

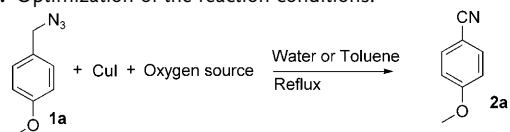
An Efficient Oxidation of Primary Azides Catalyzed by Copper Iodide: A Convenient Method for the Synthesis of Nitriles**

Manjunath Lamani and Kandikere Ramaiah Prabhu*

The nitrile group is an important functional group in organic synthesis.^[1] Therefore, the development of newer methods for the synthesis of nitriles is of significant interest among organic chemists.^[2] Typical methods for the synthesis of nitriles include the cyanation of halides,^[3,4] the Sandmeyer reaction (for aromatic nitriles),^[5] dehydration of aryl oximes,^[6] and other methods.^[7–11] Although some of these methods are attractive, they suffer from the limitations of using extreme conditions and large amounts of reagents. Therefore, the development of convenient and user-friendly procedures for the synthesis of nitriles is highly desirable. Recently, an interesting conversion of methyl arenes into aryl nitriles using phenyliodonium diacetate (PIDA) has been reported by Jiao and co-workers,^[12] whilst the use of azides in the synthesis of nitriles has also been documented.^[12,13] For example, conversion of organic azides into nitriles using bromine trifluoride was reported by Sasson and Rozen.^[14] Furthermore, Chiba et al.^[15] reported the C–C bond cleavage of α -azido carbonyl compounds to furnish nitriles and carboxylic acid. In the above reactions, the use of NH_3 , azides, or metal cyanides as the nitrogen source are required, depending upon the strategy adopted.

In continuation of our research on green chemistry^[16] and the utility of organic azides,^[17] we found that a variety of primary azides are efficiently oxidized into nitriles by a catalytic amount of CuI and *tert*-butyl hydroperoxide (TBHP). During the optimization studies, *para*-methoxybenzyl azide **1a** was reacted with stoichiometric amounts of copper iodide in the presence of a variety of oxygen sources. As shown in Table 1, the preliminary reaction of **1a** with CuI in the absence of an oxygen source or with several other oxygen sources, such as molecular oxygen, *N*-methylmorpholine-*N*-oxide (NMO), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) with oxygen, H_2O_2 , or sodium perborate did not produce any significant amount of the product and the starting material was recovered (Table 1, entries 1–6). Subsequently, we found that CuI (stoichiometric amount) with excess of TBHP (70% solution in water, 2.5 equiv) reacted

Table 1: Optimization of the reaction conditions.



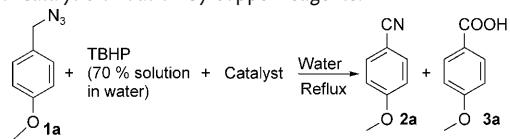
Entry	Oxygen source	Solvent	Yield [%] ^[a,b]
1	None	H_2O	n.r.
2	O_2	H_2O	n.r.
3	NMO	H_2O	n.r.
4	TEMPO + O_2	H_2O	n.r.
5	H_2O_2	H_2O	n.r.
6	$\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$	H_2O	n.r.
7	TBHP (aq 70%)	H_2O	92 ^[c]
8	TBHP (aq 70%)	toluene	89 ^[c]

[a] Reaction conditions: **1a** (1 mmol), CuI (1 mmol), water or toluene (2 mL), reflux, 20 h. [b] Yield of isolated product. [c] Reaction completed in 1 h. TBHP = *tert*-butyl hydroperoxide, n.r. = no reaction.

with the azide **1a** under refluxing conditions in aqueous solution to furnish the corresponding nitrile **2a** in excellent yield (92%, 1 h; Table 1, entry 7). The reaction proceeded well in toluene to yield **2a** in 89% (1 h; Table 1, entry 8).

In order to optimize the catalyst loading, a number of copper catalysts were screened. As seen in Table 2, the reaction did not proceed in the absence of a catalyst (entry 1, Table 2). The reaction of **1a** with catalytic amounts of copper

Table 2: Catalytic oxidation by copper reagents.



Entry	Catalyst (mol %)	TBHP [equiv]	<i>t</i> [h]	Yield [%] ^[a,b] 2a	Yield [%] ^[a,b] 3a
1	none	2.5	40	n.r.	n.r.
2	CuCl (5)	2.5	1	65 (62)	25 (25)
3	CuBr (5)	2.5	1	63 (60)	22 (20)
4	$[\text{Cu}(\text{acac})_2]$ (5)	2.5	1	70 (68)	20 (18)
5	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (5)	2.5	1	73 (70)	22 (20)
6	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (5)	2.5	1	73 (71)	22 (18)
7	CuI (5)	2.5	1	92 (89)	0 (0)
8	CuI (10)	2.5	1	92 (90)	0 (0)
9	CuI (5)	1.5	24	92 (90)	0 (0)

[a] Reaction condition: **1a** (1 mmol), copper catalyst (0.05 mmol), water or toluene (2 mL), reflux, 1 h. [b] Yield of isolated product. Yields in parenthesis refer to the reaction in toluene.

[*] M. Lamani, Dr. K. R. Prabhu
Department of Organic Chemistry, Indian Institute of Science
Bangalore 560 012, Karnataka (India)
Fax: (+91) 80-2360-0529
E-mail: prabhu@orgchem.iisc.ernet.in

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reagents, such as CuCl, CuBr, [Cu(acac)₂] (acac = acetylacetonate), Cu(OAc)₂·H₂O (Ac = acetyl), or CuSO₄·5H₂O^[18] and TBHP produced mixtures of *para*-methoxybenzonitrile **2a** and *para*-methoxybenzoic acid **3a** (Table 2, entries 2–6). Reaction of **1a** with TBHP (2.5 equiv) in the presence of CuI (5 mol %) was found to be the optimum conditions, furnishing *para*-methoxybenzonitrile **2a** in excellent yield (92 %, 1 h; Table 2, entry 7). Increasing the amount of catalyst to 10 mol % did not alter the yield of the product (Table 2, entry 8); at the same time, decreasing the amount of TBHP to 1.5 equivalents resulted in a much longer reaction time (24 h) without affording any change in the yield of the product (Table 2, entry 9). As seen from Table 1 and Table 2, the reaction proceeds well in both toluene and water, and as such we continued our investigation by using water as the solvent as it is environmentally benign.

Next, we investigated the scope of the reaction and found that a variety of primary azides were smoothly transformed into the corresponding nitriles in good to excellent yields (Table 3 and Table 4). Benzylic azides bearing electron-donating and electron-withdrawing groups underwent a smooth oxidation to provide the corresponding benzonitriles in high yields (Table 3, entries 1–5). 2-(Azidomethyl)naphthalene **1f** gave the corresponding nitrile **2f** in 82 % yield (Table 3, entry 5). Interestingly, the oxidation of benzylic azides bearing several oxidizable functional groups resulted in the formation of the corresponding nitriles in good yields. Cinnamyl azide **1g**, underwent a facile oxidation to yield cinnamionitrile **2g** in 76 % yield (Table 3, entry 6). Similarly, azido-derivatives bearing allylic ether (**1h**) and ester functionality (**1i**) furnished the corresponding nitriles **2h** and **2i** in good yields (Table 3, entries 7 and 8). Interestingly, diazide derivative 1,4-bis(azidomethyl)benzene **1j** was oxidized into its corresponding dinitrile **2j** in good yield (87 %; Table 3, entry 9). Under the optimized oxidation conditions, *para*-acetyl benzyl azide **1k** gave the corresponding nitrile **2k** in moderate yield (51 %; Table 3, entry 10).^[19] 2-(Azidomethyl)pyridine **1l** reacted smoothly to afford the corresponding nitrile **2l** in 53 % yield.^[19] Aliphatic primary azides,^[20] such as **1m**, **1n**, and **1o** reacted well to form the corresponding nitriles in good yields (70–73 %; Table 3, entries 12–14).

The scope of this reaction was further demonstrated in the oxidation of the secondary benzylic azides, such as 1-phenylethyl azide (**1p**), diphenylmethyl azide (**1q**), 1-(2-naphthyl)ethyl azide (**1r**), and 1-(*para*-methylphenyl)1-azidoethane (**1s**) resulted in the formation of their corresponding ketones in very good yields (**2p–2s**, 91–94 %; Table 4, entries 1–4). α -Azido carbonyl compound ethyl-2-azido-2-(naphthalen-1-yl)acetate (**1t**) underwent smooth oxidation to produce the corresponding α -ketoester **2t** in moderate yield (53 %; Table 4, entry 5). It is noteworthy that the reaction of

Table 3: Oxidation of primary azides.

$\text{R}-\text{CH}_2\text{N}_3 + \text{TBHP (70 \% solution in water)} + \text{CuI (5 mol \%)} \xrightarrow[\text{Reflux}]{\text{Water}} \text{R}-\text{CH}_2\text{CN}$				
Entry	Substrate	t [h]	Product	Yield [%] ^[b]
1	1b	1	2b	80
2	1c	1	2c	75
3	1d	1	2d	85
4	1e	6	2e	84
5	1f	1	2f	82
6	1g	1	2g	76
7	1h	2	2h	75
8	1i	6	2i	76
9	1j	2	2j	87
10	1k	6	2k	51 ^[b]
11	1l	8	2l	53 ^[b]
12	1m	27	2m	70 ^[c,d]
13	1n	24	2n	73 ^[c]
14	1o	14	2o	71

[a] Yield of isolated product. [b] **1k** was recovered in 25 %, **1l** was recovered in 20 %.

[c] Yield determined by GC analysis. [d] With 4 equivalents of TBHP.

1t with copper acetate under an oxygen atmosphere resulted in cleavage of the C–C bond to furnish the corresponding nitrile and carboxylic acid,^[15] whereas in the present reaction, cleavage of the C–C bond is not observed.^[21]

To get an insight into the reaction mechanism, the reaction of CuI and TBHP with **1a** was performed under an argon atmosphere and confirmed that nitrogen gas was generated during the reaction.^[22] Furthermore, it was found that the addition of a radical inhibitor (hydroquinone) had no

Table 4: Oxidation of secondary azides to ketones.

$\text{R}^1-\text{C}_6\text{H}_4-\text{N}_3-\text{R}^2 + \text{TBHP (70\% solution in water)} + \text{CuI (5 mol\%)} \xrightarrow[\text{Reflux}]{\text{Water}}$				
Entry	Substrate	t [h]	Product	Yield [%] ^[a]
1	1p	1	2p	94
2	1q	1	2q	92
3	1r	1	2r	91
4	1s	1	2s	92
5	1t	24	2t	53 ^[b]

[a] Yield of isolated product. [b] Reaction carried out at 0 °C, **1t** was recovered in 25%.

effect on the oxidation reaction of **1a** and proceeded smoothly to form **2a**, thus indicating that the reaction did not proceed through a radical intermediate.^[23] A detailed mechanistic study is currently underway within the group.

In summary, we have demonstrated that a variety of primary azides are efficiently oxidized by TBHP and CuI (5 mol %) into their corresponding nitriles in aqueous solution. This synthesis is suitable for a wide range of primary benzylic azides that contain electron-donating and electron-withdrawing functional groups. The oxidation is selective and a number of oxidizable functional groups were well-tolerated during the reaction conditions. Furthermore, oxidation of secondary azides furnished the corresponding ketones in excellent yields.

Experimental Section

Typical procedure for *para*-methoxybenzonitrile (**2a**): Aqueous TBHP (70% solution in water, 0.344 mL, 2.5 mmol) was added to a stirred suspension of 1-(azidomethyl)-4-methoxybenzene (**1a**,^[16a] 163 mg, 1 mmol) and CuI (9.5 mg, 0.05 mmol) in water (2 mL). The reaction mixture was heated at reflux until the reaction had gone to completion (1 h, monitored by TLC), cooled to room temperature, and extracted with ethyl acetate (3 × 15 mL); the combined organic layer was washed with water (2 × 50 mL), dried over sodium sulfate, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/hexane 1:19 to 1:9) to furnish 123 mg (92%) of **2a** as a colorless solid; m.p.: 55–57 °C (lit.^[24] 56–57).

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- [18] Jiao and co-workers recently proposed an azide intermediate in the conversion of methyl arenes into aryl nitriles with PIDA, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, and NaN_3 (see Ref. [12]). This reaction appeared to be an oxidation catalyzed by PIDA, as the reaction proceeded in the absence of copper reagents (see the Supporting Information, S2; also see Ref. [12]) at -40°C . However, addition of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ resulted in a nominal increase in the yield of the nitrile obtained (see the Supporting Information, S2; also see Ref. [12]). Furthermore, *para*-methoxybenzyl azide (**1a**) furnished trace amounts of the corresponding nitrile (**2a**) from the reaction with PIDA (2 equiv) and CuCl (10 mol%) under a N_2 atmosphere in CH_3CN , with the recovery of *para*-methoxybenzyl azide (**1a**) in 99% yield (see the Supporting Information, S6). Contrary to this observation, our studies revealed that the reaction of *para*-methoxybenzyl azide (**1a**) with CuCl (5 mol%) and TBHP (2.5 equiv) in water (or toluene) heated to reflux afforded the corresponding nitrile (**2a**) and acid (**3a**) in 65% and 25% yields, respectively (Table 2, entry 2). It is important to note that the method developed by Jiao and co-workers uses PIDA as the oxidant at room temperature, whereas the method described here uses aqueous TBHP as the oxygen source under refluxing conditions in water.
- [19] **1k** was recovered in 25%; **1l** was recovered in 20%.
- [20] In the oxidations of aliphatic azides, such as **1m** and **1n**, 4 equiv of TBHP was needed to furnish **2m** and **2n** in good yields.
- [21] The reaction of α -azido carbonyl compound ethyl 2-azido-2-(naphthalen-1-yl) acetate (**1r**) was performed at 0°C as the azido ester **1t** was not stable under the standard reaction conditions.
- [22] The reaction of **1a** with CuI (5 mol%) and TBHP (2.5 equiv) in water was performed under an argon atmosphere and the gas generated during the reaction analyzed by GC to find that nitrogen gas was generated during the reaction.
- [23] The reaction of **1a** with CuI and TBHP in the presence of radical inhibitors, such as hydroquinones, had no effect on the oxidation reaction, and was complete in 1 h, thus providing **2a** in good yield.
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