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Base-promoted domino reaction for the synthesis of 2,3-disubstituted indoles from 2-aminobenzaldehyde/2-amino aryl ketones, tosylhydrazine, and aromatic aldehydes

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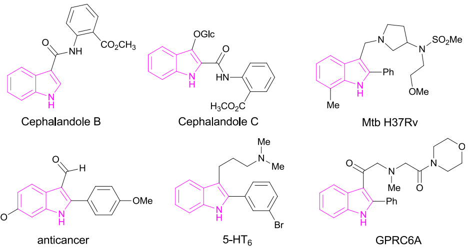
ABSTRACT

A base-promoted domino reaction to synthesize the 2,3-disubstituted indoles from 2-aminobenzaldehyde/2-amino aryl ketones, tosylhydrazine, and aromatic aldehydes has been developed. This strategy provides a simple and beneficial way for the construction of 2,3-disubstituted indole compounds from readily available starting materials under mild conditions.

1. Introduction

The 2,3-disubstituted indole skeleton is widely existed in natural products (e.g., Cephalandole B, Cephalandole C) and biologically active compounds possessing a wide spectrum of properties such as antimycobacterial, antibacterial, and anticancer. 5-HT_6 and GPRC6A have been used as several G protein-coupled receptors (Scheme 1).[1–3] In addition, 2,3-disubstituted indole scaffolds also serves as an important intermediate in synthetic organic chemistry.[4] Consequently, the development of efficient synthetic approaches to 2,3-disubstituted indoles has attracted much attention from chemists.

To date, several methods have been established for the synthesis of 2,3-disubstituted indole derivatives.[5] Among these, the most general method is probably the Fischer indole synthesis, in which 2,3-disubstituted indoles are prepared from phenylhydrazines and ketones or aldehydes in the presence of protic acid or Lewis acid catalyst (Scheme 2a).[6–8] In addition, Hupperts and co-workers reported the first titanium catalyzed carbonyl coupling reactions for the preparation of 2,3-disubstituted indoles (Scheme 2b).[9] In recent years, transition-metal-catalyzed cyclization has been developed to synthesize the 2,3-disubstituted indoles from arylamines and alkynes (Scheme 2c).[10–12] Despite these achievements, there is still a need to develop more powerful and straightforward procedures to synthesize 2,3-disubstituted indole and its related derivatives in mild conditions. Herein, we developed a base-promoted domino reaction to synthesize the 2,3-disubstituted indoles from 2-aminobenzaldehyde/2-amino aryl ketones, tosylhydrazine, and aromatic aldehydes (Scheme 2d).



Scheme 1. Natural products and pharmacological biological active compounds containing 2,3-disubstituted indole core.

2. Results and discussion

To test the feasibility of the proposed strategy, we commenced our study by choosing 1-(2-aminophenyl)ethanone (**1a**), 4-methylbenzaldehyde (**2b**) and tosylhydrazine as model

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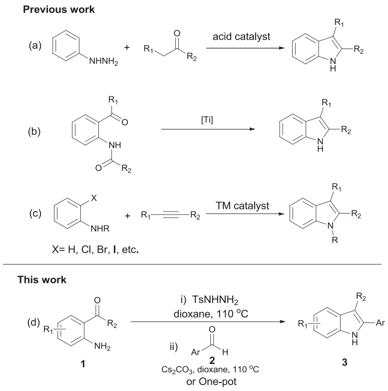
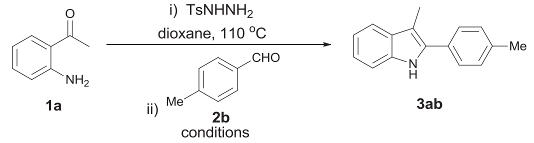


Scheme 2. Typical protocols for the synthesis of indoles. TM=transition metal.

substrates, as shown in Table 1. Initially, 1-(2-aminophenyl) ethanone (**1a**) and tosylhydrazine were conducted in 1,4-dioxane at 110 °C.[13e] Following, 4-methylbenzaldehyde was added to optimize the reaction conditions. The reaction occurred with 1.0 equiv of Cs_2CO_3 in 1,4-dioxane at 110 °C for 24 h to afford 3-methyl-2-(*p*-tolyl)-1*H*-indole (**3ab**) in 10% yield (Table 1, entry 1). When the dosage of Cs_2CO_3 was increased to 4.0 equiv, the yield increased to 55% (Table 1, entry 3). However, further increase in the amount of Cs_2CO_3 did not lead to significant difference in the yield (Table 1, entry 4). Subsequently, screening a variety of solvents revealed that the solvent had great influence on the reaction (entries 5–11), which suggested that 1,4-dioxane was the most effective solvent so far for the formation of **3ab**. Later, different bases were also tested, including K_2CO_3, Na_2CO_3, NaOH, KOH, *t*-BuOK, NaOEt, DABCO, DBU, and NEt_3 (entries 12–20), and Cs_2CO_3 was proven to be the optimal base.

With the optimized conditions in hand, the generality and scope of the aromatic aldehydes was next investigated. To our delight, the reaction demonstrated wide scope for the structure of aromatic aldehydes which proceeded smoothly to afford the corresponding products in moderate to good yields (50–68%; Table 2), regardless of their electronic or steric properties. Aryl aldehydes bearing electron-neutral (H), electron-donating (4-Me, 4-OMe) and electron-withdrawing (4-NO_2, 3-NO_2) substituents could be transformed into the corresponding products in moderate to good yields (**3aa**–**3ac**; 53–55%; **3aj**–**3ak**; 62–68%). Moderate yields were obtained for halo-substituted substrates (**3ad**–**3ai**; 53–65%). Furthermore, 2-naphthaldehyde also provided the expected products **3al** in 50% yield. Fortunately, the structure of **3aa** was further confirmed by X-ray crystallographic analysis (see Supplementary data (SI)).

Table 1
Optimization of the reaction conditions[a]

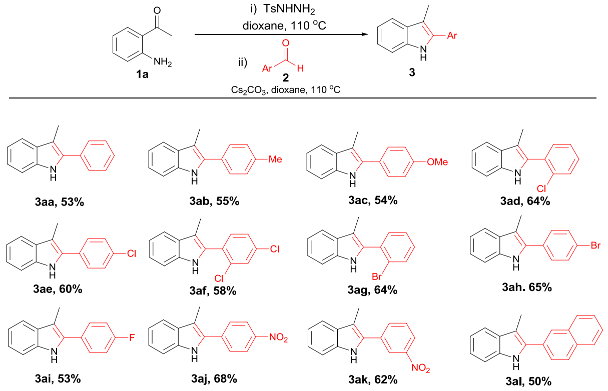


Entry	Solvent	Base (equiv)	Temp (°C)	Yield[b] (%)
1	1,4-dioxane	Cs_2CO_3 (1.0)	110	10
2	1,4-dioxane	Cs_2CO_3 (3.0)	110	20
3	1,4-dioxane	Cs_2CO_3 (4.0)	110	55
4	1,4-dioxane	Cs_2CO_3 (5.0)	110	50
5	Toluene	Cs_2CO_3 (4.0)	110	0
6	DCE	Cs_2CO_3 (4.0)	110	0
7	DMSO	Cs_2CO_3 (4.0)	110	0
8	DMF	Cs_2CO_3 (4.0)	110	0
9	H_2O	Cs_2CO_3 (4.0)	110	5
10	Glycol	Cs_2CO_3 (4.0)	110	10
11	Pyrrolidone	Cs_2CO_3 (4.0)	110	0
12	1,4-dioxane	K_2CO_3 (4.0)	110	35
13	1,4-dioxane	Na_2CO_3 (4.0)	110	40
14	1,4-dioxane	NaOH (4.0)	110	10
15	1,4-dioxane	KOH (4.0)	110	30
16	1,4-dioxane	*t*-BuOK (4.0)	110	0
17	1,4-dioxane	NaOEt (4.0)	110	20
18	1,4-dioxane	DABCO (4.0)	110	22
19	1,4-dioxane	DBU (4.0)	110	0
20	1,4-dioxane	NEt_3 (4.0)	110	50

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), tosylhydrazine (1.0 mmol, 1.0 equiv), **2b** (0.12 mmol, 1.2 equiv), base (0.4 mmol, 4.0 equiv), and solvent (3 mL) in a sealed vessel for 24 h.

[b] Isolated yields.

Table 2
Scope of aromatic aldehydes[a,b]

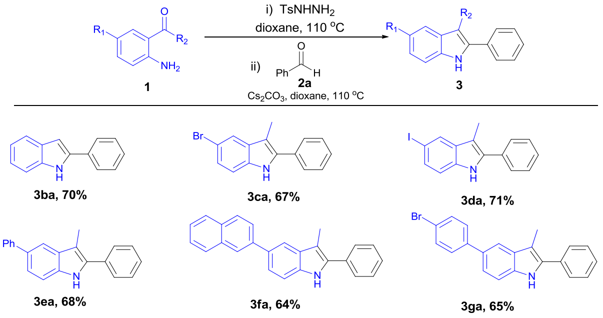


[a] Reaction conditions: 1-(2-aminophenyl)ethanone **1a** (1.0 mmol, 1.0 equiv), tosylhydrazine (1.0 mmol, 1.0 equiv) and aromatic aldehydes **2** (1.2 mmol, 1.2 equiv) and Cs_2CO_3 (4.0 mmol, 4.0 equiv) was stirred in 1,4-dioxane (10 mL) at 110 °C for 24 hours. [b] Isolated yields.

The scope of this reaction was further extended to different substituted 2-aminobenzaldehydes/2-amino aryl ketones **1** (Table 3). Pleasingly, 2-aminobenzaldehyde **1b** was well tolerated in the reaction, leading to desired product **3ba** in 70% yield. When R_2=Me, and R_1 were a bromo or iodo substituent, the reaction delivered the corresponding products **3ca** and **3da** in 67% and 71% yields respectively. Moreover, moderate yields were gained with aryl substituents in the R_1 position (**3ea**-**3ga**; 64%–68%).

Next, our attention turned to the exploration of a more efficient approach to synthesize 2,3-disubstituted indoles from commercial available starting materials. A one-pot two-step protocol was trialed for the synthesis of aromatic-3-methyl-1*H*-indoles **3** using 2-

Table 3
Scope of 2-aminobenzaldehyde/2-amino aryl ketones[a,b]



[a] Reaction conditions: **1** (1.0 mmol, 1.0 equiv), tosylhydrazine (1.0 mmol, 1.0 equiv) and benzaldehyde **2a** (1.2 mmol, 1.2 equiv) and Cs_2CO_3 (4.0 mmol, 4.0 equiv) was stirred in 1,4-dioxane (10 mL) at 110 °C for 24 hours. [b] Isolated yields.