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A facile protocol for N-alkylation of azoles using KO^{t}Bu as base under NBS-promoted conditions

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ABSTRACT

A mild, transition metal-free, and environmentally benign NBS-promoted C–N bond formation of *N*-heterocycles is successfully demonstrated. A series of heterocyclic derivatives are readily prepared under mild conditions in moderate to good yields.

In recent years, azoles have been developed as a widely used activating auxiliary for numerous condensation reactions.[1] Substituted azoles represent an important class of heterocyclic compounds used in the pharmaceutical industry, since they form the core structures of many commercial drugs.[2] In addition, they have also been frequently used as the mainstay in dyes [3] and high temperature polymers.[4] Benzotriazoles are stable, inexpensive, and biologically innocuous compounds, and 1- and 2-alkylbenzotriazoles are of wide interest due to their biological activities as herbicides, insecticides, and acricides.[5] Based on the above reasons, the synthesis of *N*-heterocycle derivatives has been the subject of continuing interest among organic and medicinal chemists for many years.

It has been reported that the N-alkylation of azoles can be achieved by different bases, such as potassium carbonate,[6] sodium hydroxide,[7] sodium bicarbonate,[8] or phase-transfer catalysis (PTC) with quaternary ammonium salt.[9,6b] N-Alkylation of azoles can also be achieved in ionic liquids or without a solvent. However, some of these methods suffer from several drawbacks including the use of hazardous and carcinogenic organic solvents such as dimethylsulfoxide (DMSO), dimethylformamide (DMF), benzene, or toluene; expensive reagents or catalysts; harsh reaction conditions; difficulty in product separation; and/or long reaction times. So, the development of an efficient, convenient, and environmentally more benign method of the N-alkylation of azoles is still a major challenge. In this Letter, we reported a facile protocol for N-alkylation of azoles using KO^{t}Bu as base under NBS-promoted conditions.

In our initial study, we started the experiment by using 0.2 mmol of 1-phenylbutane-1,3-dione **1a** and 0.2 mmol of 1*H*-benzo[*d*][1,2,3]triazole **2a** as model substrates for optimization of the reaction conditions (Table 1). The reaction gave the mixtures of 1-substituted **3a** and 2-substituted **4a** products in the presence of NBS and base.[10] The products **3** and **4** could stably exist and mutual transformation between each other would not occur. To improve the reaction efficiency, the effect of bases was then investigated (Table 1, entries 1–5). It was found that KO^{t}Bu gave the best result in 85% yield and the ratio of isomer (**3**:**4**) was 28:72, whereas other bases, such as $NaHCO_3$, K_2CO_3, and Et_3N were less effective. With an attempt to optimize the yield of the product, we further studied the influence of different reaction media (Table 1, entries 6–10). From the results obtained, it can be seen that changing the solvent from DCE, THF to DMF, CH_3CH_2OH failed to improve the yield of the product. And when using CH_2Cl_2 as solvent, we only got the product **3** in 37% yield. It should be noted that the use of different bases and solvents had different regioselectivity. Considering that the synthesis methods of **4** were less than **3** in the reported literatures,[1,10] we chose the conditions in favor of product **4**. For solvents, the polarity of the solvent itself and the solubility of raw material and base in the solvent led to different selectivities: when the polarity of the solvent is relatively small (EtOAc) and the steric hindrance of the base is relatively large

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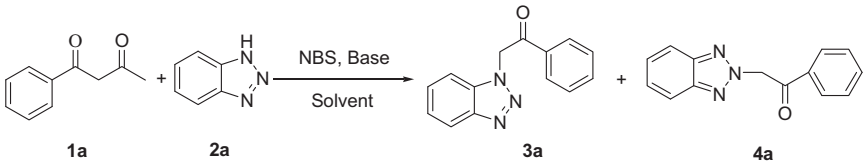
Table 1
Optimization of the reaction conditions[a]



Entry	Base	Solvent	Yield[b] (%)	Ratio of isomer (3:4)
1	$NaOCH_3$	EtOAc	76	42:58
2	$NaHCO_3$	EtOAc	42	60:40
3	K_2CO_3	EtOAc	65	75:25
4	Et_3N	EtOAc	28	100% of **3**
5	KO^{t}Bu	EtOAc	85	28:72
6	KO^{t}Bu	DCE	80	32:68
7	KO^{t}Bu	THF	68	80:20
8	KO^{t}Bu	C_2H_5OH	trace	—
9	KO^{t}Bu	DMF	trace	—
10	KO^{t}Bu	CH_2Cl_2	37	100% of **3**
11	KO^{t}Bu	EtOAc	38[c]	100% of **4**,
			72[d]	36:64
12	KO^{t}Bu	EtOAc	26[e]	42:58
			81[f]	35:65
13	KO^{t}Bu	EtOAc	0[g]	—

[a] Reaction conditions: **1a** (32.4 mg, 0.2 mmol), **2a** (23.8 mg, 0.2 mmol), NBS (1.2 equiv, 39.2 mg), base (2.0 equiv, 0.4 mmol), solvent (2 mL), 60 °C, 6 h, under air.
[b] Isolated yields.
[c] Room temperature.
[d] At 80 °C.
[e] 0.2 Equiv of NBS.
[f] 0.5 Equiv of NBS.
[g] Without NBS.

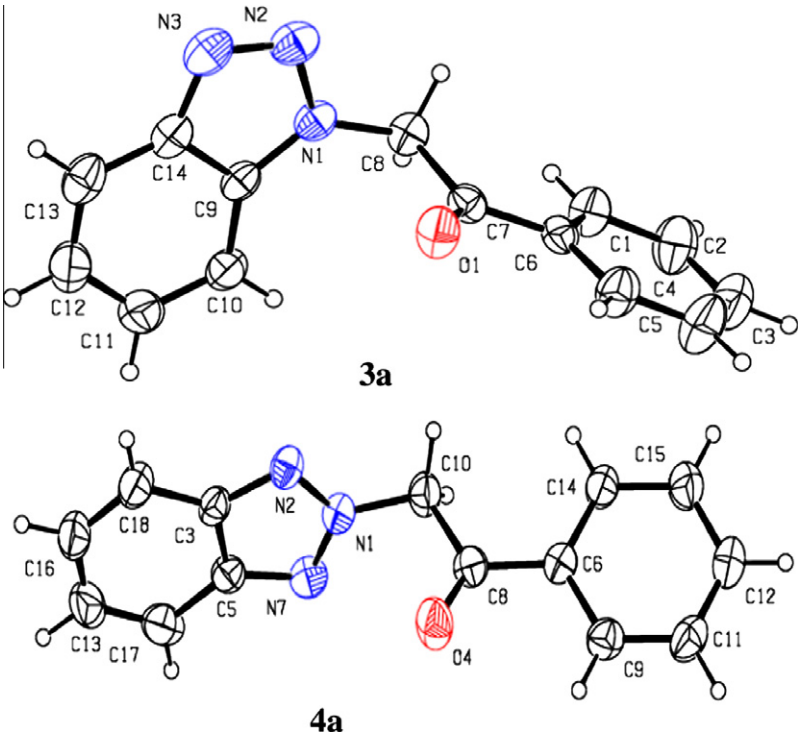
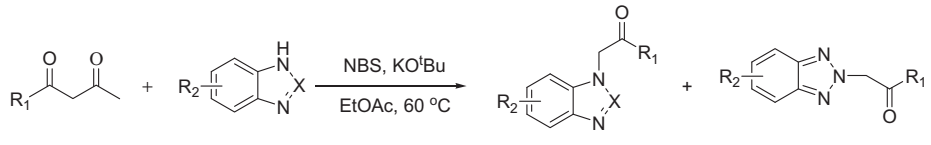


Figure 1. X-ray crystal structure of **3a** and **4a.**

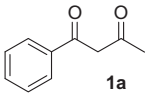
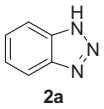
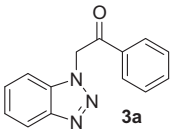
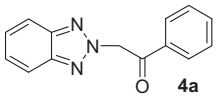
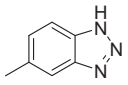
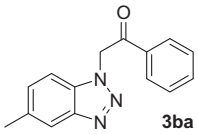
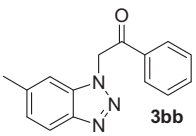
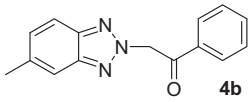
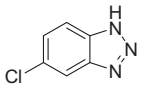
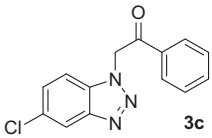
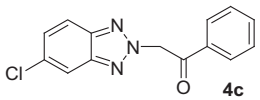
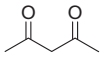
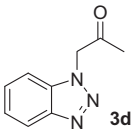
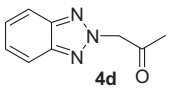
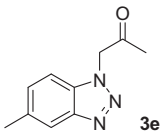
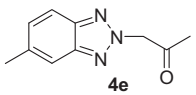
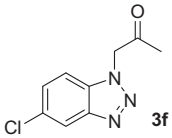
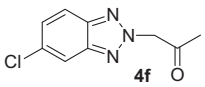
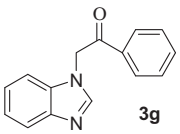
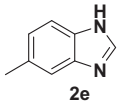
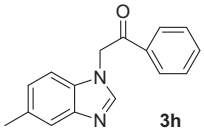
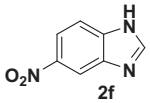
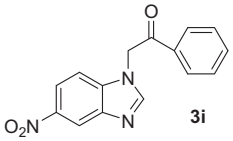
(KO^{t}Bu), we got the desired ratio of isomers (Table 1, entry 5). Furthermore, the reaction temperature was also investigated, and the yield was found to decrease with the temperature changed to rt or 80 °C (Table 1, entry 11). The NBS loading was also tested, and the yield was good at 0.5 equiv of NBS but with a lower regioselectivity, while it dropped evidently at 0.2 equiv (Table 1, entry 12), and this reaction did not work in the absence of NBS (Table 1, entry 13). With a series of detailed investigations mentioned above, the reaction conditions were eventually optimized as follows: 0.2 mmol of **1**, 0.2 mmol of **2**, 1.2 equiv of NBS, 2.0 equiv of KO^{t}Bu as base, and

Table 2
Substrate scope of aromatic *N*-Heterocycles[a]



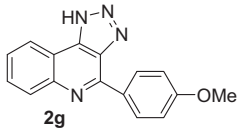
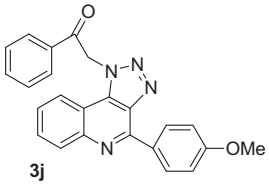
1 **2** **3** **4**

R_1 = Phenyl, Me R_2 = Me, Cl X=CH, N

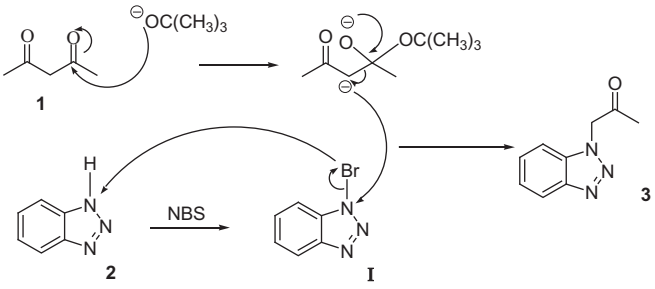
Entry	1,3-Dione	Azole	Product	Yield[b] (%)	Ratio of isomer (3:4)
1	 **1a**	 **2a**	 **3a**  **4a**	85	28:72
2	1a	 **2b**	 **3ba**  **3bb**  **4b**	74 3ba:3bb = 1.08:1	30:70
3	1a	 **2c**	 **3c**  **4c**	90	27:73
4	 **1b**	2a	 **3d**  **4d**	82	24:76
5	1b	2b	 **3e**  **4e**	67	26:74
6	1b	2c	 **3f**  **4f**	86	22:78
7	1a	 **2d**	 **3g**	72	–
8	1a	 **2e**	 **3h**	67	–
9	1a	 **2f**	 **3i**	80	–

(*continued on next page*)

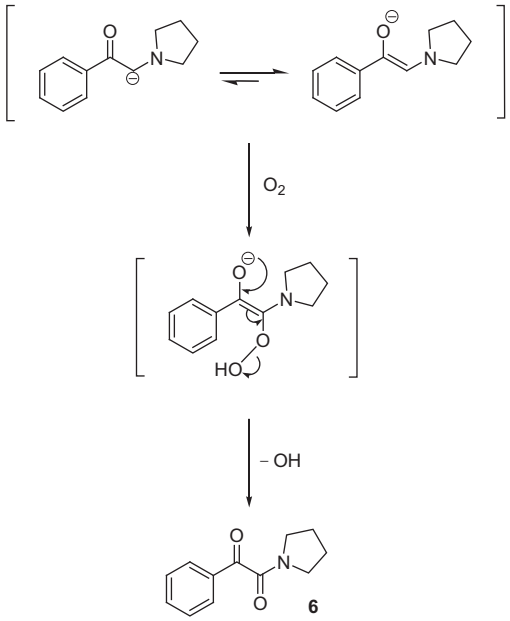
Table 2 (*continued*)

Entry	1,3-Dione	Azole	Product	Yield[b] (%)	Ratio of isomer (3:4)
10	1a	 **2g**	 **3j**	91	–

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), NBS (1.2 equiv, 39.2 mg), KO^{t}Bu (44.8 mg, 0.4 mmol), EtOAc (2 mL), 60 °C, 6 h, under air.
[b] Isolated yields.

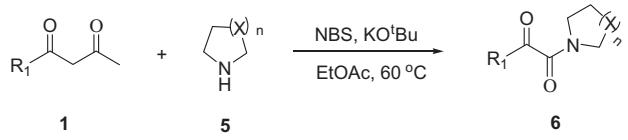


Scheme 1. Plausible reaction pathway.



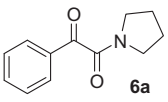
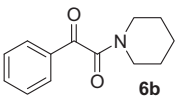
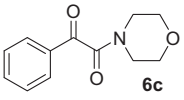
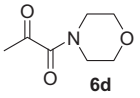
Scheme 2. Plausible reaction pathway.

Table 3
Substrate scope of aliphatic *N*-heterocycles[a]



1 **5** **6**

R_1 = Phenyl, Me X = CH_2, O n = 1, 2

Entry	1,3-Dione	*N*-Heterocycle	Product	Yield[b] (%)
1	1a	 **5a**	 **6a**	58
2	1a	 **5b**	 **6b**	64
3	1a	 **5c**	 **6c**	76
4	1b	5c	 **6d**	71
5	1a	5c	6c	87[c]21[d]

[a] Reaction conditions: **1** (0.2 mmol), **5** (0.2 mmol), NBS (1.2 equiv, 39.2 mg), KO^{t}Bu (44.8 mg, 0.4 mmol), EtOAc (2 mL), 60 °C, 6 h, under air.
[b] Isolated yields.
[c] Under oxygen.
[d] Under nitrogen.

EtOAc (2.0 mL) as solvent at 60 °C. The structure of compounds **3a** and **4a** was unambiguously confirmed by X-ray analysis (Fig. 1).

With the optimized conditions in hand, the scope of the reaction was examined. As shown in Table 2, the reaction could be performed with both aromatic and aliphatic 1,3-diones. And different azoles were also investigated. For electronic effects, electron-deficient azoles showed better results than electron-rich ones. But it should be noted that we only got one kind of product when benzimidazoles were involved in the reaction, and the product of 5-methyl-benzotriazole **3b** was a mixture of regioisomers: **3ba:3bb** = 1.08:1. Based on the above results, we found that the type of products of benzotriazoles was determined by the combined electronic effect of diones and benzotriazoles: the electron-donating effect of both phenyl from dione **1a** and methyl from benzotriazole **2b** led to a mixture of regioisomers **3b**, while other products did not appear in this kind of circumstance (**3b** vs **3a**, **3c**, **3e**).

A plausible mechanism for this reaction was proposed in Scheme 1. A deacylation followed by oxidative coupling would likely attribute to the formation of the final products. What needs to be emphasized was that 0.5 equiv of NBS also gave a 81% yield of products (Table 1, entry 12). This result proved that there was a catalytic cycle between **2** and **I** to some extent.

When the aliphatic *N*-heterocycles were used as the substrates, we got a result that was different from the aromatic *N*-heterocycles: the alkylation products were replaced by the acylation products (Table 3). The result showed that the yield of the product was gradually increased from pyrrolidine to morpholine (Table 3, entries 1–4), and this was probably due to the increased electron-withdrawing effect from carbon atom to oxygen atom. Besides,

the yield was increased under oxygen while it reduced under nitrogen (Table 3, entry 5), which proved that the oxygen participated in the reaction system.

As shown in Scheme 2, the plausible reaction pathway of product **6** was also investigated. Enolization product of **3** was oxidized by oxygen, and then a dehydroxylation step produced the target product **6**. We will focus on the systematic investigation in future studies.

In summary, a facile protocol for N-alkylation of azoles using KO^{t}Bu as base under NBS-promoted conditions was successfully demonstrated. This reaction system reveals several advantages, such as simple operation, mild and transition metal-free reaction conditions, easy availability, and moderate to good yields. Further functionalization of azoles and other heterocycles are the future goals of our research group.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.030.

References and notes

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