TBHP/I_2-Promoted Oxidative Coupling of Azoles with Benzyl Compounds via Cleavage of Nonactivated C(sp^3)–H Bonds under Solvent-Free Conditions

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Abstract: A novel and efficient TBHP/I_2-promoted oxidative coupling of azoles with benzyl compounds via cleavage of nonactivated C(sp^3)–H bonds under metal-free, base-free, and solvent-free conditions for the synthesis of N-alkylated azoles has been developed. The procedure, using I_2 as the catalyst, is a simple, economical, and environmentally friendly protocol, which could be applied to various available substrates in moderate to good yields.

Key words: solvent-free, metal-free, oxidative coupling, N-alkylated azoles, free-radical reaction

During the past few years, N-alkylated azoles were of great importance in the field of medicinal chemistry[1] (used as antiviral, anticonvulsant, and antiulcer drugs) and sciences.[2] In addition, they have been widely used as the backbone in dyes[3] and agricultural chemistry. As a consequence, developing efficient methodologies for the synthesis of N-alkylated azoles and their derivatives have caused multitudinous attentions, and many methods have been reported.[4] Among them, the most common and earliest route for N-alkylation of azoles is a nucleophilic substitution reaction of azoles with halides (Scheme 1, A). Although the most of the methods are apparently useful, their applications are limited by severe reaction conditions, low yields, long reaction time, and use of toxic solvents, strong bases, or catalysts. Recently, direct arylation of the C–H/N–H bond in azoles has emerged as a hot theme in organic synthetic chemistry[5] due to their potential possibilities for diverse transformation into a variety of useful derivatives. Great progress has been achieved for direct arylation of N–H bonds in azoles via cleavage of sp^3 C–H bonds.[6] These studies mainly focused on palladium-, iron-, ruthenium-, or copper-catalyzed arylation. For example, Chen and co-workers first reported direct C–N coupling of imidazoles with benzylic compounds via iron(III)-catalyzed oxidative activation of C(sp^3)–H bonds.[7] However, this methodology was not eco-friendly because it involves direct or indirect use of toxic and corrosive organic solvent and iron catalyst. Therefore, development of an eco-friendly and metal-free N–H/C–H bond-coupling protocol is still greatly desired for the N-alkylation of azoles.

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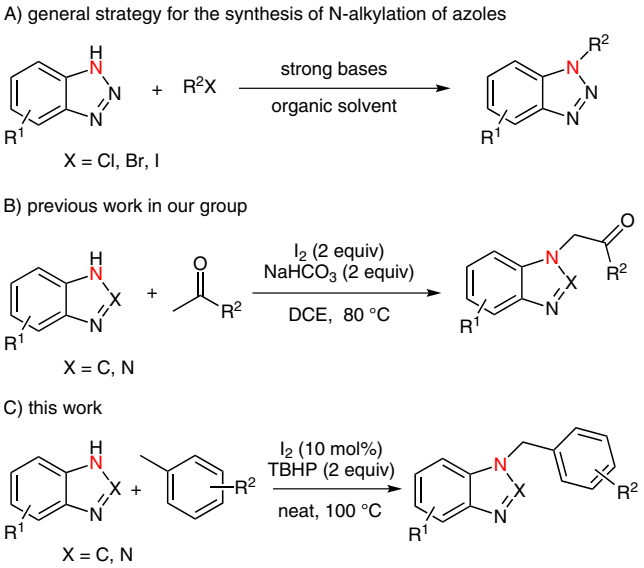
In recent years, molecular iodine has been identified as an important and effective catalyst to carry out various organic reactions because of its inexpensive, eco-friendly nature and ready availability.[8] Our group has been working on the investigation of N-alkylation of azoles[9] for many years. Earlier in this year, our group developed an efficient, metal-free, convenient, and relatively cheap method for iodine-induced direct alkylation of azoles via in situ formed alkyliodide.[10] However, the reactions were carried out in the presence of two equivalents of iodine and activated C(sp^3)–H. It is obvious that they are nucleophilic reactions. We are interesting to investigate the iodine-induced direct alkylation of azoles using a catalytic amount of iodine and nonactivated C(sp^3)–H bonds. We first presented the TBHP/I_2-promoted oxidative coupling of azoles with benzyl compounds via cleavage of nonactivated C(sp^3)–H bonds under metal-free, base-free, and solvent-free conditions for the synthesis of N-alkylated azoles. The modified method is not a nucleophilic reaction but a free-radical reaction, and it showed several advantages comparing to our previous method, such as metal-free, solvent-free, base-free, easy operation, environmental friendliness, mild reaction conditions and high yields.

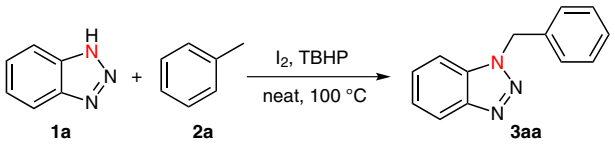
In order to develop a convenient and selective reaction procedure for N-alkylated azoles, we chose the reaction of



Scheme 1 N-Alkylation of azoles synthesis

benzotriazole (**1a**) with toluene (**2a**) as the model case to optimize the reaction conditions (Table 1). The reaction was carried out with **1a** (0.5 mmol), **2a** (1.5 mmol), in the presence of I_2 (10%), *tert*-butyl hydroperoxide (TBHP, 2 equiv) in DCE at 80 °C under air for eight hours. The desired product **3aa** was obtained in 15% yield (Table 1, entry 1). In this preliminary experiment, the N-alkylation reaction was carried out in different solvents, such as DMSO, DMF, MeCN, PhCl, and $PhNO_2$, and the reactions did not provide higher yields (Table 1, entries 2–6), but the solvent-free reaction gave good performance (Table 1, entry 7). Based on the above-studied results, we decided to develop an environmentally friendly reaction, and solvent-free conditions are clearly the most favorable. Next, we tested the reaction at other temperature. We found the yield of the desired product **3aa** could be improved by gradually increasing the reaction temperature. We were pleased to find that the yield of **3aa** was enhanced to 90% at 100 °C, and the higher temperature (>100 °C) led to decrease of the yield (Table 1, entries 7–10). Then, we investigated the reaction at different loading of I_2. We found that 10 mmol% was the best catalytic amount. Finally, the N-alkylation reactions were carried out with different oxidants. 6-Dicyanobenzoquinone (DDQ), Ag_2CO_3, O_2, and *t*-BuO*t*-Bu showed no or slight effect to promote the reaction. Moreover, the yield of the desired product **3aa** could be slightly affected by gradually increasing the amount of TBHP. Thus, two equivalents of TBHP, 10 mmol% I_2, 100 °C without solvent-free are the optimal conditions for this reaction.

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

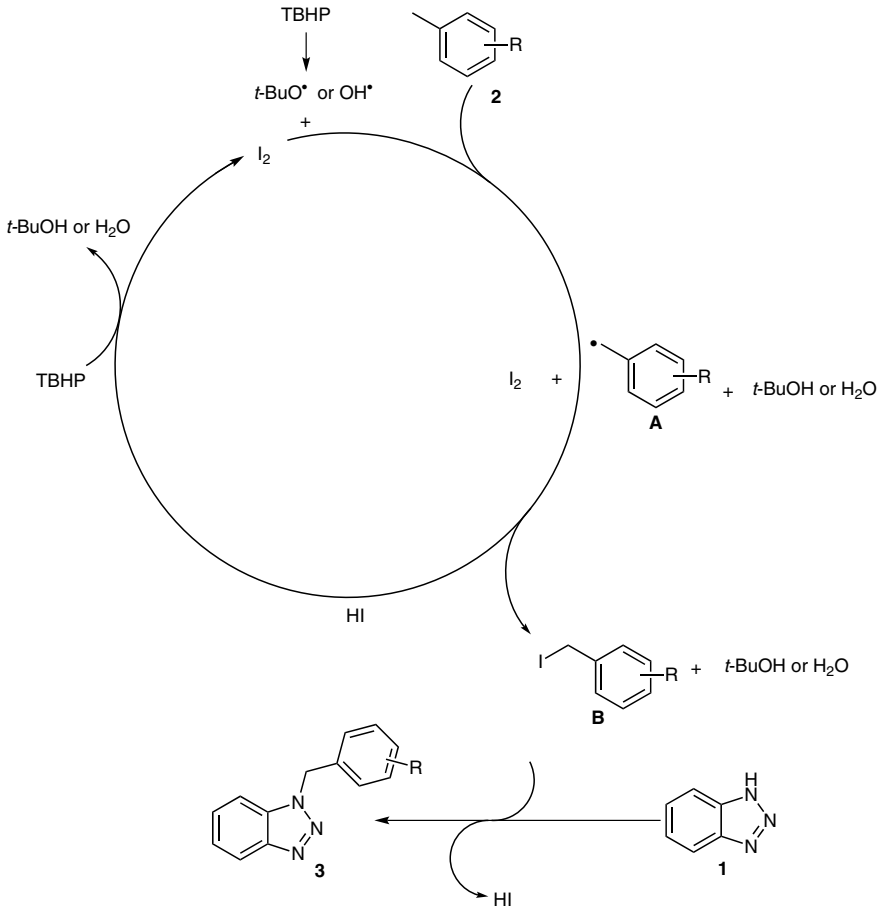
Entry	Catalyst (mmol%)	Temp (°C)	Solvent	Oxidant	Yield (%)[b]
1	I_2 (10)	80	DCE	TBHP	15
2	I_2 (10)	80	DMSO	TBHP	0
3	I_2 (10)	80	DMF	TBHP	0
4	I_2 (10)	80	MeCN	TBHP	trace
5	I_2 (10)	80	PhCl	TBHP	0
6	I_2 (10)	80	$PhNO_2$	TBHP	0
7	I_2 (10)	80	neat	TBHP	68
8	I_2 (10)	100	neat	TBHP	90
9	I_2 (10)	120	neat	TBHP	88
10	I_2 (10)	60	neat	TBHP	60
11	I_2 (20)	100	neat	TBHP	60
12	I_2 (0)	100	neat	TBHP	0
13	I_2 (10)	100	neat	O_2	0
14	I_2 (10)	100	neat	Ag_2CO_3	trace
15	I_2 (10)	100	neat	BuOO*t*-Bu	34
16	I_2 (10)	100	neat	DDQ	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 mmol), catalyst (10 mol%), oxidant (2.0 equiv), solvent (1 mL), 100 °C, 8 h.
[b] Isolated yields.

Once the viability of the method was established, this approach was then applied to the coupling of benzotriazole to a variety of benzyl compounds, and the results are shown in Table 2. Various benzyl compounds were suitable for the solvent-free and metal-free reaction conditions. The electron-donating-substituted toluenes (including *p*-xylene, *m*-xylene, *o*-xylene, and mesitylene) could be easily converted into N-alkylated azoles in good yields (Table 2, entries 1–5). On the contrary, the electron-withdrawing-substituted toluenes (including 4-bromo-1-methylbenzene, 4-chloro-1-methylbenzene, and 2-chloro-1-methylbenzene) gave lower but still acceptable yields (Table 2, entries 6–8). However, the strongly electron-withdrawing-substituted toluenes such as 4-nitro-1-methylbenzene and 4-methylbenzonitrile had not given the expected product (Table 2, entries 15 and 16). The reactions of benzotriazole with benzylic compounds also produced the corresponding cross-coupling products in moderate to good yields (Table 2, entries 9–11, 13).

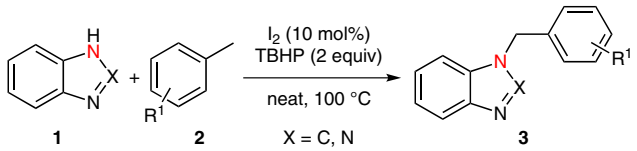
However, the cumene had not given the expected product (Table 2, entry 14). The 2-substituted benzyl compounds showed slightly lower yields than the 4-substituted ones (Table 2, entries 2–4, 7 and 8) that was probably caused by steric effect. In addition, when the reaction was carried out with benzimidazole and toluene, only 53% yield was provided (Table 2, entry 12).

After testing the coupling reaction of benzotriazole with benzyl compounds, other azoles were investigated. As shown in Table 3, a variety of azoles were found to be coupling partners, and the desired products were formed in satisfactory to excellent yields. The 5-substituted azoles **1** containing electron-withdrawing or electron-donating groups could provide the desired products in perfect yields (Table 3, entries 1–5). Unfortunately, poor regioselectivities were observed in this transformation: substrates substituted by Cl or NO_2 groups gave a mixture of regioisomers. The combined yields ranged from 94–99%, and the ratio of isomers varies from 1:1.10 to 1:1.22. Steric hindrance at the 2-position of benzimidazoles had an obvious impact on the yields. Compounds **3fa**, **3ga**, **3ha**, and **3ia** were obtained in moderate yields unless using more TBHP, prolonging the reaction times or higher temperature (Table 3, entries 6–9).



Scheme 2

Table 2 Reactions of Azoles with Various Benzyl Compounds[a]



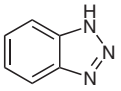
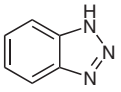
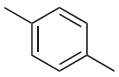
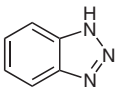
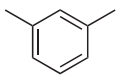
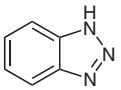
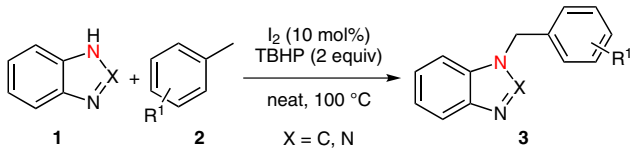
Entry	1	2	Product	Yield (%)[b]
1	 **1a**	 **2a**	**3aa**[11]	90
2	 **1a**	 **2b**	**3ab**	80
3	 **1a**	 **2c**	**3ac**	75.8
4	 **1a**	 **2d**	**3ad**	82

Table 2 Reactions of Azoles with Various Benzyl Compounds[a] (continued)



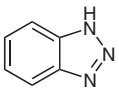
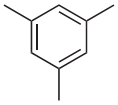
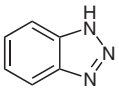
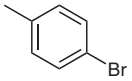
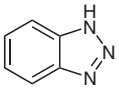
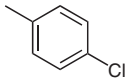
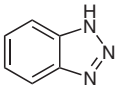
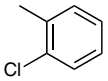
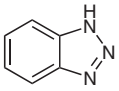
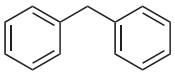
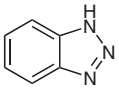
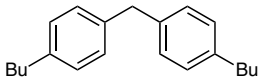
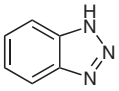
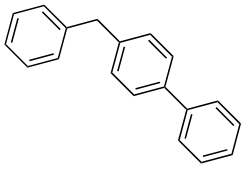
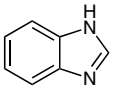
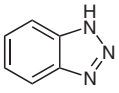
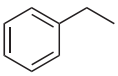
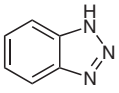
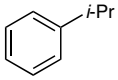
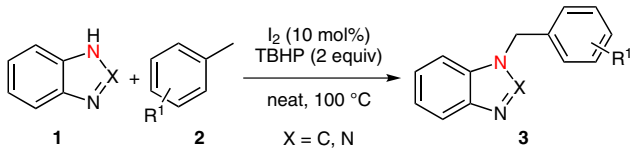
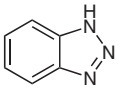
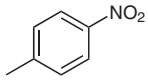
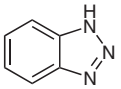
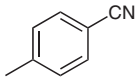
Entry	1	2	Product	Yield (%)[b]
5	 **1a**	 **2e**	**3ae**	93
6	 **1a**	 **2f**	**3af**	81
7	 **1a**	 **2g**	**3ag**	74
8	 **1a**	 **2h**	**3ah**	77
9	 **1a**	 **2i**	**3ai**	97
10	 **1a**	 **2j**	**3aj**	92
11	 **1a**	 **2k**	**3ak**	85
12	 **1e**	 **2a**	**3al**	53
13	 **1a**	 **2m**	**3am**	80
14	 **1a**	 **2n**	**3an**	0

Table 2 Reactions of Azoles with Various Benzyl Compounds[a] (continued)



Entry	1	2	Product	Yield (%)[b]
15	 **1a**	 **2o**	**3ao**	0
16	 **1a**	 **2p**	**3ap**	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 mmol), I_2 (10 mmol%), TBHP (2.0 equiv), 100 °C, 8 h.
[b] Isolated yields.

To explore the mechanism of this reaction, we first obtained 1-(iodomethyl)benzene (**A**) and 1-iodo-1*H*-benzo[*d*][1,2,3]triazole (**B**), then the reaction of **A** with benzotriazole and the reaction of **B** with toluene were investigated, respectively. We found that the former reaction did not afford the expected product. Then the reaction was carried out with **1a** (0.2 mmol), **2a** (1.0 mmol), TBHP (2.0 equiv), I_2 (10% mmol) in the presence of TEMPO (6.0 equiv) at 100 °C under solvent-free conditions for eight hours. We were surprised to find that only a trace of product was obtained. Based on the above observations, a reasonable mechanism for this reaction was proposed in Scheme 2. It may involve a free-radical process. The reaction started with abstraction of H· from **2** by TBHP giving RCH_2· (**A**). Subsequently, I_2 oxidized **A** to **B**. HI, produced during transformation of **A** to **B**, reacted with TBHP giving I_2 and *t*-BuOH or H_2O to complete the iodine-catalyst cycle. Finally, nucleophilic reaction of **1** with **B** produced the target product **3**.

In conclusion, we have developed a TBHP/I_2-promoted oxidative coupling of azoles with benzyl compounds via cleavage of nonactivated C(sp^3)–H bonds under metal-free, base-free, and solvent-free conditions for the synthesis of N-alkylated azoles. The use of a catalytic amount of I_2 as catalyst is a simple and economical protocol, which have been successfully applied to the synthesis of various available substrates. It is a useful strategy to develop new arylating reagents for the preparation of N-alkylated azoles.

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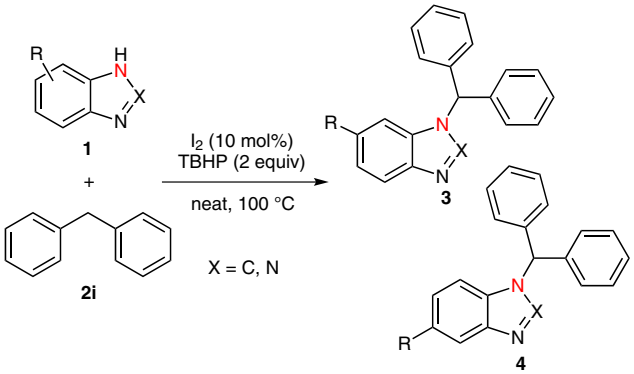
Table 3 Reactions of Diphenylmethane with Various Azoles[a]



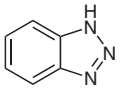
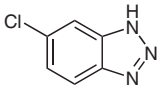
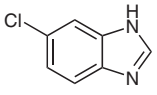
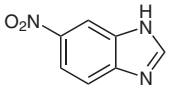
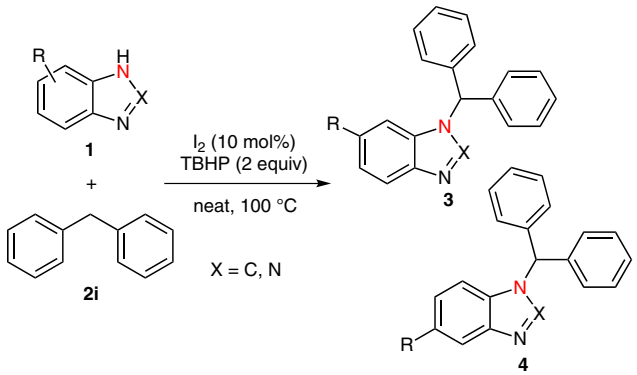
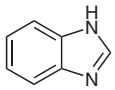
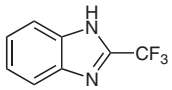
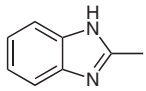
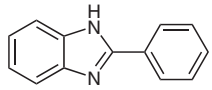
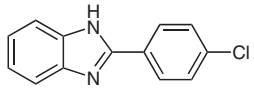
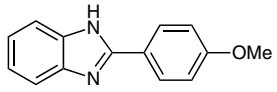
Entry	1	Product	Yield (%)[b]
1	 **1a**	**3ai**	97
2	 **1b**	**3ba** and **4ba**	94 1:1.20
3	 **1c**	**3ca** and **4ca**	97 1:1.22
4	 **1d**	**3da** and **4da**	96 1:1.10

Table 3 Reactions of Diphenylmethane with Various Azoles[a] (continued)



Entry	1	Product	Yield (%)[b]
5	 **1e**	**3ea**	90
6	 **1f**	**3fa**	73
7	 **1g**	**3ga**	62[c]
8	 **1h**	**3ha**	57[c]
9	 **1i**	**3ia**	62[c]
10	 **1j**	**3ja**	63[c]

[a] Reaction conditions: **1** (0.5 mmol), **2i** (2.0 mmol), I_2 (10 mol%), TBHP (2.0 equiv), 100 °C, 8 h.
[b] Isolated yields.
[c] TBHP (5 equiv).

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(11) **General Procedure of the Reaction between Azoles and Toluenes – Synthesis of 1-Benzyl-1*H*-benzo[*d*][1,2,3]triazole (3aa)**
All reactions were performed on a 0.50 mmol scale relative to azoles. The benzotriazole (**1a**, 0.50 mmol), toluene (**2a**, 2.0 mmol), I_2 (0.050 mmol), and TBHP (2 equiv) were taken in a round-bottom flask equipped with a stirrer. The resulting mixture was stirred for 8 h at 100 °C. After cooling to r.t., to the reaction mixture was added H_2O (2 mL) and extracted with ester (3 × 10 mL). The combined organic phases were washed with brine (2 × 5 mL), dried over anhyd $MgSO_4$, and concentrated in vacuo. The residue was subjected to flash column chromatography with hexanes–EtOAc (10:1) as eluent to obtain the desired **3aa** a light yellow solid (90%

yield). The remaining substituted triazoles were prepared in the similar manner and their characterization data are as follows. Compound **3aa** was purified by flash chromatography (hexane–EtOAc = 10:1, v/v) as light yellow solid (yield 90%), mp 113–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04–8.06 (d, *J* = 7.8 Hz, 1 H), 7.25–7.38 (m, 8 H), 5.82 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2, 134.7, 132.7, 128.9, 128.3, 127.5, 127.3, 123.8, 119.9, 109.6, 52.1.

