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A novel and one-pot method for synthesis of unprecedented 3,3-dimethyl-2-amide indoles under metal-free conditions

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ABSTRACT

A novel and efficient method for the synthesis of 3,3-dimethyl-2-amide indoles, employing a I_2/DMSO-promoted oxidative amidation reaction between 1,2,3,3-tetramethyl-3*H*-indolium iodide and cyclic secondary amines under metal-free conditions has been developed.

Substituted indoles existing in a wide variety of natural products, are probably the most ubiquitous heterocycles in nature and have been referred to as 'privileged structures' in drug discovery, because of its biological activity and application in synthetic drugs.[1] In recent years, people have found that 2-amide indoles can be used as prototypical allosteric modulator for the cannabinoid type 1 receptor (CB1).[2] A number of synthetic methods for construction of this important unit have been established in the past decades.[3] Nevertheless, most of these methods described synthesis under harsh conditions, metal salt catalytic conditions, or multi-step reactions. Remarkably, there is still no single route and one-pot method for the synthesis of 2-amide indole using 2-methyl indole as the starting material. Therefore, developing a one-pot method for the synthesis of 2-amide indoles is highly desirable.

Recently, chemistry around the oxidation of the activated methyl group has been explored by different groups.[4–6] It is a well familiar fact that the activated methyl group is oxidized into aldehydes under I_2/DMSO conditions. The higher reactivity of aldehyde of 2-oxoaldehydes compared with normal aldehyde is attributed to the electron-withdrawing ketone group. 2,3,3-Trimethyl-3*H*-indolium is a well-known structural element and synthetic agents of many Near-infrared (NIR) fluorescent dyes.[7,8] These quaternary salts contain an activated methyl group which can react with 2-chloro-l-formyl-3-(hydroxymethylene)cyclohex-l-ene as nucleophiles.[9] In this work, the first known example of a unique, convenient, and efficient method to acquire 3,3-dimethyl-2-amide indoles using a metal-free oxidative amidation approach is reported (Scheme 1).

The present method employing an iodine (I_2)/dimethyl sulfoxide (DMSO) promoted oxidative amidation reaction between 1,2,3,3-tetramethyl-3*H*-indolium iodide and secondary amines under metal-free conditions demonstrates the special properties of quaternary salt toward amine in I_2/DMSO system.

To test our hypothesis, the reaction of 1,2,3,3,5-pentamethyl-3*H*-indolium iodide (**1a**) with morpholine (**2a**) and excess iodine in DMSO was proceeded at 80 °C for 12 h. To our delight and surprise, the reaction proceeded smoothly, giving an unprecedented 3,3-dimethyl-2-indoleamide (**3aa**), (Table 1, entry 1) which was unambiguously determined by X-ray diffraction. (CCDC 1034953, Fig. 1).

The reaction possibly involves in situ oxidation of the activated 2-position methyl group which proceeds via iminium ion formation to give 2-amide indoles.[4] Same reaction when kept for 24 h could not increase the yields (Table 1, entry 2). A higher conversion rate was obtained when the temperature was increased to 100 °C for 3 h (Table 1, entry 3). No further increase in yields was observed when the reaction temperature was >100 °C (Table 1, entry 4). No desired product was acquired when the reaction was performed at 60 °C for 30 h (Table 1, entry 5). After a preliminary

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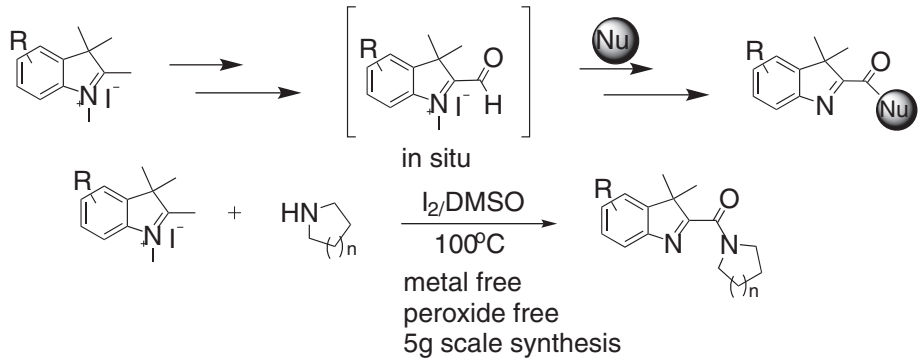
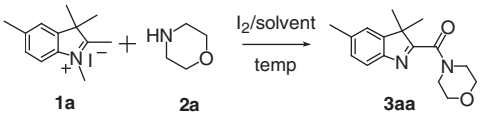


Scheme 1. Oxidative coupling reactions between the activated methyl group and nucleophiles.

Table 1
Optimization studies for the oxidative amidation of quaternary salt[a]



1a 2a 3aa

Entry	Solvent	I_2/equiv	Temp (°C)	Time (h)	Yield[b] (%)
1	DMSO (1.5 mL)	4	80	12	40
2	DMSO (1.5 mL)	4	80	24	41
3	DMSO (1.5 mL)	4	100	6	59
4	DMSO (1.5 mL)	4	120	6	53
5	DMSO (1.5 mL)	4	60	30	—
6	DMSO (1.5 mL)	5	100	3	67
7	DMSO (1.5 mL)	6	100	3	66
8	DMSO (2.5 mL)	5	100	3	64
9	DMSO (4.0 mL)	5	100	3	45
10	DMSO (0.5 mL)	5	100	3	46
11	Toluene (1.5 mL)	5	100	8	—
12	Ethanol (1.5 mL)	5	90	8	—
13	1,4-Dioxane (1.5 mL)	5	100	8	—
14	DMF (1.5 mL)	5	100	8	—
15	Water (1.5 mL)	5	100	8	—
16	DMSO (1.5 mL)	5	100	3	63[c]
17	DMSO (1.5 mL)	5	100	3	59[d]

[a] Reactants: **1a** (0.4 mmol), **2a** (0.75 mL).
[b] Isolated yields.
[c] **2a** (0.5 mL).
[d] **2a** (1.0 mL).

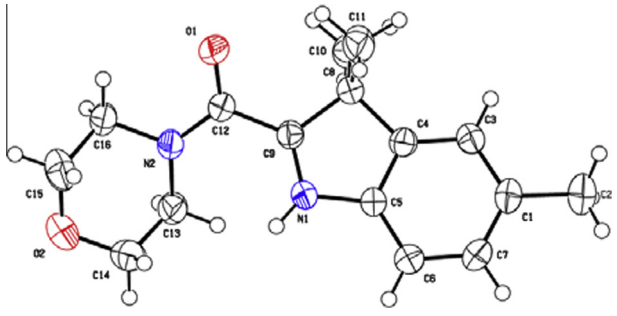
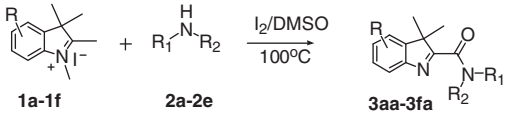
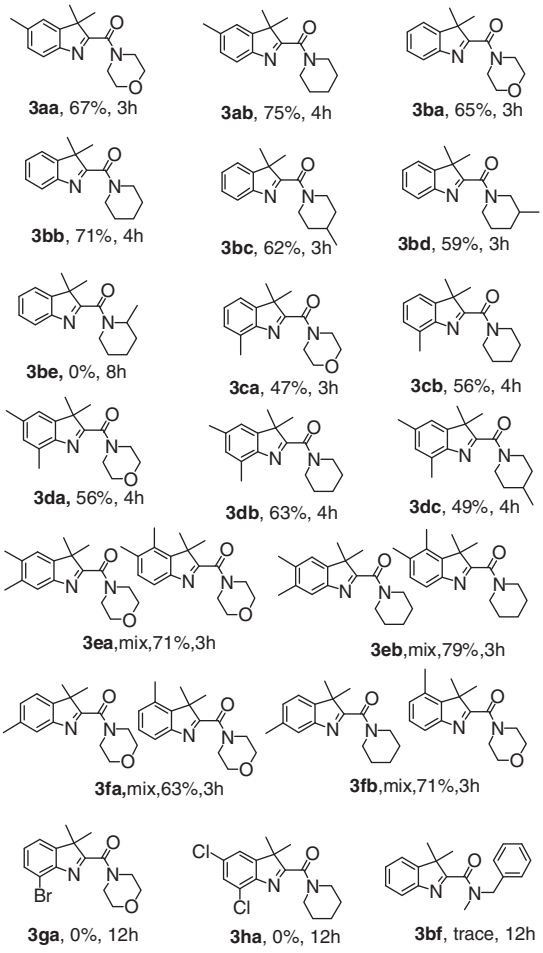


Figure 1. X-ray structure of **3aa**.

Table 2
I_2/DMSO-promoted oxidative amidation of quaternary salt (**1**) and secondary amine (**2**)[a]



1a-1f 2a-2e 3aa-3fa



[a] Isolated yields.

screening of the amount of iodine at 100 °C, it was found that 5.0 equiv of iodine was the promising amount in both terms of reactivity and conversion rate (Table 1, entry 6 and 7). To improve the yields of 2-amide indoles, the reaction conditions were further optimized by adjusting several parameters, including substrate concentration (Table 1, entries 8–10) and solvent (Table 1, entries 11–14). Several solvents were explored to examine the feasibility of the reaction, but no desired product was found. These results ascertain the role of DMSO from the other angle. Upon increasing or decreasing the dose of **2a**, both the yields were slightly decreased (Table 1, entry 16 and 17). Finally, iodine loading of