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A novel oxidative transformation of alcohols to nitriles: an efficient utility of azides as a nitrogen source†

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An efficient methodology to oxidize benzylic and cinnamyl alcohols to their corresponding nitriles in excellent yields has been developed. This methodology employs DDQ as an oxidant and TMSN₃ as a source of nitrogen in the presence of a catalytic amount of Cu(ClO₄)₂·6H₂O.

The azide functionality is one of the valuable intermediates in organic synthesis.¹ Utility of azides^{2a-c} is demonstrated in insertion of nitrogen into hydrocarbons to obtain tetrazoles,^{2d} amides^{2e} or transform allylarenes to alkenyl nitriles^{2f,g} and in click chemistry.³ Ammonia or its alternatives have been used as the source of nitrogen to synthesize amines, amides, nitriles *etc.*,⁴ which require harsh conditions such as high pressure and/or temperature. Nevertheless, these reactions have paved new avenues of utility of azides in the synthesis of nitrogen-containing heterocyclic compounds by C–H or C–C bond cleavage.⁵ The nitrile functionality is special in organic synthesis⁶ as it occurs in several natural products⁷ and can be transformed into a variety of functional groups such as amines, ketones, acids, amides *etc.* Aliphatic nitriles are synthesized using corresponding halides and metal cyanides,⁸ whereas aromatic nitriles are synthesized by employing the classical Sandmeyer reaction.⁹ Dehydration of amides,¹⁰ oximes¹¹ and oxidative conversion of alcohols¹² or amines¹³ are a few more methods reported to accomplish synthesis of nitriles. C–H functionalization of methyl arenes to corresponding nitriles has been reported by Jiao and co-workers,¹⁴ which requires activated precursors. The utility of azides to synthesize aryl, alkyl or alkenyl nitriles has been reported by various groups.^{2,15} Interestingly, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) is known to oxidize cinnamyl azide to cinnamionitrile.^{2f,g} Further, azides are easily accessed by azidation of either allylic alcohols^{2h} or allylic acetates.²ⁱ As alcohols are inexpensive and easily available or prepared, it is advantageous to synthesize nitriles directly from alcohols. It is important to note that most of the methods for synthesizing nitriles employ halides, acetates or azides, which are generally obtained from their corresponding alcohols.

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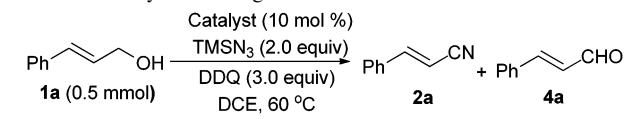
Attempts in this direction to synthesize nitriles directly from alcohols¹² require forcing conditions.¹⁶ Recently, we have reported the transformation of benzylic azides to nitriles using CuI and TBHP (*tert*-butyl hydroperoxide).¹⁷ In continuation of our investigation,¹⁸ herein we report an elegant strategy to transform cinnamyl and benzyl alcohols to their corresponding nitriles using TMSN₃ (trimethylsilyl azide) as a nitrogen source with a catalytic amount of Cu(ClO₄)₂·6H₂O in the presence of DDQ.

Initial optimization studies were carried out using cinnamyl alcohol (**1a**) and Cu(ClO₄)₂·6H₂O with a variety of oxidants (Table 1). Preliminary experiments indicated that TMSN₃ is a suitable source of nitrogen under the present reaction conditions. Contrary to our expectation sodium azide (NaN₃) did not furnish the desired product.¹⁹ Therefore, further studies were carried out using TMSN₃, Cu(ClO₄)₂·6H₂O and a variety of oxidants (Table 1). Interestingly, atmospheric air or molecular oxygen as oxidants furnished the corresponding azide **3a** as the major product (entries 1 and 2, Table 1), whereas, a similar reaction with H₂O₂ was unsuccessful (entry 3). Reaction of cinnamyl alcohol **1a** with TBHP, benzoquinone, di-*tert*-butyl peroxide (DTBP), or chloranil resulted in the formation of a

Table 1 Optimization studies of oxidants^a

Entry	Oxidant	Yield ^b (%)			
		2a	3a	4a	1a
1	Air	nd	95	nd	nd
2	O ₂	nd	75	nd	25
3	H ₂ O ₂	nd	nd	nd	100
4	Aq. TBHP(70%)	nd	52	5	43
5	TBHP in decane	Inseparable mixture			
6	Benzoquinone	Inseparable mixture			
7	DTBP	nd	42	nd	58
8	Chloranil	32	14	54	nd
9	DDQ	100	nd	nd	nd
10 ^c	DDQ	100	nd	nd	nd

^a Reaction conditions: alcohol (0.50 mmol), TMSN₃ (1.0 mmol), Cu(ClO₄)₂·6H₂O (0.05 mmol), oxidant (1.5 mmol), 1,2-dichloroethane (2 ml), RT. ^b Yields were determined by ¹H NMR analysis with respect to the starting material. ^c Reaction carried out at 60 °C for 1 h. nd = not detected (<1%).

Table 2 Catalyst screening

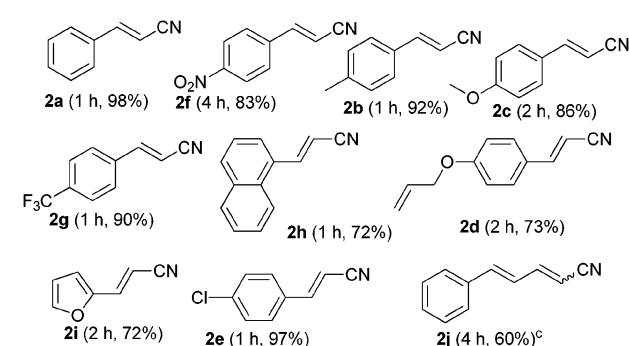
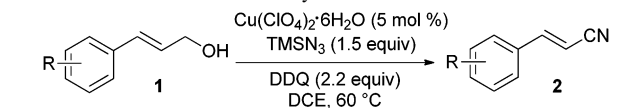
Entry	Catalyst	Yield ^a (%)	
		2a	4a
1	CuI	93	7
2	CuCl	58	42
3	CuBr	88	12
4	CuCl ₂ ·2H ₂ O	75	25
5	CuO	78	22
6	Cu ₂ O	91	9
7	Cu(OAc) ₂	67	33
8	Cu(OAc) ₂ ·1H ₂ O	87	13
9	Cu(NO ₃) ₂ ·3H ₂ O	75	25
10	CuSO ₄ ·5H ₂ O	89	11
11	Cu powder	50	50
12	Cu(OTf) ₂	100	nd
13	Cu(ClO ₄) ₂ ·6H ₂ O	100	nd
14	None	63	37

^a Yields were determined by ¹H NMR with respect to the starting material. nd = not detected (<1%).

mixture of products (entries 4–8, Table 1). Finally, it was satisfying to find that a catalytic amount of Cu(ClO₄)₂·6H₂O and TMSN₃ in the presence of DDQ was a suitable system to transform cinnamyl alcohol **1a** to cinnamionitrile **2a** at room temperature in almost quantitative yield (3 h, entry 9, Table 1). Further, it was found that the same reaction proceeds well at 60 °C in shorter duration (1 h) to furnish cinnamionitrile **2a** in quantitative yield (entry 10, Table 1).

Further studies revealed that copper catalysts such as copper halides, copper oxides, copper acetate, copper nitrate, copper sulphate and copper powder under the identical reaction conditions are not suitable catalysts as they resulted in the formation of mixtures of corresponding nitriles and aldehydes (entries 1–11, Table 2). However, Cu(OTf)₂ and Cu(ClO₄)₂·6H₂O were found to be the most suitable catalysts, as these reactions furnished the quantitative yield of **2a** (entries 12 and 13, Table 2). The reaction also proceeded in the absence of copper catalysts but unfortunately furnished the mixture of corresponding nitrile and aldehyde (entry 14, Table 2). In the solvent screening studies, it was found that dichloroethane (DCE), toluene and CH₃CN were suitable solvents for conversion of alcohol **1a** to the corresponding nitrile **2a**, whereas the reaction in THF resulted in lower yield of the product. No reaction was observed in MeOH or water as solvent (see Table S1 in ESI[†]). With the help of additional screening studies (Table S2, ESI[†]), it was found that 5 mol% Cu(ClO₄)₂·6H₂O, 1.5 equiv. TMSN₃, and 2.2 equiv. of DDQ are required for the efficient conversion of cinnamyl alcohol **1a** to cinnamionitrile **2a**.²⁰

Under the optimized reaction conditions, the scope and limitation of the reaction was investigated and the results have been compiled in Table 3. As can be seen in Table 3, a variety of substituted cinnamyl alcohols were converted to their corresponding nitriles in excellent yields. It is evident from the table that neither electron-donating substituents nor electron-withdrawing substituents have any effect on the outcome of the reaction and the reaction proceeded well to furnish

Table 3 Conversion of cinnamyl alcohols to nitriles^{a,b}

^a Reaction conditions: TMSN₃ (0.75 mmol), alcohol (0.5 mmol), Cu(ClO₄)₂·6H₂O (0.025 mmol), DDQ (1.1 mmol) in DCE (2 mL) at 60 °C. ^b Isolated yields. ^c Mixture of *E* and *Z* diastereomers (8.9 : 1.1, based on ¹H NMR).

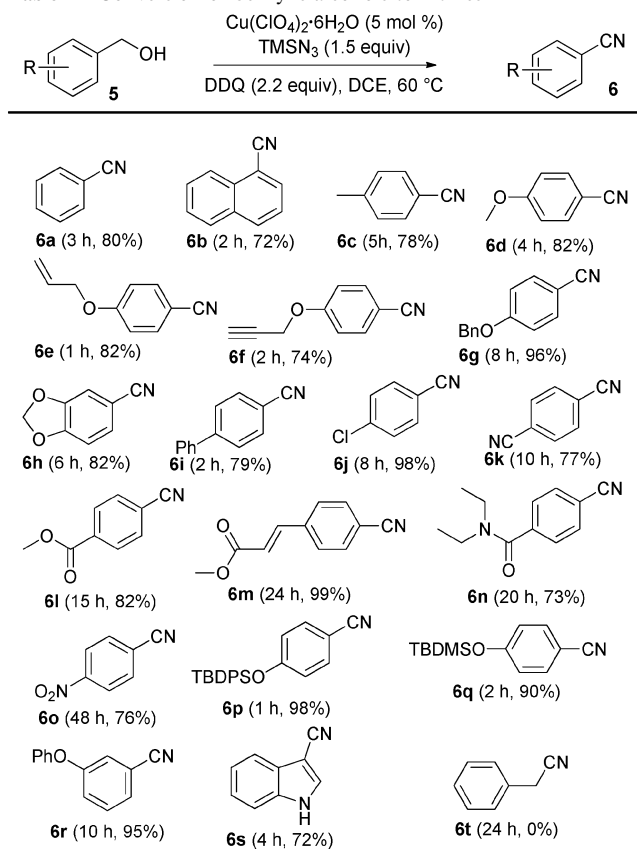
the corresponding nitriles **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i** and **2j**²¹ respectively, in good to excellent yields (Table 3).

To extend the scope of this reaction, a variety of benzylic alcohols were subjected to similar reaction conditions (Table 4). As seen in the table, this method is proved to be versatile as a variety of benzylic alcohols with electron-withdrawing and electron-donating substituents on the phenyl ring were converted to their corresponding nitriles (**6a–6s**) in good yields. However, 2-phenylethanol did not produce the corresponding nitrile, which may be due to the lack of conjugation (**6t**, Table 4). The salient feature of the above reaction is that this transformation is selective as a variety of functional groups such as allylic, propargylic, *O*-benzylic, ester groups, which are prone to oxidation, were inert under the reaction conditions. Additionally, the reaction tolerates the protecting groups such as TBDPS, TBDMS and benzylic which are prone to undergo deprotection under milder reaction conditions.

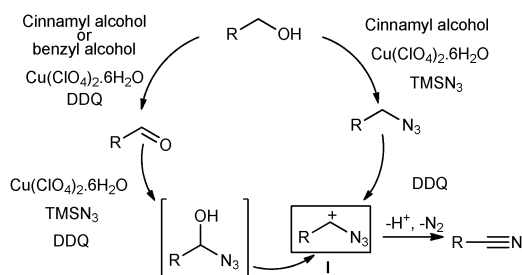
Based on a few control experiments (see Scheme S1, ESI[†]) and literature precedence,^{22–24} we believe that Cu(ClO₄)₂·6H₂O, which is a Lewis acid, activates the alcohol (or aldehyde) and assists the nucleophilic attack of TMSN₃ to form the corresponding azide, which further reacts with DDQ to form allylic or benzylic carbocation **I**, which furnishes the corresponding nitrile as presented in Scheme 1. Further work is underway in our laboratory.

In conclusion, we have demonstrated a novel, efficient and useful methodology to oxidize benzylic and cinnamyl alcohols to their corresponding nitriles in excellent yields by employing DDQ as an oxidant and TMSN₃ as a source of nitrogen in the presence of a catalytic amount of Cu(ClO₄)₂·6H₂O. Further, this method tolerates a variety of oxidizable functional groups and a few useful protecting groups. Additionally, it was also observed that cinnamyl azide can be synthesized using cinnamyl alcohol, TMSN₃ and Cu(ClO₄)₂·6H₂O which is also under investigation.

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Table 4 Conversion of benzylic alcohols to nitriles^{a,b}

^a Reaction conditions: TMSN_3 (0.75 mmol), alcohol (0.5 mmol), $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.025 mmol), DDQ (1.1 mmol) in DCE (2 mL) at 60 °C. ^b Isolated yields.

**Scheme 1** A tentative mechanism.**Notes and references**

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- The reaction of cinnamyl alcohol with $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, NaN_3 and DDQ produced quantitative yield of cinnamaldehyde.
- Reaction of cinnamyl alcohol (**1a**) with DDQ (1.2 equiv.), TMSN_3 (1.5 equiv.) and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (5 mol%) furnished cinnamionitrile in major amounts (85–90%), along with a minor amount of aldehyde (10%). To circumvent this problem, 2.2 equiv. of DDQ was employed which furnished cinnamionitrile (**2a**) exclusively in good yield (99%).
- This reaction has produced the mixture of *E* and *Z* diastereomers in the ratio of 8.9 : 1.1 (based on ¹H NMR).
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