Tetrahedron Letters 51 (2010) 4479–4481

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ultrasound-promoted synthesis of nitriles from aldoximes under ambient conditions

Nan Jiang, Arthur J. Ragauskas *

School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, USA

ARTICLE INFO

Article history:
Received 12 May 2010
Revised 14 June 2010
Accepted 14 June 2010
Available online 19 June 2010

ABSTRACT

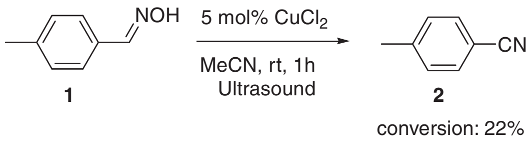
Copper(II) acetate proves to be an active catalyst for ultrasound-promoted conversion of aldoximes into nitriles. This dehydration reaction was carried out in acetonitrile under ambient conditions to provide nitriles with moderate tolerance toward water, which allows one-pot synthesis of a nitrile from an aldehyde with minimal purification.

Observed as a key constituent in various natural products, nitrile is also an important synthetic intermediate for pharmaceuticals, agricultural chemicals, and material sciences with significant commercial importance.[1] The versatility of nitriles comes from their extremely high polar-inductive effect[2] and excellent hydrogen bond acceptor properties.[3] While the synthesis of nitriles from aldoximes has been documented in the literature,[4] most procedures developed so far suffer from some disadvantages, such as the use of stoichiometric/excess amounts of corrosive, moisture-sensitive reagents,[5] or toxic and hazardous chemicals, their associated waste disposal, and tedious workup procedures.[6] In spite of several reports describing metal-catalyzed aldoxime dehydration for the synthesis of nitriles,[7] it is still highly desirable to develop a general catalysis for efficient and environmentally friendly dehydration of aldoximes into nitriles under mild conditions.

Ultrasound-promoted chemical reactions are well documented by increasing reaction kinetics, product yields, and occasionally selectivities.[8] In several cases ultrasound can facilitate organic transformation at ambient conditions as an alternative for organic reactions ordinarily accomplished by heating and prove to be very advantageous in terms of yields and reaction times.[9] We herein report ultrasound-promoted copper(II) acetate-catalyzed dehydration of aldoximes into nitriles under ambient condition. Furthermore, mild tolerance toward water of the current catalysis allows a one-pot synthesis of nitrile from aldehyde through aldoxime.

Our initial optimization experiment started with the use of a low-intensity ultrasound (LIU), laboratory cleaning bath, for the dehyration of *p*-tolualdoxime **1** into *p*-tolunitrile **2**. In the presence of 5 mol % $CuCl_2$ with acetonitrile as the solvent under ambient condition, *p*-tolunitrile **2** was obtained in 22% conversion and 14% isolated yield after 1 h ultrasound irradiation (Scheme 1).

Further efforts were then focused on optimizing the reaction conditions, and the results are summarized in Table 1. At first, four additional copper(II) salts, $CuBr_2$, $Cu(OAc)_2$, $Cu(acac)_2$, and



Scheme 1.

Table 1
Optimizing dehydration of *p*-tolualdoxime **1** into *p*-tolunitrile **2** under ultrasound irradiation[a]

Entry	Catalyst	Additive (mg)	Time (h)	Conv.[b]/yield[c] (%)
1	$CuCl_2$	N.A.	1	22/14
2	$CuBr_2$	N.A.	1	27/—
3	$Cu(OAc)_2$	N.A.	1	65/56
4	$Cu(OTf)_2$	N.A.	1	14/—
5	$Cu(acac)_2$	N.A.	1	—
6	$Cu(OH)_2$	N.A.	1	35/—
7	$SnCl_2$	N.A.	1	—
8[d]	$[RuCl_2(p\text{-cymene})]_2$	MS 4 Å (200)	1	19/—
9	$Pd(OAc)_2$	PPh_3 (26.1)	1	—
10	$Ga(OTf)_3$	N.A.	1	—
11	$Cu(OAc)_2$	N.A.	2	98/90
12[e]	$Cu(OAc)_2$	N.A.	2	6/—
13	$Cu(OAc)_2$	H_2O (100)	2	89/82

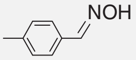
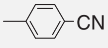
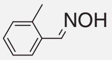
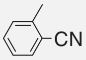
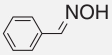
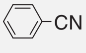
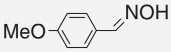
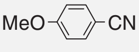
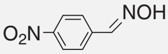
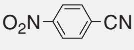
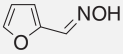
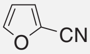
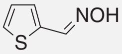
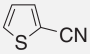
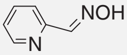
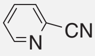
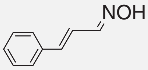
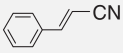
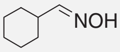
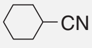
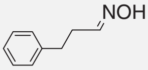
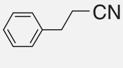
[a] 1.0 mmol *p*-tolualdoxime (135.0 mg) and 5 mol % catalyst in 1.0 mL acetonitrile at ambient temperature under ultrasound irradiation for the specific time.
[b] Conversion was determined by ^1H NMR analysis of the crude mixture.
[c] Isolated yield by flash chromatography.
[d] 2.5 mol % catalyst was employed.
[e] The reaction was carried out under ambient condition in the absence of ultrasound irradiation.

---

* Corresponding author. Tel.: +1 404 984 9701; fax: +1 404 894 4778.
E-mail address: arthur.ragauskas@chemistry.gatech.edu (A.J. Ragauskas).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.06.079

Table 2
Ultrasound-promoted $Cu(OAc)_2$-catalyzed dehydration of oximes into nitriles under ambient conditions[a]

Entry	Oximes	Product	Yield[b] (%)
1			90
2			83
3[c]			91
4			88
5[d]			73
6			83
7			90
8			74
9			82
10[d,e]			61
11[d,e]			75

[a] 1.0 mmol oxime and 5 mol % $Cu(OAc)_2$ in 1.0 mL acetonitrile at ambient temperature under ultrasound irradiation for 2 h.

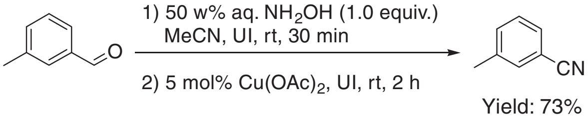
[b] Isolated yield by flash chromatography.

[c] 10.0 mmol oxime and 5 mol % $Cu(OAc)_2$ in 10.0 mL acetonitrile at ambient temperature under ultrasound irradiation for 2 h.

[d] Ultrasound irradiation for 3 h.

[e] 1.0 mol oxime and 10 mol % $Cu(OAc)_2$ was used.

$Cu(OTf)_2$, were tested as the catalyst. It is clear that $Cu(OAc)_2$ gave the best results (conversion 65% and isolated yield 56%) and Cu(acac)$_2$ showed no catalytic activity for the ultrasound-promoted dehydration of *p*-tolualdoxime **1** (Table 1, entries 1–5). Furthermore, it has been reported that the sonochemical effects on the chemical reactions can be enhanced when a solid acts as catalyst,[10] therefore copper(II) hydroxide, $Cu(OH)_2$, was also investigated for aldoxime dehydration. However, only 35% conversion was observed for $Cu(OH)_2$ as the catalyst (Table 1, entry 6). In addition, various transition-metal salt systems, including $SnCl_2$,[7a] $[RuCl_2(p\text{-cymene})]_2$/molecular sieves (MS, 4 Å),[7b] $Pd(OAc)_2/PPh_3$,[7c] and $Ga(OTf)_3$,[7d] which have been reported to be effective catalysts for the dehydration of oximes under heating condition, have also been investigated and the results showed very low or no conversion of *p*-tolualdoxime into *p*-tolunitrile under identical conditions (Table 1, entries 7–10). With $Cu(OAc)_2$ showing optimum catalytic activity for ultrasound-promoted dehydration of *p*-tolualdoxime under ambient condition, increasing the time of ultrasound irradiation to 2 h afforded excellent conversion and isolated yield (98% conversion and 90% isolated yield, Table 1, entry 11). Furthermore, extremely low conversion of *p*-tolualdoxime into *p*-tolunitrile was observed under ambient condition without sonication irradiation (6%, Table 1, entry 12), which confirmed that both ultrasound irradiation and $Cu(OAc)_2$ are crucial for successful dehydration of *p*-tolualdoxime under ambient condition.



Scheme 2. One-pot synthesis of *m*-tolunitrile from *m*-tolualdehyde.

In spite of the water as the byproduct of dehydration of oximes, many of previously reported catalytic dehydrations of oximes have required anhydrous solvents, and in some cases the molecular sieve has been used as the additive.[7b] Therefore, it is worthy of noting that the current catalysis shows moderate tolerance toward water and the use of 11% wet acetonitrile as the solvent afforded a slightly reduced isolated yield (Table 1, entry 13). Although other organic solvents, such as toluene, THF, ethyl acetate, and some ionic liquids, including [bmim]Cl, $[bmim]PF_6$, and $[bmim]BF_4$, were tested under identical condition, very low conversions (less than 10% after 2 h) were observed under ambient and ultrasound irradiation conditions.

Subsequently, the ultrasound-promoted catalysis[11,12] dehydrated various aromatic, allylic, and aliphatic aldoximes into nitriles, as summarized in Table 2. It is clear that all aromatic aldoximes with electron-rich, electron-neutral, or electron-poor substitutes were selectively converted into nitriles in high yields (Table 2, entries 1–5). It has to be pointed out that the dehydration of benzaldoxime in a larger scale (10 mmol scale) afforded a paralleled isolated yield (Table 2, entry 3).

In addition, heteroaromatic aldoximes were compatible with the employed catalysis. For example, 2-pyridinealdoxime, 2-thiophenealdoxime, and 2-furanealdoxime were smoothly converted into the corresponding nitriles in good yields (Table 2, entries 6-8). *trans*-Cinnamonitrile was also conveniently obtained with the intact double bond (Table 2, entry 9). However, the aliphatic aldoximes such as 3-phenylpropanaldoxime and cyclohexanecarboxaldoxime were less reactive and an increased catalyst loading (10 mol %) was needed to provide good isolated yield (Table 2, entries 10 and 11).

Due to the moderate water tolerance of the current catalysis, one-pot synthesis of *m*-tolunitrile from *m*-tolualdehyde was established through *p*-tolualdoxime,[13] as shown in Scheme 2.[14] *m*-Tolualdoxime was first formed from the *m*-tolualdehyde by adding 50 wt % aqueous hydroxylamine and followed by 30 min sonication. After flushing with molecular oxygen for 1 min, 5 mol % $Cu(OAc)_2$ was added into the reaction mixture, which then undergoes ultrasound-promoted dehydration of *m*-tolualdoxime under ambient condition to afford *m*-tolunitrile in 73% isolated yield.

In conclusion, an efficient ultrasound-promoted dehydration of various aldoximes into nitriles by using copper(II) acetate/acetonitrile system under ambient conditions was developed. Furthermore, the current catalytic system is notably not deactivated by heteroatom-containing (S, N, and O) compounds and shows moderate tolerance toward water, which allows one-pot synthesis of *m*-tolunitrile from *m*-tolualdehyde in good yield with minimal purification.

Acknowledgment

This project was supported by the Georgia Institute of Technology Focused Research Program.

References and notes

1. (a) Moruoka, K.; Yamamoto, H. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Winterfeld, E., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 381; (b) Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1983; pp 1057–1061; (c) Miller, J. S.; Manson, J. L. *Acc. Chem. Res.* **2001**, *34*, 563–570.
2. Bradamante, S.; Pagani, G. A. *Adv. Carbanion Chem.* **1996**, *2*, 189.
3. le Questel, J.-Y.; Berthelot, M.; Laurence, C. *J. Phys. Org. Chem.* **2000**, *13*, 347.
4. *Comprehensive Organic Transformation, A Guide to Functional Group Preparation*; Larock, L. C., Ed.; VCH: New York, 1989.
5. (a) Denis, J. N.; Krief, A. *Chem. Commun.* **1980**, 544; (b) Olah, G. A.; Vankar, Y. D.; Garcia-Luna, A. *Synthesis* **1979**, 227; (c) Carotti, A.; Campagna, F. *Synthesis* **1979**, 56.
6. (a) Dulcere, J. P. *Tetrahedron Lett.* **1981**, *22*, 1599; (b) Konwar, D.; Boruah, R. C.; Sandhu, J. S. *Tetrahedron Lett.* **1990**, *31*, 1063; (c) Fukuzawa, S.; Yamaishi, Y.; Furuya, H.; Terao, K.; Iwasaki, F. *Tetrahedron Lett.* **1997**, *38*, 7203.

7. (a) Loupy, A.; Regnier, S. *Tetrahedron Lett.* **1999**, *40*, 6221; (b) Yang, S. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209; (c) Choi, E.; Lee, C.; Na, Y.; Chang, S. *Org. Lett.* **2002**, *4*, 2369; (d) Yan, P.; Batamack, P.; Prakash, G. K. S.; Olah, G. A. *Catal. Lett.* **2005**, *101*, 141; (e) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3922; (f) Kim, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1717.
8. (a) Mason, T. *J. Chem. Soc. Rev.* **1997**, *26*, 433–451; (b) Del Campo, F. J.; Maisonhaute, E.; Compton, R. G.; Marken, F.; Aldaz, A. *J. Electroanal. Chem.* **2001**, *506*, 170–177; (c) *Practical Sonochemistry: Uses and Applications of Ultrasound*; Mason, T. J., Peters, D., Eds.; Horwood Publishing Ltd: London, UK, 2002; (d) Meciarova, M.; Toma, S.; Magdolen, P. *Ultrasonics Sonochem.* **2003**, *10*, 265–270; (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771–11835; (f) Cella, R.; Stefani, H. A. *Tetrahedron* **2006**, *62*, 5656–5662.
9. (a) Scondo, A.; Dumarcay-Charbonnier, F.; Barth, D.; Marsura, A. *Tetrahedron Lett.* **2009**, *50*, 5582; (b) Luzzio, F. A.; Chen, J. *J. Org. Chem.* **2008**, *73*, 5621; (c) Li, J.-T.; Zhai, X.-L.; Lin, Z.-P.; Zhang, X.-H. *Lett. Org. Chem.* **2008**, *5*, 579; (d) Zlotin, S. G.; Bogolyubov, A. V.; Kryshtal, G. V.; Zhdankina, G. M.; Struchkova, M. I.; Tartakovsky, V. A. *Synthesis* **2006**, 3849; (e) Wang, J.; Yuan, G.; Dong, C.-Q. *Chem. Lett.* **2004**, *33*, 286; (f) Ross, N. A.; Bartsch, R. A. *J. Org. Chem.* **2003**, *68*, 360; (g) Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2003**, 693; (h) Lopez-Pestana, J. M.; Avila-Rey, M. J.; Martin-Aranda, R. M. *Green Chem.* **2002**, *4*, 628; (i) Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616.
10. (a) Suslick, K. S.; Casadonte, D. J.; Green, M. L. H.; Thompson, M. E. *Ultrasonics* **1987**, *25*, 56; (b) Peters, D. *J. Mater. Chem.* **1996**, *6*, 1605.

11. A general procedure for ultrasound-promoted dehydration of *p*-tolualdoxime into *p*-tolunitrile follows: *p*-tolualdoxime (135.0 mg, 1.0 mmol), $Cu(OAc)_2$ (9.0 mg, 0.05 mmol), and 1.0 mL acetonitrile were added into a 10 mL vial. After being capped, the vial was suspended into the ultrasonic bath (Branson Ultrasonics, UltraSonic bath Model 3510, 40 kHz frequency) under ambient condition for specific time in a continuous irradiation mode. At the end of the reaction period, the reaction mixture was concentrated in vacuo. The residue was subjected to ^1H NMR analysis, and then was purified by flash chromatography (*n*-pentane/ethyl ether = 6:1) to afford *p*-tolunitrile (105.1 mg, yield 90%).
12. The possible mechanism for the $Cu(OAc)_2$-catalyzed aldoxime dehydration suggests the initial formation of the intermediate RHC=NOCuOAc and the subsequent rearrangement under ultrasound irradiation leading to the nitrile and Cu(OH)OAc, which could be the active copper(II) species. The second best catalytic performance of $Cu(OH)_2$ among various copper(II) salts could be due to Cu(OH)OAc being more soluble and thus more active in acetonitrile than $Cu(OH)_2$.
13. The use of 50 wt % aqueous hydroxylamine is crucial for the one-pot synthesis of *m*-tolunitrile, and the use of hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$)/K_2CO_3 to replace aqueous 50 wt % hydroxylamine led to significant reduced conversion of *m*-tolualdoxime into *m*-tolunitrile (less than 30%) under identical condition.
14. A one-pot synthesis of *m*-tolunitrile from *m*-tolualdehyde follows: aqueous 50 wt % hydroxylamine (66.0 mg, 1.0 mmol) was added into the solution of *m*-tolualdehyde (120.0 mg, 1.0 mmol) in 1.0 mL acetonitrile in 10 mL vial. After being capped, the reaction mixture was under continuous ultrasound irradiation for 30 min. After flushing the reaction mixture with molecular oxygen for 1 min, $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) was added into the vial. After capping the vial, the reaction mixture was under continuous ultrasound irradiation for another 2 h. After sonication, the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (*n*-pentane/ethyl ether = 6:1) to afford *m*-tolunitrile (colorless oil, 85.2 mg, yield 73%).