

Direct Conversion of Benzyl Ethers into Aryl Nitriles

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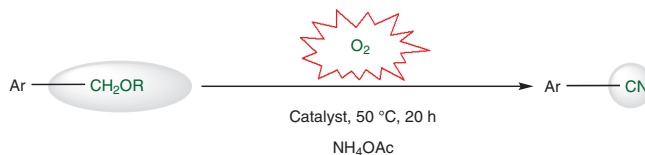
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Abstract A direct method was developed for the conversion of benzyl ethers into aryl nitriles by using NH_4OAc as the nitrogen source and oxygen as the terminal oxidant with catalysis by TEMPO/ HNO_3 ; the method is valuable for both the synthesis of aromatic nitriles and for the deprotection of ether-protected hydroxy groups to form nitrile groups in multistep organic syntheses.

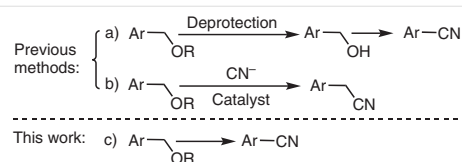
Key words benzyl ethers, aryl nitriles, cyanation, oxidation, organo-catalysis

Aryl nitriles have a wide range of applications in modern organic synthesis because they frequently occur as useful structural motifs in many natural products, pharmaceuticals, herbicides, and dyes.¹ In addition, they have served as versatile intermediates for many synthetic targets, including amines, amides, carboxylic acids, and nitrogen-containing heterocycles.² As a result, the preparation of aromatic nitriles has attracted considerable attention.³ Up to now, aromatic nitriles have been synthesized from various substrates, such as arenediazonium salts,⁴ aryl halides,⁵ arenes,⁶ amines,⁷ amides,⁸ azides,⁹ oximes,¹⁰ aldehydes,¹¹ ketones,¹² arylboronic acids,¹³ terminal alkynes,¹⁴ arylcarboxylic acids,¹⁵ and phenols.¹⁶ Another attractive method for synthesizing aromatic nitriles involves the stepwise conversion of benzyl alcohols into aromatic nitriles, in which the oxydehydrogenation of the benzyl alcohol is followed by oxidative condensation of the resulting aryl aldehyde.¹⁷

Although many effective methods for the preparation of aromatic nitriles have been developed,^{3–17} it remains a desirable research objective to use ethers as substrates to synthesize aromatic nitriles because the ether group is widely present in natural organic compounds.¹⁸ Moreover, this



process is valuable for the deprotection of ether-protected hydroxy groups¹⁹ to form nitrile groups in multistep organic syntheses [Schemes 1(a) and (b)]. In fact, the direct conversion of benzyl ethers into aryl nitriles through nucleophilic substitution has been reported [Scheme 1(b)],^{19e–h} although the direct conversion of benzyl ethers into aryl nitriles is unknown [Scheme 1(c)]. Consequently, the objective of this work was to develop an effective method for the preparation of aromatic nitriles from benzyl ethers [Scheme 1(c)]. Here we report the realization of this goal.



Scheme 1 Conversion of benzyl ethers into nitriles

Our initial study involved the attempted transformation of benzyl methyl ether with NH_4OAc as a nitrogen source in a model reaction aimed at validating the feasibility of our idea. According to the law of charge conservation, this reaction requires the presence of an oxidant. Therefore, two equivalents of TEMPO/ HNO_3 were added to the reaction system as an oxidizing reagent; these conditions gave the desired benzonitrile product in 63% yield [see Supplementary Information; Table S1, entry 2], along with a considerable amount of benzaldehyde and a nitration byproduct.²⁰ Because inexpensive and green molecular oxygen is a more attractive oxidant from both economic and green-chemistry viewpoints,²¹ we attempted to develop a method for the present transformation that uses molecular oxygen as the terminal oxidant with catalysis by some active species from TEMPO/ HNO_3 . Fortunately, the presence of 1 MPa oxygen permitted the loading of TEMPO/ HNO_3 to be decreased to

50 mol%, and as much as 86% yield of the target product was obtained under these conditions (Table S1, entry 3). Moreover, the yield of benzaldehyde decreased to 2% and no nitration byproduct was obtained. It was noteworthy that the optimal loading of TEMPO/HNO₃ was 50 mol%. We tried gradually reducing the promoter loading to 5 mol%, but we found that this was not possible without sacrificing product yield, even when the reaction time was prolonged to 48 hours. Other promoters such as NaNO₂ and NO₂ were tested as replacements for HNO₃ in the reaction (Table S1, entries 3–5), and the results showed that HNO₃ was the most effective one.

The reaction was highly dependent on the reaction temperature. For example, the reaction at 30 °C provided the desired product in a low yield of 47% (Table S1, entry 6), whereas 78% benzonitrile product was obtained at 60 °C (Table S1, entry 7). The yield of the targeted product significantly increased on increasing the reaction temperature to 50 °C, but decreased as the temperature was increased further (Table S1, entries 3 and 6–9), revealing that 50 °C was the optimal reaction temperature. Of the screened nitrogen sources (Table S1, entries 3 and 10–13), NH₄OAc turned out to be the most effective. The reaction with NH₄I also gave the target product in a high yield of 80% (Table S1, entry 12), whereas no benzonitrile product was observed in the cases of NH₄HCO₃, NH₄HCO₃, or NH₃·H₂O. On the other hand, only acetic acid was highly effective among the screened solvents (Table S1, entries 3 and 14–18), and the reactions did not proceed when tetrahydrofuran (THF), toluene, *N,N*-dimethylformamide (DMF), or ethanol was used as the solvent. The concentration of oxygen was also found to have an important effect on the reaction (Table S1, entries 3 and 19–21). No benzonitrile product was observed in the case of 1 atm O₂, whereas 1 MPa O₂ allowed the substrate to be converted into the required product in 86% yield, and a similar result was obtained in the case of 2 MPa (Table S1, entry 21).

Subsequently, we conducted preliminary studies with a variety of representative benzyl methyl ethers to explore the scope and generality of this reaction under the optimal conditions (Table 1).²² Generally, the present reaction was compatible with various groups, e.g. alkyl, alkoxy, chloro, bromo or iodo. A series of benzyl methyl ethers substituted with electron-donating groups were good substrates (Table 1, entries 2–8). For example, *o*-, *m*-, and *p*-methylbenzyl methyl ethers gave the required products in yields of 74–78% (entries 2–4). A yield as high as 97% yield was obtained in the case of 4-*t*-butylbenzyl methyl ether (entry 5). The presence of electron-withdrawing groups on the benzene rings had a negative effect on the reaction. For example, when 4-bromobenzyl methyl ether was employed as the substrate, only a 36% yield was obtained (entry 10). Even substrates bearing strongly electron-withdrawing groups (e.g., nitro or cyano) were less reactive (Table S2, entries 19

and 20; Supplementary Information). Another group of excellent substrates were the alkoxy-naphthalenes; both 2-methoxynaphthalene and 2-ethoxynaphthalene underwent the present conversion with high yields (entries 13 and 14). We examined the reactions of several heterocyclic substrates, but only 2-(methoxymethyl)thiophene was smoothly converted into the targeted product in 31% yield (entry 15); hardly any nitrile products were observed in the cases of other heterocyclic substrates, including 2-(methoxymethyl)furan, 2-(methoxymethyl)pyridine, 4-(methoxymethyl)pyridine, and *N*-methyl-2-(methoxy-methyl)pyrrole (not shown). Because the methoxymethyl ether groups is among the most widely used hydroxy-protecting groups in synthetic organic chemistry,²³ we examined this type of substrate. Several methoxymethyl ethers were smoothly converted into the required products under the present conditions (entries 16–18), which is very valuable for the deprotection of ether-protected hydroxy groups to form nitrile groups in multistep organic syntheses. In addition, we examined the reactions of alkyl ethers, but the results revealed that these substrates were less reactive (Table S2, entries 24 and 25).

Table 1 Oxidative Conversion of Benzyl Ethers into Aryl Nitriles^a

$$\text{Ar}-\text{CH}_2\text{OR} \xrightarrow[\text{TEMPO/HNO}_3, 50^\circ\text{C}, 20\text{ h}]{\text{O}_2, \text{NH}_4\text{OAc}} \text{Ar}-\text{CN}$$

Entry	Ar	R	Yield ^b (%)
1	Ph	Me	80
2	2-Tol	Me	74
3	3-Tol	Me	78
4	4-Tol	Me	74
5	4- <i>t</i> -BuC ₆ H ₄	Me	97
6	3-MeOC ₆ H ₄	Me	86
7	1,3-benzodioxol-5-yl	Me	85
8	3,4,5-(MeO) ₃ C ₆ H ₂	Me	90
9	4-ClC ₆ H ₄	Me	47
10	4-BrC ₆ H ₄	Me	36
11	4-IC ₆ H ₄	Me	67
12	4-PhC ₆ H ₄	Me	86
13	Naph	Me	82
14	Naph	Et	85
15	2-thienyl	Me	31
16	4-MeOC ₆ H ₄	MOM	71
17	4-Tol	MOM	53
18	1,3-benzodioxol-5-yl	MOM	62

^a Reaction conditions: ArCH₂OH (0.5 mmol), NH₄OAc (1.5 mmol), TEMPO (0.25 mmol), HNO₃ (0.25 mmol), AcOH (2 mL), O₂ (1 MPa), 20 h, 50 °C.

^b Isolated yield.

The procedure was readily applicable to a multigram-scale preparation of aryl nitriles. For example, the reaction of benzyl methyl ether proceeded efficiently on a 1.2 g scale, and gave benzonitrile in 72% isolated yield (see Supplementary Information, Scheme S1). Moreover, this experimental result was highly reproducible.

To gain insight into the reaction mechanism, we performed several control experiments. As shown in Schemes 3(a) and 4(a), benzyl methyl ether underwent oxidation to give benzaldehyde in a high yield in the absence of NH_4OAc , and the reaction between benzaldehyde and NH_4OAc also proceeded well under our conditions. These results indicated that the present transformation is a stepwise reaction in which the oxidation of benzyl methyl ether to benzaldehyde is followed by conversion of benzaldehyde into benzonitrile.

Catalyst system	O_2	Yield of aldehyde
a) TEMPO/ HNO_3	1 MPa	89%
b) TEMPO/ HNO_3	–	27%
c) TEMPO	1 MPa	trace
d) HNO_3	1 MPa	trace
e) $[\text{TEMPO}^+]$	1 MPa	32%
f) $[\text{TEMPO}^+]/\text{NO}_2$	1 MPa	77%

Scheme 2 Control experiments on the oxidation of the benzyl ether ($[\text{TEMPO}^+] = 4\text{-acetamido-TEMPO}^+\text{BF}_4^-$; for the reaction conditions, see Supporting Information, Scheme S2)

Catalyst system	O_2	Yield of nitrile
a) TEMPO/ HNO_3	1 MPa	81%
b) TEMPO/ HNO_3	–	20%
c) TEMPO	1 MPa	5%
d) HNO_3	1 MPa	trace
e) $[\text{TEMPO}^+]$	1 MPa	27%
f) $[\text{TEMPO}^+]/\text{NO}_2$	1 MPa	73%

Scheme 3 Control experiments for the conversion of benzaldehyde into benzonitrile ($[\text{TEMPO}^+] = 4\text{-acetamido-TEMPO}^+\text{BF}_4^-$; for the reaction conditions, see Supporting Information, Scheme S2)

In accord with this conclusion, benzaldehyde was present throughout the reaction, its concentration decreasing toward the end of the cyanation reaction (Figure 1). In addition, when benzyl methyl ether was oxidized to benzaldehyde in 65% yield in 0.5 hours, only small amount of benzonitrile was observed, suggesting the rate of oxidation of the benzyl ether far exceeds the rate of the other step.

Finally, our attention was drawn to gaining an understanding of the roles of oxygen, TEMPO, and HNO_3 in the reaction. It is reasonable to assume that oxygen serves as the terminal oxidant for the two oxidation steps. Indeed, re-

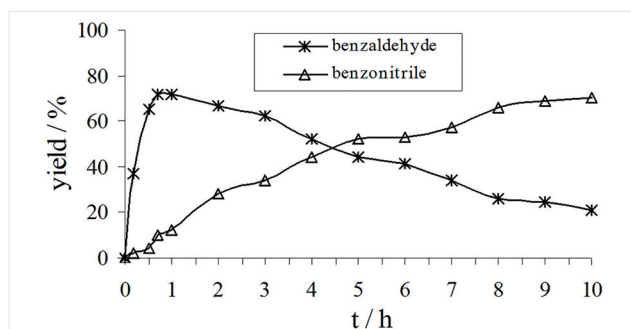
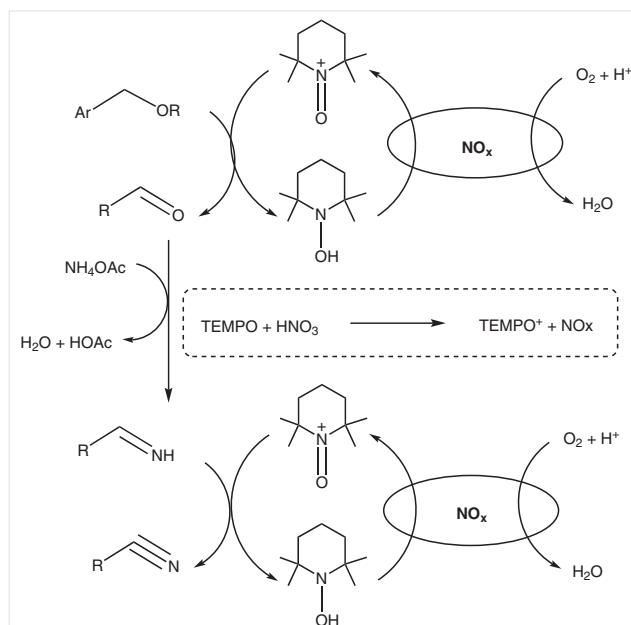


Figure 1 Conversion of benzyl methyl ether into benzonitrile (For reaction conditions, see Supplementary Information, Scheme S3)

moval of oxygen from the reaction system resulted in a marked decrease in the product yield in the two cases shown in Schemes 3(b) and 4(b). The oxidation of benzyl methyl ether did not occur in the presence of either TEMPO or HNO_3 alone [Schemes 3(c) and 3(d)], and the same conditions hardly allowed any reaction between benzaldehyde and NH_4^+ to give benzonitrile [Scheme 4(c) and 4(d)], which suggests that both TEMPO and HNO_3 are not the real catalytic species for the two steps in the present stepwise reaction. Therefore, on the basis of previous reports in the literature,^{24,25} the oxoammonium (TEMPO^+) and NO_x species from the oxidation of TEMPO by HNO_3 under our conditions appear to be involved in the catalytic cycle. In accord with this inference, the two aerobic oxidation steps proceeded smoothly under catalysis by $\text{TEMPO}^+/\text{NO}_2$ [Schemes 3(f) and 4(f)].



Scheme 4 Proposed pathway for conversion of benzyl ethers into benzonitriles

On the basis of the above results and previous reports in the literature,^{11,24,25} a possible mechanism is proposed (Scheme 4). The present stepwise reaction starts with oxidation of the benzyl ether to give benzaldehyde under catalysis by an active species from TEMPO/HNO₃.²⁴ Subsequently, it is possible that the resulting benzaldehyde reacts with [NH₃] from NH₄OAc to form an imine intermediate.^{11,25} This is followed by the formation of the benzonitrile product through oxydehydrogenation of the resulting imine.^{11,25}

In conclusion, we have developed a direct method for the conversion of benzyl ethers into aromatic nitriles by using NH₄OAc as the nitrogen source and oxygen as the terminal oxidant with catalysis by TEMPO/HNO₃. Under the present conditions, various benzyl ethers were smoothly converted into aromatic nitriles in a low to high yields. Preliminary mechanistic investigations suggested that the present transformation involves a stepwise reaction in which the oxidation of the benzyl methyl ether to a benzaldehyde is followed by conversion of the benzaldehyde into an imine intermediate that can undergo oxydehydrogenation to give the benzonitrile product. These results are valuable for both the synthesis of aromatic nitriles and for the deprotection of ether-protected hydroxy groups to form nitrile groups in multistep organic syntheses.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611062>.

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- (22) **Conversion of Benzyl Ethers into Aryl Nitriles; General Procedure**
The reactions were carried out a ~40 mL, Teflon-lined, stainless-steel autoclave. AcOH (2 mL), TEMPO (0.25 mmol), HNO₃ (0.25 mmol), the appropriate benzylic methyl ether (0.5 mmol), and NH₄OAc (1.5 mmol) were added sequentially to the autoclave. Subsequently, the autoclave was pressurized to 1 MPa with O₂, and the reaction mixture was heated with magnetic stirring at 50 °C for 20 h, then cooled to r.t. The mixture was then diluted with Et₂O (15 mL) and H₂O (5 mL), and adjusted to pH 7–8 with 2 M aq NaOH. The two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 15 mL). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated to a volume of approximately 3 mL in a rotary evaporator. GC analysis of the concentrated organic phase, with biphenyl or 1,2,4,5-tetramethylbenzene as internal standard, provided the GC yield of the product. The crude product in the concentrated organic phase from another parallel experiment was purified by column chromatography [silica gel (200–300 mesh), EtOAc–PE]. **3,4,5-Trimethoxybenzonitrile (Table 1, Entry 8)**⁵
Pale-yellow solid, yield: 96.6 mg (90%); mp 92–94 °C (Lit.⁵ 93–95 °C). ¹H NMR (500 MHz, CDCl₃): δ = 6.87 (s, 2 H, Ph), 3.91 (s, 3 H, CH₃), 3.89 (s, 6 H, 2CH₃). ¹³C NMR (125 MHz, CDCl₃): δ = 153.6, 142.4, 119.0, 109.5, 106.7, 61.1, 56.4.
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