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A novel multi-component reaction of indole, formaldehyde, and tertiary aromatic amines

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ABSTRACT

A novel multi-component reaction of indoles, formaldehydes, and tertiary aromatic amines is described for the synthesis of dialkylaminoarylated indoles using silica-supported perchloric acid ($HClO_4–SiO_2$) as an inexpensive and highly efficient catalyst. The key features of this multi-component reactions are operational simplicity, mild reaction conditions, regioselectivity, and recycling of catalyst.

Multi-component reactions (MCRs) have offered many fascinating and challenging transformations in organic synthesis.[1] The atom-economy, convergent character, operational simplicity, structural diversity, and complexity of the molecules are the major advantages associated with multi-component reactions. Besides this multi-component reactions are emerging as a powerful tool in the synthesis of biologically important compounds.[2] Thus, the discovery of novel multi-component reactions is of much importance. Most of the previously known MCRs were invented by serendipity rather than logically designed multi-component reactions. Recently, much effort is devoted for rational design of new multi-component reactions. There are three major ways of designing new MCRs such as combinatorial chemistry, MCR sequences, and smallest atom connectivity.

We wish to report here a new multi-component reaction involving indoles, formaldehydes, and tertiary aromatic amines for the synthesis of dialkylaminoarylated indoles.

Substituted 3-alkyl indole moieties are of much importance as they are widely distributed in nature and reveal a broad range of biological activity.[3] Indoles with substituents at the 3-position are considered as venerable pharmacophores[4] in drug discovery as well as found in various ranges of natural products such as 5-$HT_1B/1D$ receptor agonist activities used in the treatment of migraine **I**, aromatase inhibitor for breast cancer **II**[5] and HIV-1 integrase inhibitor **III**,[6] Gramine **IV**, Ergine **V**, and Sumatriptan **VI** (Fig. 1). The immense potential of indole nucleus as drug candidates prompted us to design a novel substituted 3-alkyl indole based on multi-component reactions.

In continuation of our work on MCRs,[7] we report here a novel multi-component reaction of indoles, formaldehydes, and tertiary aromatic amines for the synthesis of dialkylaminoarylated indoles using silica-supported perchloric acid as a catalyst (Scheme 1).

Our initial efforts were focused on the search for an efficient catalyst for the three-component reaction of indoles with formaldehydes, and tertiary aromatic amines.[8] In order to screen the

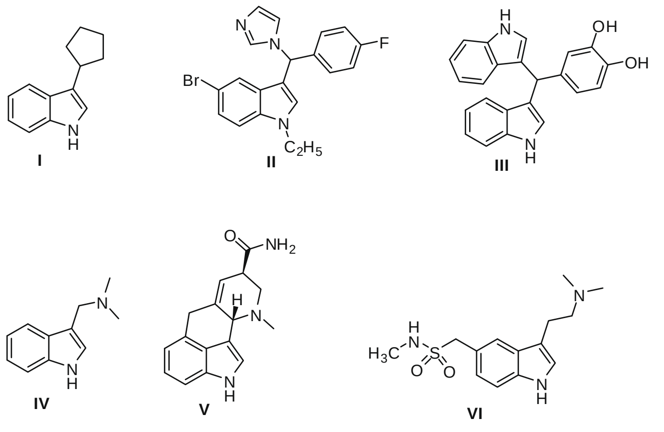

Figure 1. Some biologically active 3-substituted indoles.

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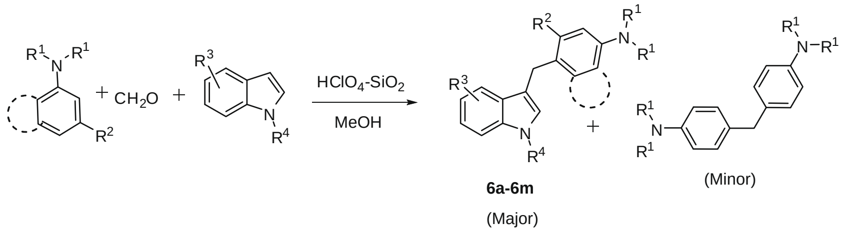


Scheme 1. Three-component reaction of indoles, formaldehydes, and tertiary aromatic amines.

catalysts, the reaction of indole, formaldehyde, and *N,N*-dimethylaniline was taken as a model reaction. Several Bronsted acids (hydrochloric acid, sulfuric acid, acetic acid, PTSA, methane sulfonic acid, and TFA) were employed for this multi-component synthesis. However all these Bronsted acids gave poor yields of **6a** (Table 3), and 4,4′-methylenebis(*N,N*-dimethylaniline) was formed as a major product.

Then we turned our attention towards silica-supported acids ($HClO_4$, H_2SO_4), which have received considerable attention as inexpensive and recyclable catalysts for numerous organic transformations.[9] $HClO_4–SiO_2$ was prepared by the reported procedure of Chakraborti et al.[9a] Use of silica-supported perchloric acid as catalyst gave excellent yield (84%) of **6a** (Table 3) in methanol. Using 2 mol % of $HClO_4–SiO_2$ was sufficient to push the reaction forward, and further increasing the amount of catalyst did not increase the yields. While $H_2SO_4–SiO_2$ afforded **6a** as a major product, use of other catalysts resulted in **7** (Fig. 2) also in considerable yields (Table 1). A similar reaction with normal silica did not produce any of the desired products even after 3 days at room temperature. In addition to the simplicity of the product isolation, the catalyst can be recycled several times.[10] Even after five cycles, the catalyst did not show any significant change in reactivity. The results of this study are summarized in Table 1.

Various solvents such as EtOH (57%), CH_3CN (29%), THF (39%), and $CHCl_3$ (27%) were used to optimize the model reaction. Polar solvents gave better yields in comparison to non-polar solvents and best results were obtained with MeOH (84%). The results of this study are shown in Table 2.

Table 1
Condensation of indole, formaldehyde, and *N,N*-dimethylaniline under different catalysts

Entry	Catalyst	Solvent	Time (h)	Yield **6a**[a] (%)	Yield **7**[a] (%)
1	—	—	10	—	—
2	HCl	MeOH	1	11	69
3	Acetic acid	MeOH	1	21	72
4	Sulfuric acid	MeOH	1	9	79
5	PTSA	MeOH	1	23	71
6	MSA	MeOH	1	11	73
7	TFA	MeOH	1	21	56
8	SiO_2	MeOH	3[b]	—	—
9	$H_2SO_4–SiO_2$	MeOH	1	71	24
10	$HClO_4–SiO_2$	MeOH	1	84	Trace

[a] Isolated yield.
[b] Days

Table 2
Solvent effect on the coupling of indole, formaldehyde, and *N,N*-dimethylaniline[a]

Entry	Solvent	Yield **6a**[b] (%)	Yield **7**[b] (%)
1	EtOH	57	25
2	CH_3CN	29	33
3	THF	39	34
4	$CHCl_3$	27	49
5	MeOH	84	>5

[a] Reaction conditions: Indole (1.0 mmol), formaldehyde (1.0 mmol), *N,N*-dimethylaniline (1.0 mmol), and $HClO_4–SiO_2$ (2 mol %), rt, 1 h.
[b] Isolated yield.

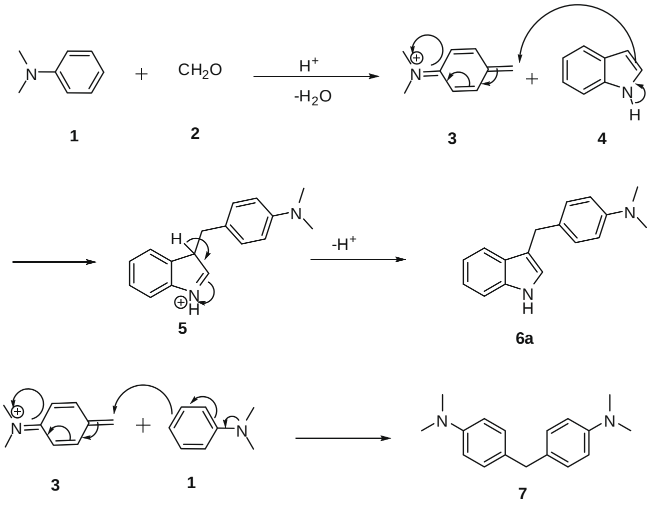


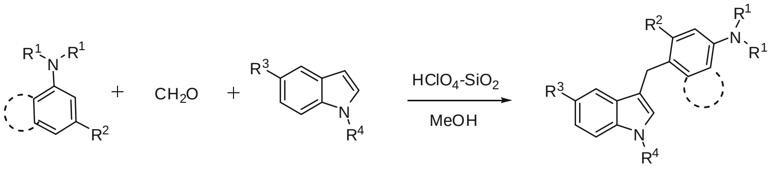
Figure 2. Plausible mechanism of three component reaction.

In order to determine the scope of the reaction, we synthesized a number of compounds using substituted indoles and tertiary aromatic amines using the optimized reaction protocols (Table 3). All the compounds were well characterized by mass spectrometry, NMR, and IR spectroscopy.[11]

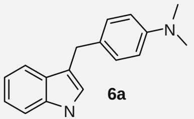
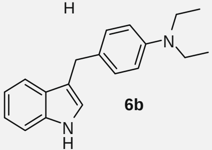
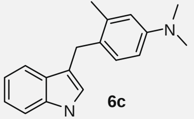
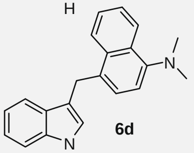
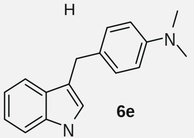
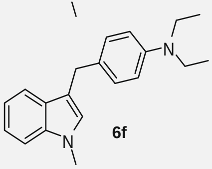
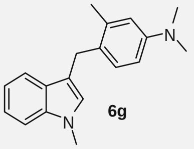
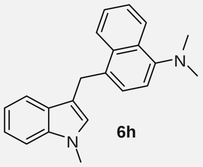
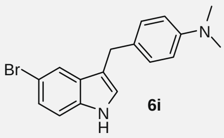
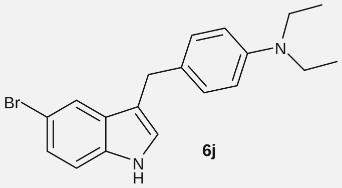
The plausible mechanism of the reaction is given in Figure 2. Tertiary aromatic amine reacts with formaldehyde to generate an intermediate *N*-methyl-*N*-(4-methylenecyclohexa-2,5-dienylidene)methanaminium **3**, which on addition of indole gave the desired *N,N*-dialkyl amino arylated indoles. Compound **7** was also formed by the attack of tertiary aromatic amine **1** on intermediate **3**.

In summary, we have developed a novel three-component reaction of indoles, formaldehydes, and tertiary aromatic amines using silica- supported perchloric acid as a catalyst. The reaction is operationally simple and offers high yields of the 3-alkylated indoles. Further work is in progress at utilizing these molecules for biological activity studies.

Table 3
A novel multi-component reaction of indoles, formaldehydes, and tertiary aromatic amines[a]

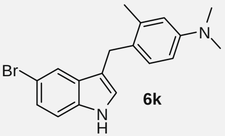
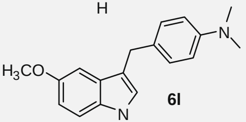
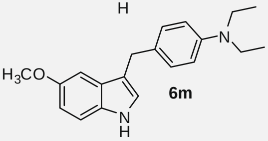


6a-6m

S.No.	R^1	R^2	R^3	R^4	Product	Time (h)	Yield[b]
1	CH_3	H	H	H	 **6a**	0.5	84
2	C_2H_5	H	H	H	 **6b**	0.5	81
3	CH_3	CH_3	H	H	 **6c**	0.5	82
4	CH_3	H	H	H	 **6d**	0.5	88
5	CH_3	H	H	CH_3	 **6e**	1	82
6	C_2H_5	H	H	CH_3	 **6f**	1	84
7	CH_3	CH_3	H	CH_3	 **6g**	1	73
8	CH_3	H	H	CH_3	 **6h**	1.5	68
9	CH_3	H	Br	H	 **6i**	1	76
10	C_2H_5	H	Br	H	 **6j**	1	78

(continued on next page)

Table 3 (*continued*)

S.No.	R^1	R^2	R^3	R^4	Product	Time (h)	Yield[b]
11	CH_3	CH_3	Br	H	 **6k**	1	82
12	CH_3	H	OCH_3	H	 **6l**	1	82
13	C_2H_5	H	OCH_3	H	 **6m**	1	74

[a] Reaction conditions: Indole (1.0 mmol), formaldehyde (1.0 mmol), *N*,*N*-dialkylaniline (1.0 mmol), and $HClO_4–SiO_2$ (2 mol %), MeOH, rt, 0.5–1.5 h.
[b] Isolated yield.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.046.

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8. *General experimental procedure*: A mixture of indole (117 mg, 1.0 mmol), *N*,*N*-dimethylaniline (121 mg, 1.0 mmol) and $HClO_4–SiO_2$ (2 mol %) was stirred in MeOH (5 ml) at room temperature for 5 min. Thereafter formaldehyde (formalin solution) 1.0 mmol, 0.086 ml was added dropwise to the stirred solution. The reaction was monitored by TLC. The products precipitated from the reaction mixture. The precipitate was filtered off, dissolved in hot MeOH and the catalyst was removed by hot filtration. The filtrate was kept at room temperature and the resulting crystallized product **6a** was collected by filtration and washed with cold EtOH to get 210 mg (84%) of the crystallized product.
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10. Recycling of $HClO_4–SiO_2$ was done according to the reported procedure. The catalyst was dried at 100 °C for 24 h to give recycled $HClO_4–SiO_2$. The reaction of *N*,*N*-dimethylaniline, formaldehyde, and indole was repeated with recycled catalyst and the yields were found to remain in the range of 80% for five recycles.
11. *Spectral data for selected compounds*: Table 3, **6a**. Isolated yield 84%; White crystals. 4-((1-*H*-indol-3-yl)methyl)-*N*,*N*-dimethylaniline; ^1H NMR (300 MHz, $CDCl_3$) δ 2.86 (S, 6H), 4.06 (s, 2H), 6.73 (2H, d, J = 8.42 Hz), 6.91 (s, 1H), 7.08–7.13 (m, 1H), 7.18–7.23 (m, 3H), 7.35 (d, 1H, J = 8.01 Hz), 7.56 (d, 1H, J = 8.01 Hz), 7.94 (s, 1H); ^{13}C NMR (75 MHz) δ 30.43, 40.96, 109.35, 113.13, 116.51, 119.57, 119.83, 122.23, 125.28, 129.34, 135.74, 149.42; IR (KBr, cm^{-1}) 3463.4, 1216.9 cm^{-1}; ESI MS (m/z, % int.) 251 (100) $[M+H]^+$. Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.39; H, 7.21; N, 10.97.