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Oxidative transformation of azides to aryl nitriles using DIB/TBHP: scope and mechanistic insights

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ABSTRACT

Bis(*tert*-butylperoxy)iodobenzene, generated in situ by the reaction between diacetoxyl iodobenzene (DIB) and *tert*-butyl hydroperoxide (TBHP), was used in the oxidative transformation of primary azides to nitriles, and secondary azides to ketones.

Nitriles are important and useful organic building blocks.[1] In particular, aryl nitriles are essential elements of natural products,[2] pharmaceuticals,[3] agricultural chemicals,[4] materials, and dyes.[5] To date, a number of methods have been developed for their synthesis including substitution of alkyl halides with inorganic cyanides,[6] replacement of the aryl diazo-compound (Sandmeyer reaction),[7] dehydration of amides or oximes,[8] and oxidation of azides. Among these methods, transforming azides into nitriles has attracted much attention. Efforts have involved the use of metallic reagents/catalysts including Pd,[9a] Cu(II),[9b,9c] Cu(I),[9d] Fe,[9e] and $Ru(OH)_x/Al_2O_3$.[9f] In contrast, sporadic studies have been reported on non-metallic-based methods.[10]

Recently, we developed a novel protocol using diacetoxyl iodobenzene (DIB) (**1**)/*tert*-butyl hydroperoxide (TBHP) (**2**) toward allylic oxidation (Scheme 1, Eq. 2),[11] and for the oxidation of unactivated and remote methylene sp^3 C–Hs to ketones (Scheme 1, Eq. 3).[12] Based on the observations in these studies, bis(*tert*-butylperoxy)iodobenzene (**3**), which was generated in situ by the reaction between DIB (**1**) and TBHP (**2**), would provide a reactive but controllable *t*BuOO· species for methylene proton abstraction and oxidation in specific solvents (Scheme 1, Eq. 1). Herein, we report an efficient, mildly acidic, and non-metallic-based oxidative transformation of azides into aryl nitriles using the DIB/TBHP protocol. The same protocol can also be used to convert secondary azides into ketones (Scheme 1, Eq. 4). The reaction proceeded at 0 °C which is preferential with organic azides due to their potentially explosive nature.

An initial experiment was performed using 1-(azidomethyl)-4-methoxybenzene (**8a**) together with DIB/TBHP in MeCN at 0 °C. To our delight, a 52% isolated yield of the desired 4-methoxybenzonitrile (**9a**) was obtained when using a 2:4 ratio of DIB/TBHP (Table 1, entry 1). Bearing this preliminary result in mind, the ratio of DIB/TBHP was varied systematically and it was found that the reaction occurred very smoothly when the ratio was 3:4, resulting in the formation of 4-methoxybenzonitrile (**9a**) in 83% yield (Table 1, entries 2–5).

Having identified the appropriate ratio of DIB and TBHP, other solvents were screened and it was found that acetonitrile remained superior (Table 1, entries 2 and 6–9). Using these optimized conditions, other substrates were examined.[13] In general, the reactions proceeded smoothly with excellent selectivity and good yields, resulting in the formation of the corresponding nitriles (Table 2). Benzylic azides bearing electron-donating groups underwent efficient oxidation to provide the corresponding benzonitriles in high yields (Table 2, entries 3 and 4). Electron-deficient benzylic azides are known to be less active toward such oxidative transformations. Nevertheless, the DIB/TBHP protocol promoted the reactions in good yields (Table 2, entries 5 and 6). Double oxidation of diazide **8h** also worked well to offer dinitrile **9h** (Table 2, entry 7). Notably, sensitive functional groups survived under the reaction conditions. For instance, cinnamyl azide **8i** underwent facile oxidation to afford the corresponding cinnamonitrile **9i** in 76% yield (Table 2, entry 8). Moreover, azide **8j** was oxidized smoothly to yield the

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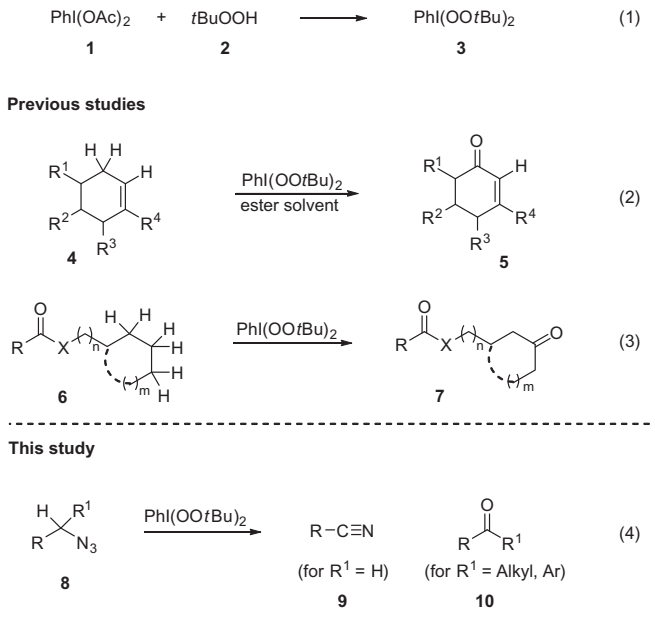
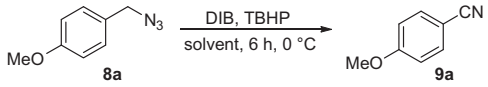


Scheme 1. Comparison of previous studies and the present work.

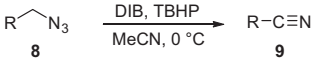
Table 1
Optimization of the DIB/TBHP azide oxidation

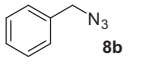
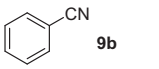
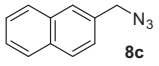
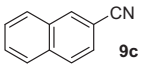
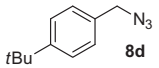
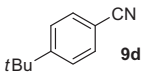
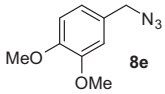
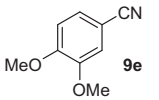
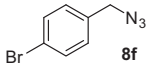
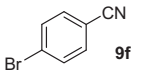
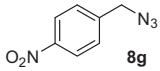
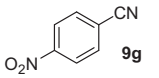
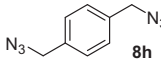
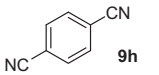
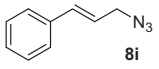
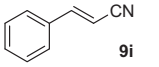
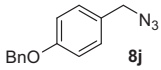
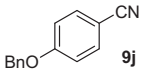
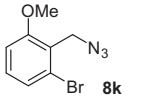
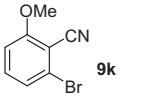
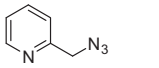
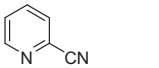


Entry[a]	Solvent	DIB (equiv)	TBHP (equiv)	Yield (%)[b]
1	MeCN	2	4	52
2	MeCN	3	4	83
3	MeCN	4	4	65
4	MeCN	3	3	61
5	MeCN	3	5	70
6	EtOAc	3	4	59
7	THF	3	4	35
8	toluene	3	4	51
9	CH_2Cl_2	3	4	68

[a] Reactions were carried out with substrate (0.5 mmol) in solvent (0.5 mL) at 0 °C.
[b] Isolated yield.

Table 2
Oxidation of azides **8**



Entry[a]	Substrate	Product	Time (h), yield (%)[b]
1			6, 71
2			6, 70
3			6, 72
4			6, 73
5			10, 72
6			10, 78
7			12, 69
8			10, 76
9			6, 73
10			12, 50
11[c]			12, 61

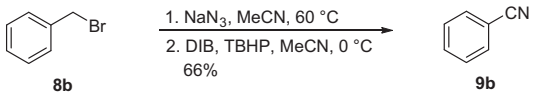
[a] Reactions were carried out with substrate (1.0 mmol), DIB (3.0 mmol), and TBPH (4.0 mmol) in MeCN (1.0 mL) at 0 °C.
[b] Isolated yield.
[c] Reaction was conducted at 40 °C.

desired nitrile without affecting the benzyl group (Table 2, entry 9).[11] The sterically bulky 2,6-disubstituted substrate **8k** provided a moderate yield of the expected nitrile **9k** (Table 2, entry 10). For the oxidation of 3-(azidomethyl)pyridine **8l**, an increase in the temperature was required to achieve a reasonable reaction rate (Table 2, entry 11).

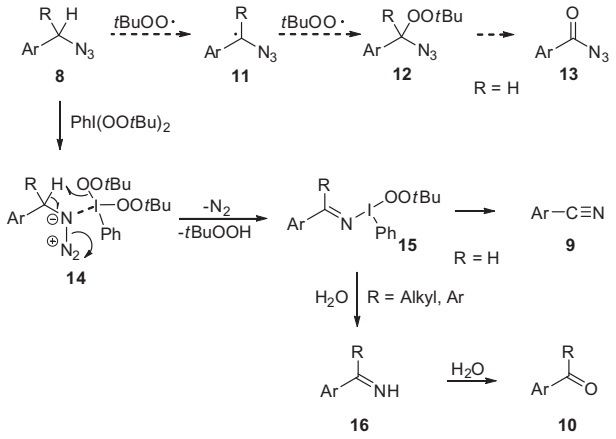
This reaction could also be conducted in a one-pot fashion. For example, benzyl bromide (**8b**) reacted firstly with sodium azide in MeCN. After consumption of benzyl bromide (**8b**), the DIB/TBHP reagent was added to the same pot to yield the desired nitrile **9b** (Scheme 2).

We attempted to understand the mechanism from several aspects. Unlike the allylic oxidation in our previous report,[11,12] this azide oxidation is relatively less solvent dependent (Table 1). A Lewis basic solvent was essential for obtaining high yields in the DIB/TBHP allylic oxidation.[11] In contrast, less polar solvents such as toluene led to yields comparable to those obtained using ethyl acetate and dichloromethane in the present study (Table 1, entries 8 vs 6 and 9). A possible explanation is that the solvent may not participate in the iodine reagent interaction as was observed in the DIB/TBHP allylic oxidation study.

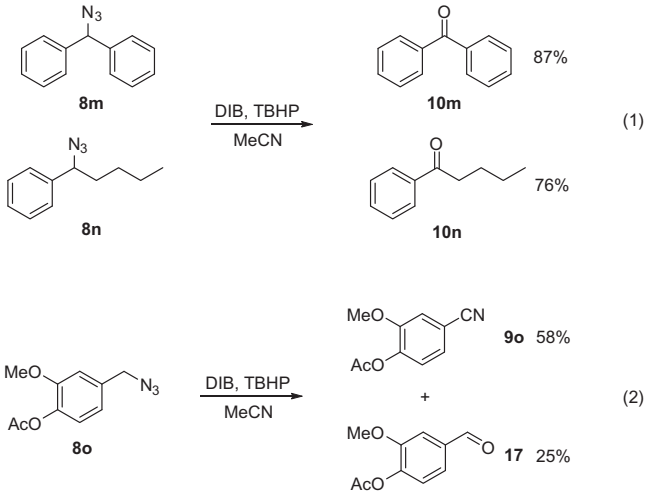
Based on the DIB/TBHP allylic oxidation reaction mechanism,[11] the benzylic proton in **8** can be abstracted by a peroxy radical followed by benzylic/*tert*-butylperoxy radical coupling to give peroxy species **12** (Scheme 3). However, no peroxy **12** associated products (e.g., **13**) were observed which imply that a dissociated *tert*-butylperoxy radical may not be dominant in the mechanism of this type of reaction.



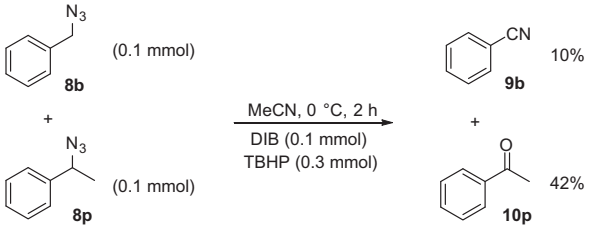
Scheme 2. Synthesis of nitrile **9a** in a one-pot fashion.



Scheme 3. Proposed mechanism for the azide oxidation.



Scheme 4. Oxidation of azides to carbonyl compounds.



Scheme 5. Competitive experiment between **8b** and **8p**.

The above-mentioned phenomena led us to speculate that the hypervalent iodine species may coordinate to the azide and may react through a metal-like transition state.[9c,9f,14] A proposed mechanistic pathway is shown in Scheme 3. The azide may be involved in a weak interaction with the reactive species, bis(*tert*-butylperoxy)iodobenzene (**3**) to yield complex **14**. Subsequent benzylic proton abstraction accompanied by elimination of dinitrogen can give imine intermediate **15**. Finally, benzylic methine proton abstraction followed by the collapse of complex **15** (R = H) affords the aryl nitrile product **9**.

We have also examined the oxidation of secondary azides **8m** and **8n**. Under the standard conditions, ketones **10m** and **10n** were obtained as the sole products (Scheme 4, Eq. 1). These products might be produced through the hydrolysis of the imine intermediate **15** (R = alkyl, Ar) during the work-up (Scheme 3); further oxidation of such an imine to a nitrile was impossible due to the absence of a methine proton. A careful study on the oxidation of azide **8o** using limited reagents and a shorter reaction time allowed us to obtain an appreciable amount of aldehyde **17** (Scheme 4, Eq. 2), a product that was potentially generated through the decomposition of imine intermediate **15** (R = H) (Scheme 3).

The radical nature of this reaction was indicated by conducting a radical scavenger experiment, in which the reaction was shut down upon the addition of BHT. A competitive experiment on the oxidation of azides **8b** and **8p** was performed (Scheme 5). The result showed that the oxidation occurred more readily on **8p**. This selectivity may be ascribed to a radical deprotonation process which occurs preferentially on a secondary carbon. We acknowledge that the mechanism remains unclear and requires further investigation.

In summary, a mild and efficient azide oxidation using inexpensive and commercially available DIB/TBHP has been developed. Further investigation on the mechanistic profile is in progress.

Acknowledgments

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