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NHC triggered cascade metal-free synthesis of 2,3-diarylated indoles under solvent-free conditions

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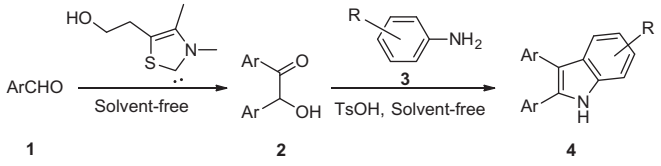
ABSTRACT

A new cascade strategy to the synthesis of 2,3-diarylated indoles via the metal-free reaction of aryl aldehyde and aryl amine triggered by *N*-heterocyclic carbene (NHC) under solvent-free conditions, has been disclosed. The protocol has the advantages of easy work-up, high yields, wide application scope, and an environmentally benign procedure compared with the reported methods.

Introduction

The indole skeleton is one of the most prominent frameworks found in numerous natural products and synthetic compounds with vital medicinal value.[1] The synthesis of indoles has captivated chemists for more than a century and numerous approaches have been developed, such as the classical Fisher indole synthesis,[2] the Gassman indole synthesis,[2,3] the Reissert indole synthesis,[2] the Leimgruber–Batcho indole synthesis[2,4], and the Bischler indole synthesis.[2,5] Indole derivatives, particularly 2,3-disubstituted indoles play an important role in the field of medicinal chemistry due to their various potential biological and pharmacological activities.[6] It has gained broad attention to the synthesis of 2,3-disubstituted indoles in recent years.[7] The classical strategy to the synthesis of 2,3-disubstituted indoles should be metal-catalyzed transformations.[8] Only a few compounds were synthesized concisely via the reaction of benzoin[9] or 2-bromo-1,2-diphenylethanone[10] with aryl amines. Although these methods are effective, some limitations are associated with these procedures, including tedious workup, low yields, long reaction times, and the use of organic solvents. Thus, developing a general and economical process for the synthesis of 2,3-disubstituted indoles remains a continuing challenge for organic chemists. Recently, the progress in the field of solvent-free reactions is gaining much attention for their high efficiency and eco-friendliness.[11] Many organic reactions and complex transformations have been reported to proceed efficiently under solvent-free conditions.[11–13]



Scheme 1. A NHC-triggered cascade solvent-free synthesis of 2,3-diarylated indoles.

In past decades, *N*-heterocyclic carbene (NHC)-catalyzed umpolung reactions have drawn considerable attention of a number of organic chemists due to their wide applications in organic synthesis.[14] A large number of NHC-catalyzed inter- and intramolecular benzoin condensation reactions[15] have been reported to construct various functionalized organic compounds. Cascade reactions have been widely applied in preparing compound libraries to screen for functional molecules due to their inherent simple experimental procedures, high bond forming efficiency, and great diversity generating potential.[16,17] Several successful cases of NHC-triggered cascade reactions were reported recently.[14,17] Inspired by this and in continuing our work on the design and efficient synthesis of biologically potential active heterocyclic compounds,[18] we shall disclose herein a rapid and facile method to prepare the 2,3-diarylated indoles via a NHC triggered cascade reaction (Scheme 1) under solvent-free and metal-free conditions.

Results and discussion

Firstly, we examined the benzoin reaction of 3-chlorobenzaldehyde in different solvents in the presence of carbene precursor **B**

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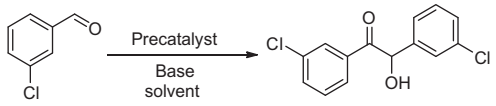
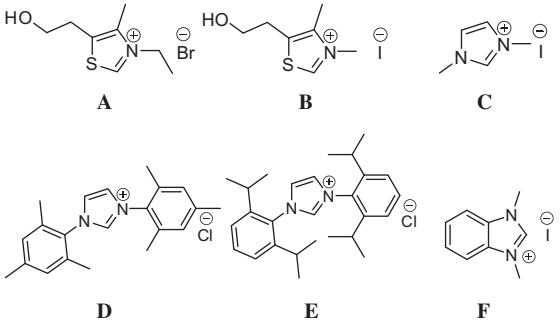
Table 1
Condition screening for the benzoin reaction of 3-chlorobenzaldehyde



Entry	Precatalyst (mol %)	Base (mol %)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	**B** (10)	DBU (50)	C_2H_5OH	50	5	56
2	**B** (10)	DBU (50)	THF	50	5	32
3	**B** (10)	DBU (50)	DMF	50	5	28
4	**B** (10)	DBU (50)	H_2O	50	5	37
5	**B** (10)	DBU (50)	Solvent-free	50	3	66
6	**A** (10)	DBU (50)	Solvent-free	50	4	27
7	**C** (10)	DBU (50)	Solvent-free	50	4	19
8	**D** (10)	DBU (50)	Solvent-free	50	4	23
9	**E** (10)	DBU (50)	Solvent-free	50	4	37
10	**F** (10)	DBU (50)	Solvent-free	50	4	0
11	**B** (10)	Et_3N (50)	Solvent-free	50	3	28
12	**B** (10)	K_2CO_3 (50)	Solvent-free	50	3	58
13	**B** (10)	Cs_2CO_3 (50)	Solvent-free	50	3	62
14	**B** (10)	DBU (60)	Solvent-free	50	3	68
15	**B** (10)	DBU (70)	Solvent-free	50	2	70
16	**B** (10)	DBU (75)	Solvent-free	50	0.75	82
17	**B** (10)	DBU (80)	Solvent-free	50	0.75	68
18	**B** (5)	DBU (75)	Solvent-free	50	1.5	62
19	**B** (20)	DBU (75)	Solvent-free	50	0.75	82
20	**B** (30)	DBU (75)	Solvent-free	50	0.75	79
21	**B** (10)	DBU (75)	Solvent-free	55	0.75	86

[a] Isolated yield.



A **B** **C**

D **E** **F**

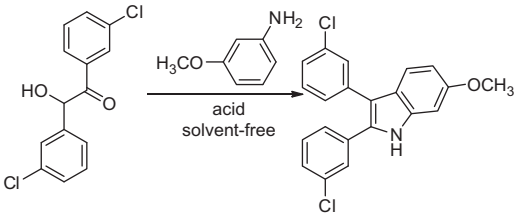
and an amine base (DBU, 1,8-diazabicyclo[5.4.0]-undec-7-ene) at 50 °C. As can be seen in Table 1, the solvent-free system exhibits better yield and greater reaction rate than the other counterparts. Next, the precatalyst and base effect on the reaction was investigated under solvent-free conditions. Precatalyst **F** proved to be unsuitable for this reaction. Precatalyst **A** and **C** as well as precatalyst **D** and **E** are less active for this reaction. Organic bases Et_3N resulted in poor conversion (28%). A similar result was obtained in the case of inorganic base K_2CO_3 (58%) and Cs_2CO_3 (62%). It indicated that DBU was the optimal base. Subsequently, the reaction was performed with different catalyst loading, base loading under solvent-free conditions, and repeated many times at 50 °C. It was found that the reaction proceeded better in the presence of 10 mol % of **B** and 75 mol % of DBU under solvent-free conditions. Later, we examined the temperature effect on the reactions. As can be seen in Table 1, the highest yield of the product was obtained at 55 °C. To promote the conversion of benzoin to substituted indoles, a range of nonvolatile Brønsted acids and aryl amines were added directly to the reaction system after the benzoins were formed. In order to optimize the reaction conditions of cyclization, the loadings of several acids were investigated under solvent-free conditions at different temperatures (Table 2). The results showed that the reaction catalyzed by *p*-toluenesulfonic acid (TsOH) loading of 200 mol % under solvent-free conditions at 140 °C gave the expected product in the highest yield (78%). Unfortunately, the product was obtained in low yields when the reaction was catalyzed by SA and H_2SO_4.

On the basis of the optimized reaction conditions identified, the application scope of this reaction sequence was examined. The results are summarized in Table 3. Both amines bearing either electron-donating groups (such as methoxyl group) or electron-withdrawing groups (such as halide group) afforded high yields of 2,3-diarylated indoles derivatives. Besides, the reaction between benzoins and 3-methoxyaniline gave 6-methoxy-2,3-aryl-1*H*-indoles regiospecifically. Meanwhile, the results also indicated that this protocol could successfully be applied to the aromatic aldehydes bearing electron-withdrawing groups, such as halogens. However, electron-rich aromatic aldehydes, heteroaromatic aldehyde, and fatty aldehyde could not participate in this cascade reaction.

All of the synthesized compounds were characterized by IR, ^1H NMR, and HRMS. The structure of **4d** was also confirmed by X-ray crystallographic analysis (Fig. 1).[19]

Although the detailed mechanism of the above mentioned reaction remains to be fully clarified, the formation of 2,3-diarylated indoles could be explained by a possible reaction sequence presented in Scheme 2. In the initial step, aryl aldehyde was converted to benzoin in the presence of NHC. The subsequent reaction between benzoin and amine with the aid of an acid gave the corresponding indoles.

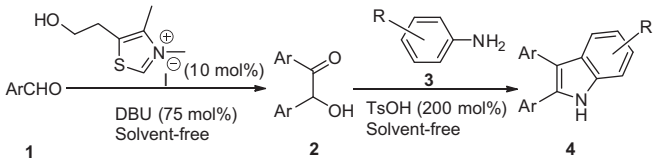
Table 2
Condition optimization for the reaction of 1,2-bis(3-chlorophenyl)-2-hydroxyethanone and 3-methoxyaniline



Entry	Acid (mol %)	Temp (°C)	Time (h)	Yield[a] (%)
1	SA (120)	130	6	24
2	H_2SO_4 (120)	130	6	11
3	TsOH (120)	130	5	35
4	TsOH (100)	130	5	26
5	TsOH (150)	130	4.5	47
6	TsOH (180)	130	4.5	52
7	TsOH (190)	130	4	66
8	TsOH (200)	130	3.5	72
9	TsOH (210)	130	3.5	72
10	TsOH (220)	130	4	70
11	TsOH (200)	120	6	26
12	TsOH (200)	140	3	78
13	TsOH (200)	150	3.5	69

[a] Isolated yield.

Table 3
Synthesis of product **4** under solvent-free conditions



Entry	Ar	R	Product	Yield[a] (%)
1	4-FC_6H_4	3-CH_3O	**4a**	88
2	3-FC_6H_4	3-CH_3O	**4b**	85
3	2-FC_6H_4	3-CH_3O	**4c**	84
4	4-BrC_6H_4	3-CH_3O	**4d**	65
5	4-ClC_6H_4	3-CH_3O	**4e**	63
6	3-ClC_6H_4	3-CH_3O	**4f**	78
7	3,4-$Cl_2C_6H_3$	3-CH_3O	**4g**	71
8	3-$CH_3OC_6H_4$	3-CH_3O	**4h**	74
9	Thien-2-yl	3-CH_3O	**4i**	Trace
10	4-FC_6H_4	H	**4j**	78
11	3-FC_6H_4	H	**4k**	80
12	3,4-$Cl_2C_6H_3$	H	**4l**	67
13	4-FC_6H_4	4-Cl	**4m**	85
14	4-FC_6H_4	4-CH_3	**4n**	83
15	4-FC_6H_4	4-CH_3O	**4o**	80
16	C_6H_5	H	**4p**	78

[a] Isolated yield.

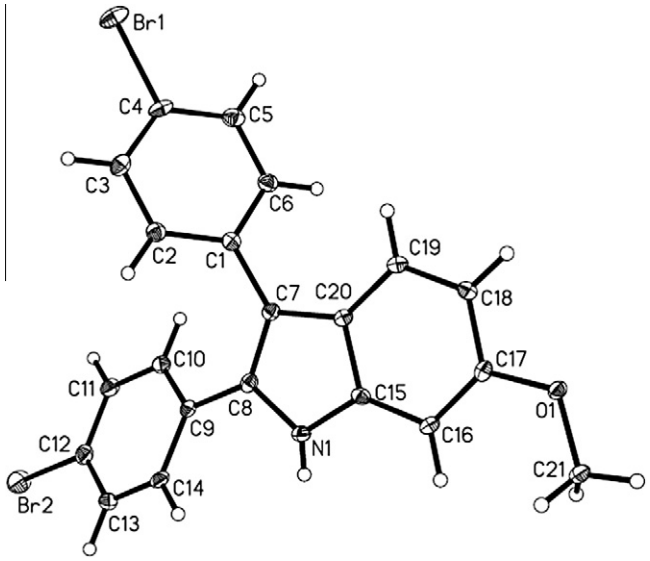
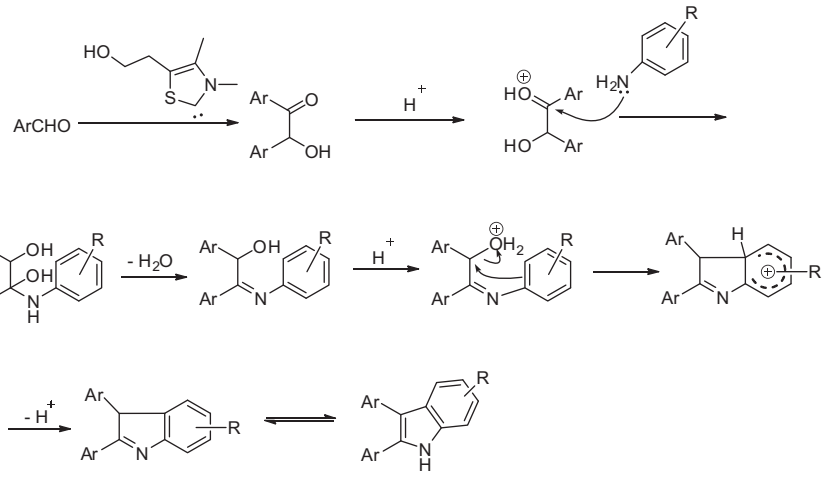


Figure 1. Crystal structure of **4d**.

In summary, we have developed a novel cascade reaction triggered by NHC, which is a more direct and efficient way to construct skeletons of indoles. The ready availability of the starting materials, atom economy of the reaction, and the useful skeleton of the products would make this strategy quite attractive.

Experimental section

Aryl aldehyde (1.0 mmol), Precatalyst **B** (0.029 g) and DBU (0.114 g) were triturated together in an agate morlar for 45 min at 55 °C. Then, TsOH (0.344 g) and aryl amines (0.5 mmol) were added and the mixture was kept at 140 °C. Upon completion, monitored by TLC, the reactant was cooled to room temperature and was purified by column chromatography (silica gel, mixtures of ethyl acetate/petroleum ether, 1:20, v/v) to afford the desired pure product. 4**f** mp: 160.1–162.0 °C; IR (potassium bromide) (ν, cm^{-1}): 3326, 1595, 1197, 1016, 788, 697; ^1H NMR (400 MHz, DMSO-d_6):δ 11.62 (s, 1H, NH), 7.51 (s, 1H, ArH), 7.43 (t, J = 7.6 Hz, 1H, ArH), 7.36 (d, J = 8.0 Hz, 5H, ArH), 7.31(t, J = 7.6 Hz, 2H, ArH), 6.95 (s, 1H, ArH), 6.75 (d, J = 8.8 Hz, 1H, ArH), 3.81 (s, 3H, CH_3); HRMS (ESI) m/z: Calcd for $[M-H]^-$ $C_{21}H_{14}Cl_2NO$: 366.0452 found: 366.0450; ^{13}C NMR (100 MHz, DMSO-d_6):δ 156.5, 137.2, 137.0, 134.2, 133.2, 131.5, 130.5, 130.3, 129.0, 128.3, 127.3, 127.1, 126.5, 126.2, 121.9, 119.3, 112.7, 110.5, 94.4, 55.2.



Scheme 2. A proposed reaction mechanism.

Acknowledgments

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.041.

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19. The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed using a Rigaku Saturn diffractometer. Crystal data for **4d**: $C_{21}H_{17}Br_2NO$, colorless, crystal dimension $0.20 \times 0.20 \times 0.10$ mm, *Monoclinic*, space group *P*2(1)/c, $a = 17.212(10)$, $b = 8.315(4)$, $c = 13.649(8)$ Å, $\beta = 112.819(9)^{o}$, $V = 1800.6(17)$ Å^3, $Mr = 457.16$, $Z = 4$, $Dc = 1.686$ g/cm^3, $\lambda = 0.71073$ Å, μ(Mokα) = 4.510 mm^{-1}, $F(000) = 904$, $S = 1.011$, $R_1 = 0.0443$, $wR_2 = 0.0887$.