ORGANIC LETTERS

2013
Vol. 15, No. 8
1850–1853

Highly Practical Synthesis of Nitriles and Heterocycles from Alcohols under Mild Conditions by Aerobic Double Dehydrogenative Catalysis

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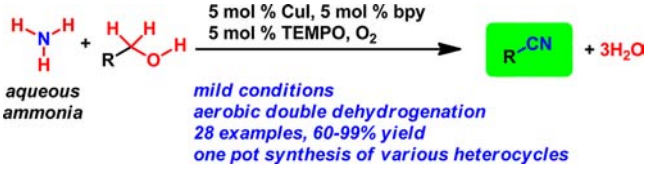
Received February 19, 2013

ABSTRACT



A mild, aerobic, catalytic process for obtaining nitriles directly from alcohols and aqueous ammonia is described. The reaction proceeds via a dehydrogenation cascade mediated by catalytic CuI, bpy, and TEMPO in the presence of O_2. The substrate scope is broad including various functionalized aromatic and aliphatic alcohols. This protocol enabled the one-pot synthesis of various biaryl heterocycles directly from commercially available alcohols.

Nitriles are vital synthetic intermediates for pharmaceuticals, material, agricultural, and fine chemicals. Numerous methods have been developed for nitrile production.[1] Representative general synthetic strategies include halide/CN exchange,[2] oxidation of amines,[3] and dehydration of amides and aldoximes.[4,5] Often, high temperature, pressure, toxic reagents, and wastes or their combinations are employed to promote efficient nitrile formation. There is a growing demand for a highly practical nitrile synthesis from cheap commercially available starting materials such as alcohols and aqueous ammonia under ambient conditions. Formation of the unique C≡N functionality often requires chemical stripping of hydrogen, oxygen, or other heteroatoms off a C═N moiety. This elimination is quite difficult, as bonds on sp^2 atoms are significantly stronger compared with their sp^3 counterparts.[6] Therefore, such a transformation requires the use of stoichiometric amounts of oxidants.[7] Quite recently, catalytic aerobic reactions have emerged as one of the preferred green oxidation strategies.[8] In this vein, the direct synthesis of a nitrile, via a transition-metal catalyzed aerobic oxidative reaction,

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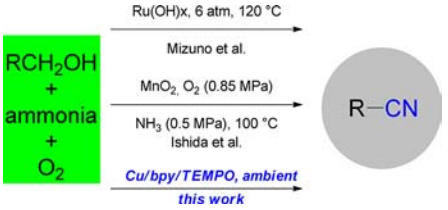
10.1021/ol400459y
Published on Web 04/05/2013

from an inexpensive commodity source, such as alcohols and ammonia, would be a highly valuable process.

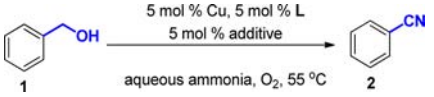
Scheme 1. Catalytic Aerobic Oxidation of Alcohols to Nitriles



Intrigued by the old industrial method of ammoxidation,[9] we were interested in developing a highly practical method for converting alcohols to nitriles using molecular oxygen and ammonia. To the best of our knowledge, direct conversion of alcohols to nitriles using oxygen and ammonia only existed in the heterogeneous catalysis paradigm (Scheme 1). Recently, Mizuno reported a direct nitrile synthesis from alcohols using a heterogeneous $Ru(OH)_x/Al_2O_3$ catalyst and excess aqueous ammonia under 6 atm of air pressure at 120 °C.[10c] Ishida et al. subsequently disclosed a parallel process using metal oxide (MnO_2) under pressured oxygen (0.85 MPa) and NH_3 gas (0.5 MPa) at 100 °C.[10a] Challenges for this particular transformation include (1) the formation of catalytically dead Werner complexes in the presence of ammonia and homogeneous transition metals; (2) difficulty in undergoing "N−H activation" due to the high strength of the N−H bond of ammonia (107 kcal/mol);[11] and (3) a double dehydrogenative mechanism which requires strong oxidative conditions, preventing an efficient aerobic catalytic cycle.

Cu/TEMPO has been extensively studied as an efficient catalyst for alcohol oxidation to the aldehyde.[12] Recently, a simple Cu/TEMPO/NMI/bpy system was developed by Stahl et al. that permitted room temperature aerobic oxidation of alcohols to aldehydes.[12e] We decided to explore the possibility of double dehydrogenation of alcohols to access nitriles directly via in situ aldehyde/imine formation. However, aerobic oxidation of aldehydes to nitriles in the presence of ammonia and a transition metal is a challenging task. In 1963, Brackman and Smit reported two examples (15% and 30% yield) of nitrile synthesis from aldehyde and ammonia.[13a] The poor yields might be attributed to the formation of Werner's amine complexes $Cu[NH_3]_4X_2$. Subsequently, Capdevielle reported that aromatic nitriles could be obtained in high yield from benzaldehyde derivatives and ammonium chloride using stoichiometric (1.5−2.0 equiv) copper powder in pyridine.[13b] In addition, enolizable aliphatic aldehydes were not tolerated.

Table 1. Preliminary Study of Cu/TEMPO Catalyst System for the Synthesis of Nitriles from Alcohols[a]



entry	Cu	L	add.	sol.	conv (%)[b]
1	$CuBr_2$	none	none	DMSO	N.R.
2	$CuBr_2$	none	TEMPO	DMSO	45
3	$CuBr_2$	bpy	TEMPO	DMSO	64
4	$CuBr_2$	bpy	TEMPO	EtOH	80
5	CuBr	bpy	TEMPO	EtOH	86
6	CuOTf	bpy	TEMPO	EtOH	93
7	CuCl	bpy	TEMPO	EtOH	91
8	CuI	bpy	TEMPO	EtOH	100
9[c]	**CuI**	**bpy**	**TEMPO**	**EtOH**	**100**

[a] Reaction conditions: 1.0 mmol of alcohol, 5 mol % Cu, 5 mol % ligand, 5 mol % additive, 2.0 equiv of aqueous ammonia (25−28%, w/w), 2 mL of solvent, oxygen balloon, 55 °C, 24 h. [b] Determined by GC using biphenyl as an internal standard. [c] The reaction was carried out at room temperature for 24 h.

Our initial investigation involved mixing benzyl alcohol, a copper salt, a ligand, an additive, and 2 equiv of aqueous ammonia under an oxygen atmosphere. After the reaction mixture was stirred for 24 h at 55 °C, aliquots were taken and conversions were determined by GC (Table 1; for complete condition screening, see the Supporting Information). Gratifyingly, aqueous ammonia did not inhibit the initial aldehyde formation and we were able to eliminate NMI required in the Stahl protocol without effecting the catalytic activity. Preliminary screening revealed the following characteristics: (1) Cu alone did not catalyze nitrile formation; (2) TEMPO was essential for both alcohol-to-aldehyde and aldehyde-to-nitrile steps; (3) a chelating bpy ligand significantly improved nitrile formation by accelerating the aldehyde formation step. Cu(I) and Cu(II) salts were equally effective.[14] By using CuI, we were able to achieve a 100% GC yield.

To our delight, the reaction at room temperature was equally effective (Table 1, entry 9). The substrate scope was explored under the optimized ambient conditions. Good-to-quantitative yields were achieved for a broad

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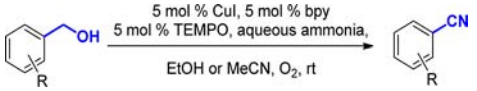
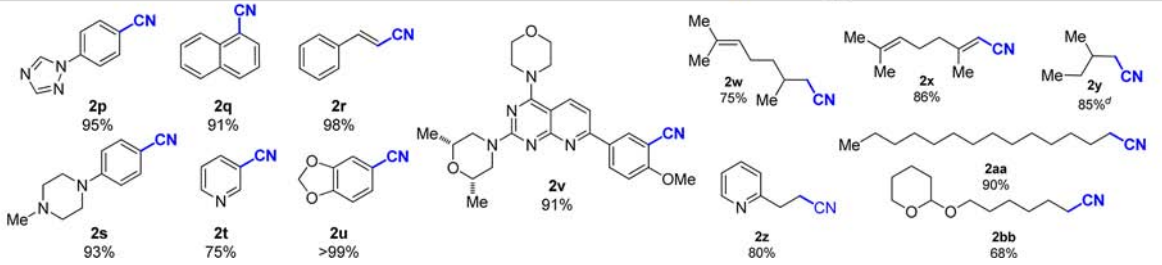
(14) There was a greater rate difference between Cu(I) and Cu(II) for the alcohol oxidation to aldehyde step in Stahl's studies; see ref 12e.

Table 2. Scope of Alcohols for Aerobic Double Dehydrogenation[a]

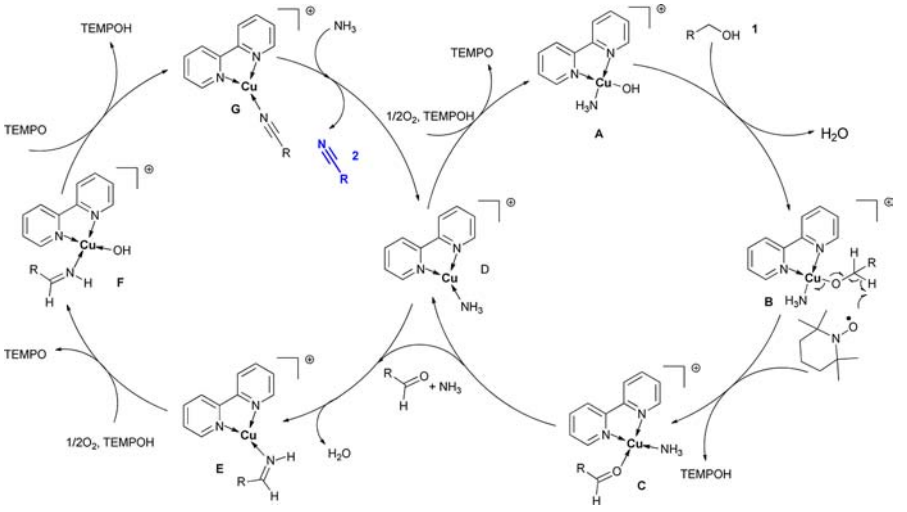


entry	product	R	yield (%)	entry	product	R	yield (%)[b]
1		**2a** H	97	8		**2h** 3-F, 4-MeO	92
2		**2b** 2-MeO	>99 (92[c])[c]	9		**2i** 3-Cl	85
3		**2c** 3-MeO	90	10		**2j** 4-Br	91
4		**2d** 4-MeO	>99	11		**2k** 4-Me_2N	93
5		**2e** 4-Me	>99	12		**2l** 4-AcNH	93
6		**2f** 3-Me, 4-Me	>99	13		**2m** 4-NO_2	60
7		**2g** 2-Me, 4-F	93	14		**2n**	78
				15		**2o**	71



[a] 1.0 mmol of alcohol, 2 mL of solvent, oxygen balloon, 24 h. [b] Isolated yield. Reactions of aromatic alcohols occurred in EtOH at rt. Reactions of aliphatic alcohols occurred in MeCN at 50 °C. [c] Yield in parentheses reflected a 3 g scale reaction. [d] GC yield due to low boiling point of the product.

Scheme 2. A Proposed Reaction Mechanism



range of benzyl alcohols (Table 2). A number of functional groups were tolerated. The reactions were particularly efficient for electron-rich and -neutral benzyl alcohols. Over 90% isolated yields were obtained uniformly. Halogen, basic amine, and heterocyclic substituents did not interfere with this double dehydrogenation reaction. The reactions involving strongly electron-deficient benzyl alcohols were compromised by the competing oxidation of an in situ generated hemiacetal, due to the strong electrophilic nature of the corresponding aldehydes. For 4-nitro benzyl alcohol, the corresponding benzoic acid ethyl ester was isolated as the major side product and the corresponding nitrile was obtained in 60% isolated yield. Heteroaromatic substrates and vinylogous benzyl alcohols were also successfully oxidized in good-to-excellent yields. The robustness of this process was challenged using KU0063794 (Stemolecule, **1v**),[15] a potent and selective inhibitor for

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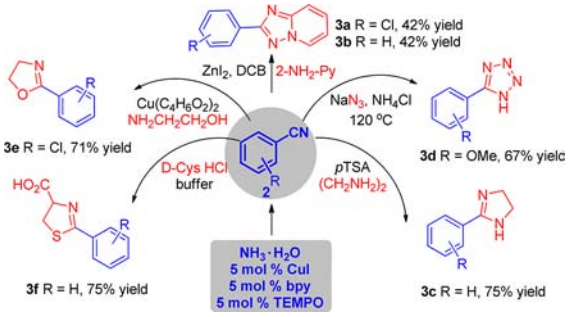
mTORs (mammalian target of rapamycin). The corresponding nitrile analogue was isolated in high yield despite the rich functionality present in this molecule. The reactions of aliphatic alcohols were very slow at room temperature. The first alcohol-to-aldehyde oxidation was the rate limiting step for those substrates, which justified the usage of EtOH as solvent for benzyl alcohol substrates. Gratifyingly, heating to 50 °C (in acetonitrile) rendered full conversions to the corresponding aliphatic nitriles in high yields. Regardless of the steric hindrance, primary alcohols bearing secondary, tertiary, and quaternary carbon side chains afforded the corresponding nitriles in excellent yields. The appealing synthetic practicality is underscored by the workup procedures. For most substrates, simple evaporation and filtration through a silica gel plug led to analytically pure products. Reproducible yields were obtained on 3 g scales.

It is unambiguous that the aldehyde is a key intermediate in these reactions. The first dehydrogenation is faster than the second oxidation step, as evidenced by early stage aldehyde accumulation. Independent experiments have shown that TEMPO plays central roles in both oxidation steps. The detailed mechanism of Cu/TEMPO catalyzed dehydrogenative oxidation is quite complicated. Very recently, Stahl reported detailed mechanistic studies on Cu(I)/TEMPO catalyzed aerobic oxidation of an alcohol to an aldehyde. The authors found that this particular catalyst system resembled binuclear type 3 Cu enzymes for O_2 activation.[16] Combining our experimental data and Stahl's mechanism, we propose a Cu(II)−OH mediated TEMPO oxidation pathway (Scheme 2). Cu(I)−L is converted to Cu(II)−OH (**A**) by O_2 and TEMPOH. Ligand exchange would lead to Cu(II)−OR (**B**) which could be oxidized by TEMPO through a hydrogen abstraction mechanism, to generate the corresponding aldehyde. The aldehyde is then converted to the imine rapidly in the presence of ammonia. The transient imine intermediate, being a better ligand than either the aldehyde or the nitrile, would form a more favored Cu(I)−imine complex (**E**) which could trigger the second oxidation cycle to afford the nitrile product **2**.

This aerobic double dehydrogenative nitrile synthesis was tied to various heterocyclization processes, to provide a one-pot synthesis of substituted tetrazoles,[17] imidazolines,[18] oxazoline,[19] thiazoline,[20] and triazolopyridines[21] (Scheme 3). Generally, the reagents for the heterocyclizations were introduced after a full conversion of nitrile had been achieved. For imidazolines, oxazolines, and thiazolines, no oxidation to the corresponding heteroaromatics was observed.

Scheme 3. One-Pot Synthesis of Biaryl Heterocycles



In summary, we have reported a general and practical protocol for the synthesis of nitriles under mild conditions using cheap commercially available reagents: CuI, TEMPO, bipyridine, and alcohols. Both functionalized benzyl and aliphatic alcohols are well suited for this protocol. This aerobic dehydrogenation cascade reaction enables a series of one-pot syntheses of pharmaceutically attractive heterocycles. Preliminary experiments suggest a radical mechanism mediated by a copper(II)−OH complex.

Acknowledgment. This work is financially supported by the National Basic Research Program of China (2012CB722602), grants of Shenzhen special funds for the development of biomedicine (JC201104210111A and JC201104210112A), Shenzhen innovation funds (GJHZ20120614144733420), and the Shenzhen Peacock Program (KQTD201103).

Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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