

Direct synthesis of nitriles from aldehydes using tetrabutylammonium tribromide in aqueous ammonia

Yi-Zhong Zhu · Chun Cai

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Abstract A convenient method for direct conversion of aldehydes into nitriles has been developed by using tetrabutylammonium tribromide in aqueous ammonia.

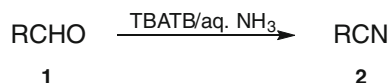
Keywords Tetrabutylammonium tribromide · Aqueous ammonia · Nitriles · Aldehydes · Oxidation

Introduction

Nitriles are important compounds not only because of their interesting biological properties, but also 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 transition-metal-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 by using reagents such as $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{NEt}_3/\text{phthalic anhydride}$ [19], $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{peroxymonosulfate-alumina}$ [20], $\text{NH}_2\text{OH}\cdot\text{HCl}/N\text{-methylpyrrolidine}$ [21], $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{ammonium acetate}$ [22], $\text{NH}_4\text{OH}/\text{MgSO}_4/\text{MnO}_2$ [23], $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{dry Al}_2\text{O}_3/\text{MeSO}_2\text{Cl}$ [24], $\text{NH}_2\text{OH}\cdot\text{HCl}/$

HY-zeolite [25], $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{graphite}/\text{MeSO}_2\text{Cl}$ [26], $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{NaI}/\text{MeCN}$ [27], $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{KF-Al}_2\text{O}_3/\text{DMF}$ [28], $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{DBU}/\text{EtOPOCl}_2/\text{MS } 3\text{Å}$ [29], and $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{KI}/\text{ZnO}/\text{CH}_3\text{CN}$ [30]. 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 as an expedient method and has been studied with $\text{NH}_3/\text{O}_2/\text{CuCl}_2\cdot\text{H}_2\text{O}/\text{MeONa}$ in MeOH [31], $\text{NH}_3/\text{Pb}(\text{OAc})_4$ in dry benzene [32], $\text{NH}_3/\text{I}_2/\text{MeONa}$ in MeOH [33], $\text{NH}_3/\text{S}_8/\text{NaNO}_2$ [34], $\text{NH}_3/\text{H}_2\text{O}_2/\text{CuCl}$ in 2-propanol [35], NH_3/I_2 in THF–water [36], NH_3/CAN [37], NH_3/NBS [38], NH_3/IBX in acetonitrile–water [39], and $\text{NH}_3/\text{NaICl}_2$ [40]. Although some of these methods present advantages over other reaction pathways in that the reactions could be carried out at low temperatures, drawbacks such as the formation of by-products [33], harsh reaction conditions [34], production of explosive $\text{NI}_3\cdot\text{NH}_3$ [36], or use of expensive reagents [32, 39] have extremely limited their application. The development of this methodology using new reagents under mild conditions is therefore of interest. Tetrabutylammonium tribromide (TBATB) is a brominating agent which is crystalline, easy to handle, and has not been used for this transformation. Following our interest in the synthesis of nitriles [41, 42], herein we report a convenient method for direct transformation of aldehydes to nitriles by using TBATB [43] in aqueous ammonia under mild conditions (Scheme 1).



Scheme 1

Y.-Z. Zhu · C. Cai (✉)
Chemical Engineering College, Nanjing University of Science and Technology, Nanjing 210094, People's Republic of China
e-mail: c.cai@mail.njust.edu.cn

Table 1 Conversion of aldehydes into nitriles using TBATB and aqueous ammonia

Entry	RCHO	RCN	Period (h)	Yield (%) ^b	Mp or bp/p (°C or °C/Torr)	Mp or bp/p (°C or °C/Torr) [Ref.]
1	C ₆ H ₅ CHO	2a	2	89	188–190/760	187/760 [24]
2	4-ClC ₆ H ₄ CHO	2b	3	92	91–92	90 [26]
3	3-ClC ₆ H ₄ CHO	2c	3	93	39–40	38–40 [44]
4	2-ClC ₆ H ₄ CHO	2d	4	91	42–44	42 [24]
5 ^a	4-MeC ₆ H ₄ CHO	2e	5	81	217–218/760	216–218/760 [21]
6 ^a	4-MeOC ₆ H ₄ CHO	2f	6	82	58–59	60 [26]
7	4-CF ₃ C ₆ H ₄ CHO	2g	8	83	37–38	39–41 [45]
8	4-FC ₆ H ₄ CHO	2h	12	80	186–188/760	188/750 [45]
9	3-Pyridinecarboxaldehyde	2i	8	84	47–48	47 [26]
10	CH ₃ (CH ₂) ₃ CHO	2j	12	82	139–140/760	138/760 [26]
11	CH ₃ (CH ₂) ₅ CHO	2k	12	81	186–187/760	186/760 [21]

Reaction conditions: aldehyde (2 mmol), aqueous ammonia (10 cm³), TBATB (3 mmol), rt

^a TBATB (4 mmol) was used

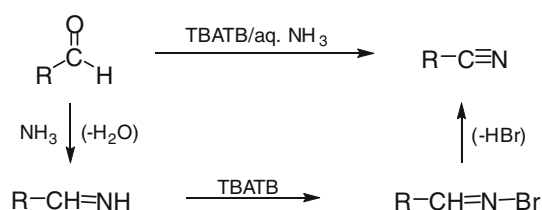
^b Isolated yields

Results and discussion

Benzaldehyde was chosen as a model substrate. After surveying a series of reaction conditions, we found that the optimal conditions were benzaldehyde (2 mmol), TBATB (1.5 equiv.), and ammonia water (10 cm³) at room temperature (rt) for 2 h, which provided the desired product **2a** in 89% yield. Encouraged by that result, we examined a range of aldehydes. As shown in Table 1, various aromatic, heterocyclic, and aliphatic aldehydes were efficiently transformed into their corresponding nitriles in good yields. As expected, no bromination products were observed in these reactions.

A plausible reaction pathway for the conversion of aldehydes into the corresponding nitriles with TBATB is similar to that with molecular iodine suggested by Togo and co-workers (Scheme 2) [46]. Thus, the reaction proceeded via oxidation of the aldehyde with TBATB to give an *N*-bromo aldimine intermediate, which eliminated an HBr molecule in the presence of NH₃ to afford the nitrile product. Here, TBATB may play not only the role of an oxidant, but also a phase transfer reagent.

In summary, we disclosed a new and efficient one-pot reaction for the synthesis of nitriles from aldehydes through oxidation of in situ formed aldimines by using TBATB/aq. NH₃, which offers a useful synthetic method for the preparation of nitriles due to its simplicity and good yields.



Scheme 2

Experimental

Typical procedure for the conversion of aldehydes into nitriles

A suspension of an aldehyde (2 mmol) and 10 cm³ ammonia water was stirred for 10 min at room temperature, resulting in formation of a turbid solution. TBATB (3 mmol), prepared from tetrabutylammonium bromide according to ref. [43], was added slowly at room temperature to this turbid solution. Then the mixture was stirred strongly for an appropriate time (see Table 1) as indicated by TLC. After the reaction was completed, solid products were collected by simple filtration, whereas liquid products were obtained by usual work-up through extraction with ethyl acetate (2 × 25 cm³). The combined organic layer was washed with H₂O (2 × 15 cm³). Then the organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. If necessary, the product was purified by flash chromatography on silica gel with EtOAc–petroleum ether as the eluent. All prepared nitriles are known compounds and were identified by mp or bp and GC–MS.

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