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A Metal-Free Cross-Dehydrogenative Coupling Reaction of Amides to Access *N*-Alkylazoles

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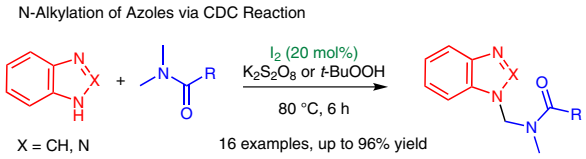

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Abstract An iodine-catalyzed cross-dehydrogenative coupling reaction of *N*-alkyl amides and azoles is reported. The catalytic system provides an efficient method for introducing amides onto azoles, especially onto benzotriazoles.

Key words cross-dehydrogenative coupling, amides, benzotriazoles, benzimidazoles

Since its discovery by Murahashi in 1995, and the promotion of the concept by Li in 2003, cross-dehydrogenative coupling (CDC) has been developed as an efficient method for the simple and straightforward construction of new C–C or C–N bonds that has the advantages of atom economy and of being environmentally friendly.[1] In this reaction, catalyst systems without transition metals have attracted much attention, as the use of transition metals is not favored in the pharmaceutical industry. Generally, di-*tert*-butyl peroxide (TBP),[2] *tert*-butyl hydroperoxide (TBHP),[3] DDQ,[4] or $PhI(OAc)_2$[5] has been employed as a radical initiator to promote the CDC reaction. Iodine and its derivatives, which are used in many other oxidative reactions, are also efficient catalysts for promoting the reaction.[6]

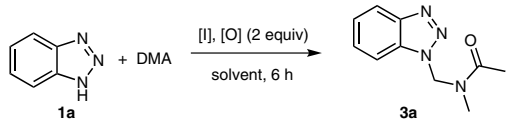
N-Substituted amides such as *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMA) are not only in common use as organic solvents, but also serve as attractive precursors for various organic transformations.[7] Recently, compounds of this type have been employed as amide or methylene sources through activation of the sp^3 C–H bond adjacent to the nitrogen atom of the amide group. For example, Xiao and co-workers reported a Ru-catalyzed α-methylation of ketones with DMF as the carbon source.[8] Xu and co-workers prepared a series of terminal aromatic alkenes by iron-catalyzed C–H activation of *N*-methyl amides with quinoxalines.[9] Then, Miura and co-workers developed an α-methylenation of benzylpyridines with DMF as a carbon source.[10] At about the same time, Lei and co-workers demonstrated a copper-catalyzed methylenation of ketones through sp^3 C–H activation of DMF.[11] We also developed an iodine-catalyzed C–N bond cleavage reaction of DMA for the construction of methylene compounds that could be subsequently converted into the corresponding 2,3-difuran molecules.[12]

On the other hand, the introduction of an amide moiety into molecules through construction of a C–N bond has also been achieved. Xia and Chen disclosed an iron-catalyzed N-alkylation of azoles through a CDC reaction with amides. The method tolerated a variety of amides, including aromatic amides, alkyl amides, and sulfonamides.[13] Subsequently, Reddy demonstrated a catalytic system for the synthesis of *N*-alkyl azoles or *N*-benzyl azoles from *N*-alkylanilines and amides.[3,14] Although they represent considerable advances, these two methods for the construction of C–N bonds employ transition metals as catalysts and are not efficient for use with benzotriazoles as substrates. Here, we report an iodine-catalyzed reaction for the N-alkylation of various azoles with amides.

Initially, we chose DMA and benzotriazole as model substrates for optimization of the reaction. The reaction did not occur when the two substrates were mixed without any additive at 80 °C for six hours under a nitrogen atmosphere (Table 1, entry 1). When *t*-BuOOH (TBHP) was employed as an oxidant with no catalyst, it failed to promote the reaction (entry 2). When iodine (20 mol%) was used as a catalyst in the presence of TBHP amide **3a** was obtained in 40% yield (entry 3). This prompted us to examine the effects of a series of catalysts containing iodine. In the presence of TBHP, the high-valent iodine compounds NIS and $NaIO_4$ did not catalyze this transformation (entries 4 and 5), whereas NH_4I, CuI, and TBAI catalyzed the reaction to give amide **3a**

in 42, 65, and 70% yield, respectively (entries 6–8). Gratifyingly, the use of NaI or LiI gave the desired product in good yields (entries 9 and 10), and KI provided the best yield (86%, entry 11). Next, we tested various oxidants in an attempt to find the optimal one. TBP, O_2, H_2O_2, Oxone, benzoquinone, and $PhI(OAc)_2$ all failed to promote the reaction in the presence of KI (entries 12–17), whereas CAN, $K_2S_2O_8$, and $(NH_4)_2S_2O_8$ gave amide **3a** in 60, 96, and 90% yield, respectively (entries 18–20). Temperature tests showed that 80 °C is the optimal temperature, as higher temperatures did not improve the yield (entries 21 and 22). Additionally, this catalytic system is not efficient for benzimidazole substrates; however, when $K_2S_2O_8$ alone (catalytic system B) was used as an oxidant, the transformation was highly efficient.

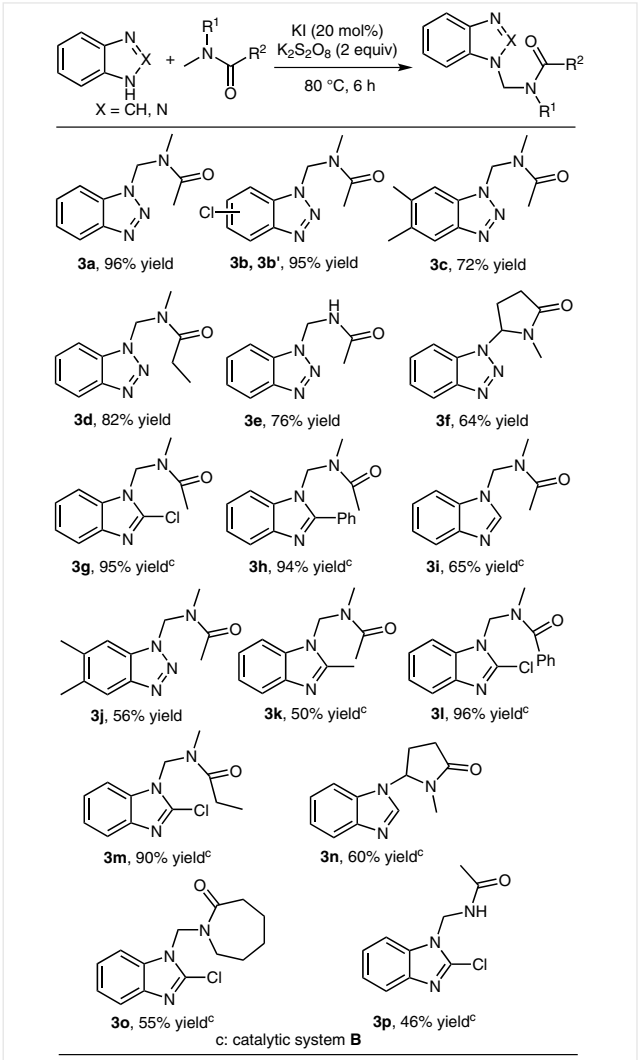
Table 1 Optimization of the Reaction[a]



Entry	Oxidant	Catalyst	T (°C)	Yield[b] (%)
1	–	–	80	0
2	TBHP	–	80	0
3	TBHP	I_2	80	40
4	TBHP	NIS	80	0
5	TBHP	$NaIO_4$	80	0
6	TBHP	NH_4I	80	42
7	TBHP	CuI	80	65
8	TBHP	TBAI	80	70
9	TBHP	NaI	80	83
10	TBHP	LiI	80	85
11	TBHP	KI	80	86
12	TBP	KI	80	0
13	O_2	KI	80	0
14	H_2O_2	KI	80	0
15	Oxone	KI	80	trace
16	BQ	KI	80	trace
17	$PhI(OAc)_2$	KI	80	0
18	CAN	KI	80	60
19	$K_2S_2O_8$	KI	80	96
20	$(NH_4)_2S_2O_8$	KI	80	90
21	$K_2S_2O_8$	KI	100	82
22	$K_2S_2O_8$	KI	60	trace

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (20 mol%), oxidant (1.0 mmol), DMA (2 mL), 6 h.
[b] Isolated yield.

With the optimized conditions in hand, we studied the scope and limitation of the reaction with respect to the substrate (Scheme 1). 6-Chlorobenzotriazole partially isomerized during the $K_2S_2O_8$/KI-catalyzed reaction with DMF and gave the isomeric coupling products **3b** and **3b′** in 95% total yield. 5,6-Dimethylbenzotriazole gave the desired product **3c** in 72% yield. The reaction of benzotriazole with *N*,*N*-dimethylpropanamide gave product **3d** in 82% isolated yield. Other amides were also tolerated by this catalytic system; for example, *N*-methylacetamide gave the corresponding product **3j** in 76% yield and 1-methylpyrrolidin-2-one gave **3k** in 64% yield. Benzimidazoles bearing an electron-withdraw group at the 2-position showed a high activity in the presence of catalyst system B ($K_2S_2O_8$ alone). For example, 2-chlorobenzimidazole and 2-phenylbenzimidazole coupled with DMA to give the corresponding products **3g** and **3h** in 95 and 94% yield, respectively. The presence of an

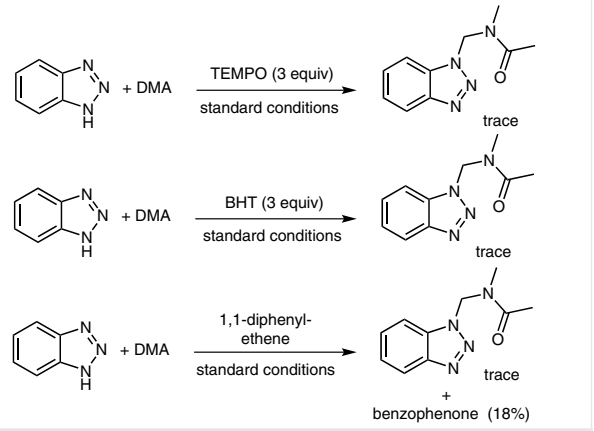


Scheme 1 The scope of the reaction

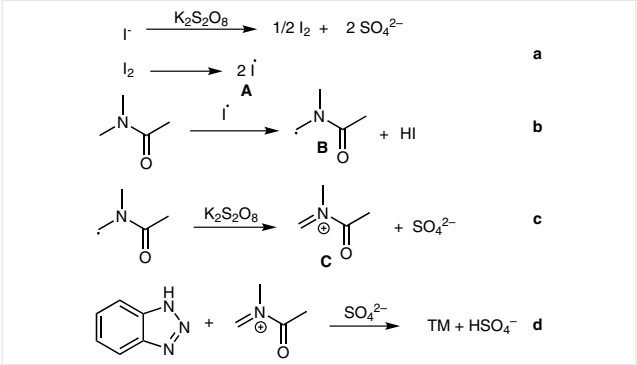
electron-donor group affected the reactivity of the benzimidazole; when **1i** was employed in the transformation, **3i** was isolated in 65% yield, and **1j** and **1k** gave **3j** and **3k** in moderate yields. *N*,*N*-Dimethylbenzamide and *N*,*N*-dimethylpropanamide coupled with 2-chlorobenzimidazole to give the desired products **3l** and **3m**, respectively, in high yields. The cyclic amides 1-methylpyrrolidin-2-one and 1-methylazepan-2-one similarly gave the corresponding products **3n** and **3o** in 60 and 55% yield, respectively. Furthermore, when the monosubstituted amide *N*-methylacetamide was employed in this transformation, the reaction proceeded smoothly to give the coupling product **3p** in 46% yield.

To investigate the mechanism of the reaction, some basic control reactions were conducted. First, when a radical scavenger [TEMPO or 2,6-di-*tetra*-butyl-4-methylphenol (BHT)] was added to the reaction mixture under the standard conditions, the corresponding product was not formed, suggesting that the reaction might involve a radical process (Scheme 2). Secondly, when 1,1-diphenylethene was present, it also inhibited the reaction, giving a red mixture with the formation of benzophenone as a byproduct, indicating that the radical-forming step involves $K_2S_2O_8$ and I_2.

A possible mechanism (Scheme 3) is proposed on the basis of the control experiments and previous work.[15] First, iodine ion is oxidized to form SO_4^{2-} and I_2, and the latter dissociates into radical species **A** (Scheme 3, Step a). Radical **A** abstracts a hydrogen atom from the amide to give radical **B** and HI (Step b). Next, $K_2S_2O_8$ oxidizes radical **B** to give the iminium ion **C** (Step c). Finally, nucleophilic addition between the azole and **C** delivers the desired product in the absence of base (Step d).



Scheme 2 Control experiments for the reaction



Scheme 3 Proposed mechanism of the reaction

In conclusion, we have developed a method for the metal-free N-alkylation of azoles by a CDC reaction.[16] This provides an efficient method to introduce amide groups onto azoles under mild conditions. Furthermore, two different novel catalytic systems have been developed to realize the N-alkylation of benzimidazoles and benzotriazoles.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588307.

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(16) ***N*-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-*N*-methylacetamide (3a); Typical Procedure**

A 50 mL Schlenk tube equipped with a stirrer bar was charged with KI (16.6 mg, 0.1 mmol), benzotriazole (59.5 mg, 0.5 mmol), DMA (2 mL), and $K_2S_2O_8$ (270 mg, 1 mmol) under air. The mixture was then stirred at 80 °C for 6 h (TLC monitoring), poured into H_2O (20 mL), and extracted with EtOAc (3 ×). Then the organic phase was evaporated under vacuum, and the crude product was purified by column chromatography [silica gel, PE–EtOAc (10:1 to 2:1)] to give a colorless oil; yield: 98 mg (96%); ^{1}H NMR (400 MHz, $CDCl_3$): d = 8.04 (d, *J* = 8.3 Hz, 1 H), 7.90 (d, *J* = 8.7 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 6.21 (s, 2 H), 3.11 (s, 3 H), 2.13 (s, 3 H).

***N*-[(6-Chloro-1*H*-1,2,3-benzotriazol-1-yl)methyl]-*N*-methylacetamide (3b) and *N*-[(5-Chloro-1*H*-1,2,3-benzotriazol-1-yl)methyl]-*N*-methylacetamide (3b′)**

Combined yield: 113 mg (95%)

3b

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.85 (m, 2 H), 7.28 (d, *J* = 8.9 Hz, 1 H), 6.09 (s, 2 H), 3.07 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (101 MHz, CDCl3): δ = 171.60, 144.66, 134.48, 133.03, 125.65, 120.47, 110.95, 57.72, 35.03, 21.60; HRMS: *m/z* [M + Na]$^+$ calcd for $C_{10}H_{11}ClN_4NaO$: 261.0514; found: 261.0512.

3b′

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.88 (dd, *J* = 8.8, 1.4 Hz, 1 H), 7.48 – 7.43 (m, 1 H), 6.18 (d, *J* = 1.5 Hz, 2 H), 3.12 (d, *J* = 1.8 Hz, 3 H), 2.13 (d, *J* = 1.8 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 128.87, 118.91, 112.23, 57.83, 35.05, 21.63; HRMS: *m/z* [M + Na]$^+$ calcd for $C_{10}H_{11}ClN_4NaO$: 261.0514; found: 261.0512.

***N*-[(5,6-Dimethyl-1*H*-1,2,3-benzotriazol-1-yl)methyl]-*N*-methylacetamide (3c)**

Colorless oil; yield: 84 mg (72%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 7.61 (s, 1 H), 6.15 (s, 2 H), 3.08 (d, *J* = 1.3 Hz, 3 H), 2.40 (d, *J* = 9.4 Hz, 6 H), 2.13 (d, *J* = 1.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.48, 138.40, 134.22, 118.62, 110.22, 57.32, 34.82, 21.75, 20.93, 20.43; HRMS: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{16}N_4NaO$: 255.1216; found: 255.1219.