–116/760	115/760[1d]
2	C_5H_{11}	4	**2b**	81	160–162/760	162–170[1d]
3	$HO_2C(CH_2)_5$	4.5	**2c**	80	162–164	162[1d]
4	Ph	2	**2d**	90	189–190/760	189–191/760[14]
5	4-MeC_6H_4	2	**2e**	91	216–218/760	217–218/760[14]
6	4-$MeOC_6H_4$	2	**2f**	90	61–63	61–63[14]
7	4-$NO_2C_6H_4$	2.5	**2g**	90	148–150	148–150[14]
8	4-$Me_2NC_6H_4$	2	**2h**	91	75–77	74–76[14]
9	(*E*)-PhCH=CH	2	**2i**	90	253–254/760	254–255/760[14]
10	1-naphthyl	1.5	**2j**	90	145–147/12	106–107/1[15]
11	3-(4-methoxybenzyloxy)C_6H_4	2	**2k**	89	94–95	94–96[16]
12	3,4-$(HO)_2C_6H_3$	2	**2l**	91	154–156	153–154[17]
13	2-ClC_6H_4	2	**2m**	90	228–229/760	228–230/760[17]
14	3,4-$(CH_2O_2)C_6H_3$	2	**2n**	90	93–95	92–94[17]
15	2-furyl	2	**2o**	89	148–149	146–148[1d]
16	3-pyridyl	2	**2p**	89	52–54	50–52[1f]
17	piperonyl	2.5	**2q**	89	70–72	68–70[1f]

[a] All products were identified by comparison with their spectral data (IR, ^1H NMR and GC/MS) and physical properties with those of the authentic samples.
[b] Yields of isolated pure product.

(2 × 10 mL), aq 1 N HCl (2 × 5 mL) and H_2O (3 × 10 mL), and dried (Na_2SO_4). Evaporation of solvent under reduced pressure gave the crude product, which was distilled to afford pure **2d** (10.6 g, 90%) as a colorless oil; bp 189–190 °C/760 Torr (Lit.[14] bp 189–191 °C/760 Torr).

References

(1) (a) Chen, F. E.; Peng, Z. Z.; Fu, H.; Li, J. D.; Shao, L. Y. *J. Chem. Res., Synop.* **1999**, 726. (b) Kametani, T.; Takahashi, K.; Ohsawa, T.; Ihara, M. *Synthesis* **1977**, 245. (c) Capdevielle, P.; Lavigne, A.; Sparfel, D.; Baranne-Lafont, J.; Cuong, N. K.; Maumy, M. *Tetrahedron Lett.* **1990**, *31*, 3305. (d) Feldhues, U.; Schafer, H. J. *Synthesis* **1982**, 145. (e) Yamazaki, S.; Yamazaki, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 301. (f) Capdevielle, P.; Lavigne, A.; Maumy, M. *Synthesis* **1989**, 451. (g) Griffith, W. P.; Reddy, B.; Shoair, A. G. G.; Suriaatmaja, M.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1998**, 2819. (h) Gao, S.; Herzig, D.; Wang, B. *Synthesis* **2001**, 545.

(2) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *Synlett* **2001**, 1641.

(3) Hiegel, G. A.; Rubino, M. *Synth. Commun.* **2002**, *32*, 2691.

(4) Medonca, G. F.; Sanseverino, A. M.; de Mattos, M. C. S. *Synthesis* **2003**, 45.

(5) Zolfigol, M. A.; Choghamarani, A. G.; Hazarkhani, H. *Synlett* **2002**, 1002.

(6) Zolfigol, M. A.; Ghaemi, E.; Medrakian, E. *Synlett* **2003**, 9.

(7) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041.

(8) Hiegel, G. A.; Bayne, C. D.; Donde, Y.; Tamashiro, G. S.; Hilberath, L. A. *Synth. Commun.* **1996**, *26*, 2633.

(9) Rodrigues, R. D.; de Aguiar, A. P. *Synth. Commun.* **2001**, *31*, 3075.

(10) Zhong, P.; Guo, M. P. *Synth. Commun.* **2001**, *31*, 1825.

(11) Zhong, P.; Guo, M. P. *Synth. Commun.* **2001**, *31*, 1507.

(12) Xiong, Z. X.; Huang, N. P. *Synth. Commun.* **2001**, *31*, 245.

(13) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384.

(14) Chen, F. E.; Fu, H.; Meng, G.; Chang, Y.; Lu, X. X. *Synthesis* **2000**, 1519.

(15) Saednya, A. *Synthesis* **1982**, 190.

(16) Lai, G.; Bhamare, N. K.; Anderson, W. K. *Syntlett* **2001**, 230.

(17) Feng, J. C.; Liu, B.; Dai, L.; Bian, N. S. *Synth. Commun.* **1998**, *28*, 3765.