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# One-pot three-component coupling reaction: solvent-free synthesis of novel 3-substituted indoles catalyzed by PMA–$SiO_2$

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ABSTRACT

Solvent-free PMA–$SiO_2$-catalyzed synthesis of 3-substituted indole derivatives by a one-pot three-component coupling reaction between aldehyde, *N*-methyl aniline and indole is described.

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Concepts such as 'atom economy' and 'green chemistry' have focused significant interest on multicomponent reactions[1] (MCR), wherein at least three simple partners are added together to result in a single diverse complex structure which allows the formation of several new bonds. The strategy of multicomponent reactions has been instrumental in playing a significant role in the preparation of structurally diverse chemical libraries. The utility of MCR is well represented in the synthesis of privileged medicinal scaffolds such as 1,4-dihydropyridines, dihydropyrimidines, decahydroquinolin-4-ones[2] or substituted indoles[3]. Recently, indole derivatives have become increasingly useful and important in the field of pharmaceuticals.[4] Their biological properties have attracted many synthetic chemists to explore different methods suitable for the synthesis of substituted indoles. Despite several methods present in the literature for the synthesis of substituted indoles,[5] the development of simple, efficient and environmentally benign approaches for indole derivatives is highly desirable.

In our previous reports, we have demonstrated that phosphomolybdic acid (PMA) together with silica ($SiO_2$) works efficiently for organic transformations[6] such as the nucleophilic substitution reactions of aryl propargyl alcohols, propargylation of aromatic compounds and synthesis of β-keto enol ethers. In continuation of our efforts for exploring PMA–$SiO_2$ as an acid catalyst for multicomponent coupling reactions,[7] we herein describe a one-pot multicomponent condensation reaction of indole with aldehydes and *N*-methylaniline to form a novel skeleton of 3-substituted indoles (Scheme 1).

Initially, we investigated the multicomponent reaction of benzaldehyde, aniline and indole in dichloromethane in the presence of 5 mol % PMA–$SiO_2$ as a catalyst at room temperature. Unfortunately, the reaction did not proceed according to expectations. However, we were delighted to find that the reaction proceeded well when aniline and dichloromethane were replaced with *N*-methylaniline and acetonitrile[8] resulting in a novel 3-substituted indole as a single product. This result encouraged us to investigate further the scope of this methodology yielding 3-substituted indoles.

In due course, owing to the importance of green chemistry, we attempted similar transformations (coupling between benzaldehyde, *N*-methyl aniline and indole) in the absence of a solvent. Interestingly, we found that the reaction occurs much faster (1.75 h) than in the presence of a solvent ($CH_3CN$, 3.5 h). To study the role of PMA–$SiO_2$, an experiment was conducted in the presence of silica without PMA and we found that the reaction proceeds with longer periods (36 h with 70% yield). However, when PMA alone was used, the reaction occurred in 1.75 h resulting in the formation of the desired product (80% yield) along with a byproduct bisindolylmethane (10%). Thus the combination of PMA–$SiO_2$ was necessary to obtain a single desired product. With respect to the quantity of the catalyst, there was no significant enhancement in yields when the concentration was increased from 5 mol % to 20 mol %. Attempts were also made to study this protocol with TsOH and other Lewis acids such as $NbCl_5$, $FeCl_3$ and iodine (20 mol % each). With TsOH, the reaction progressed well with the formation of the corresponding product (80%) along with the byproduct bisindolylmethane (10%). In the case of $NbCl_5$ and $FeCl_3$ the bis indolyl products were the major products formed (>60%), whereas with iodine, the starting materials were recovered.

After optimizing the reaction conditions, different aldehydes, both aromatic and aliphatic, aromatic aldehydes with electron-donating and electron-withdrawing groups were investigated for the present protocol.[9] It was found that all the reactions proceeded well and produced the corresponding products in good yields (Table 1). All the products were characterized by $^1H$ NMR, $^{13}C$ NMR, IR and mass spectroscopy.[10] No significant change in yield was observed when either substituted indoles or substituted aromatic aldehydes were used. Surprisingly, cinnamaldehyde, butyraldehyde and *n*-octanal did not work under the present protocol.[11] Mechanistically, we presume that when *N*-methyl

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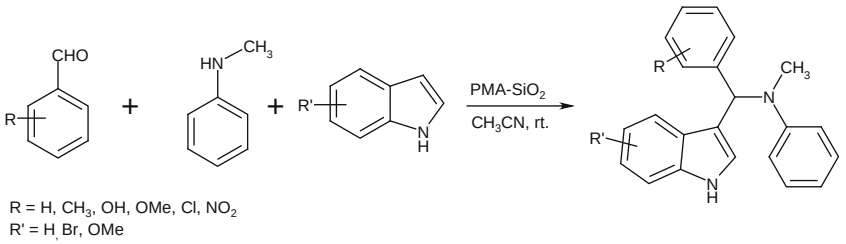



**Scheme 1.**

**Table 1**
Synthesis of 3-substituted indoles via multicomponent coupling reaction

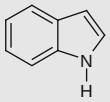
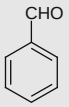
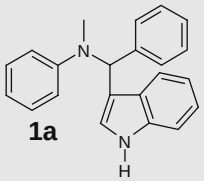
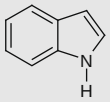
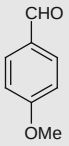
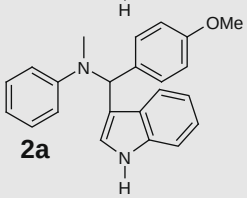
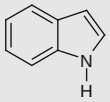
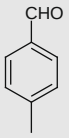
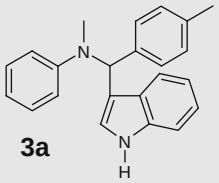
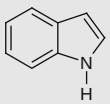
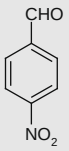
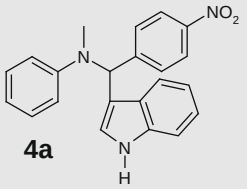
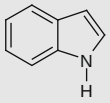
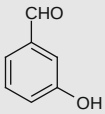
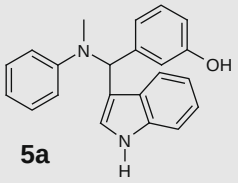
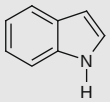
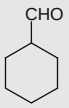
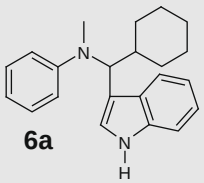
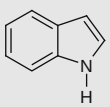
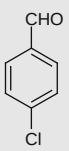
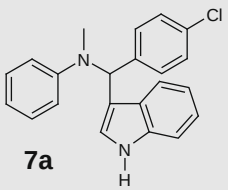
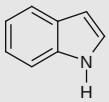
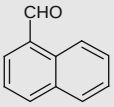
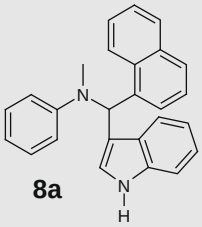
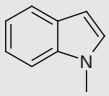
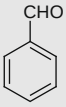
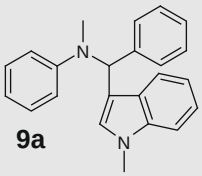
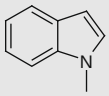
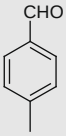
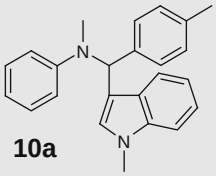
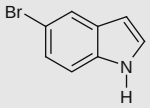
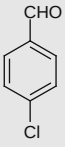
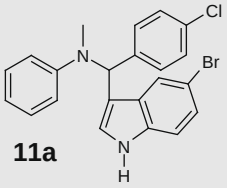
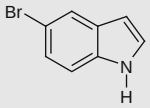
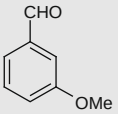
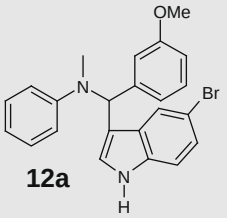
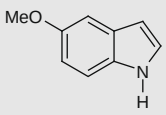
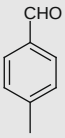
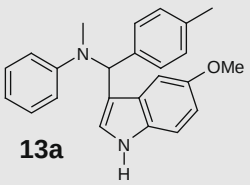
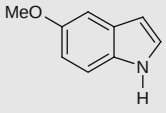
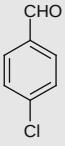
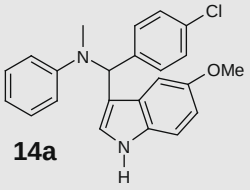
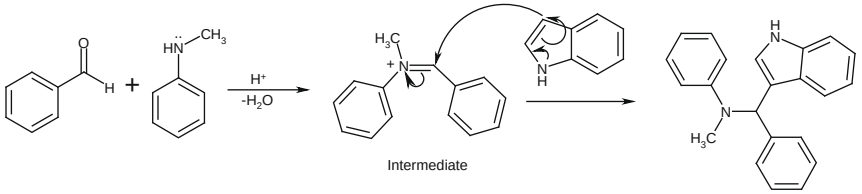
| Entry | Indole | Aldehyde | Product | Yield[a] (%) | Time[a] (h) | Yield[b] (%) | Time[b] (h) |
|---|---|---|---|---|---|---|---|
| 1 |  |  |  **1a** | 90 | 1.75 | 80 | 3.5 |
| 2 |  |  |  **2a** | 92 | 1.75 | 83 | 3.5 |
| 3 |  |  |  **3a** | 93 | 1.75 | 85 | 3.75 |
| 4 |  |  |  **4a** | 89 | 2.5 | 78 | 4.0 |
| 5 |  |  |  **5a** | 95 | 1.75 | 84 | 3.0 |
| 6 |  |  |  **6a** | 85 | 2.5 | 65 | 4.5 |
| 7 |  |  |  **7a** | 91 | 2.0 | 75 | 3.0 |

Table 1 (*continued*)

| Entry | Indole | Aldehyde | Product | Yield[a] (%) | Time[a] (h) | Yield[b] (%) | Time[b] (h) |
|---|---|---|---|---|---|---|---|
| 8 |  |  |  **8a** | 91 | 2.5 | 76 | 3.5 |
| 9 |  |  |  **9a** | 92 | 2.5 | 80 | 4.0 |
| 10 |  |  |  **10a** | 90 | 2.5 | 80 | 4.25 |
| 11 |  |  |  **11a** | 92 | 2.5 | 83 | 3.75 |
| 12 |  |  |  **12a** | 90 | 2.75 | 82 | 4.0 |
| 13 |  |  |  **13a** | 90 | 2.5 | 83 | 4.25 |
| 14 |  |  |  **14a** | 93 | 2.25 | 80 | 4.0 |

[a] Reaction performed under solvent-free conditions.
[b] Reaction performed with acetonitrile as solvent.




**Scheme 2.**

aniline is treated with aldehyde in the presence of acid, an iminium ion intermediate is formed which is attacked by an electron rich indole to get the 3-substituted indole (Scheme 2).

In conclusion, efficient synthesis of novel 3-substituted indoles has been achieved by a one-pot three-component coupling reaction of aldehyde, *N*-methylaniline and indole. Simple reaction procedures, inexpensive catalysts and single product formation make this an attractive protocol over the existing procedures.

## Acknowledgements

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## Supplementary data

Supplementary data (spectroscopic data of products **2a**–**5a**, **7a** and **9a**–**13a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.176.

## References and notes


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8. The reaction also works with THF as the solvent. However the duration of the reaction was found to be high (48 h with 80% yield) at rt.
9. *General procedure for multicomponent coupling reaction*: Solvent-free procedure: A mixture of aldehyde (1 mmol), *N*-methyl aniline (2 mmol)[12] and PMA–$SiO_2$ (5 mol %) was stirred at rt for 1 h and to this was added indole (1 mmol) and the reaction mixture was stirred till the completion of the reaction. The reaction mixture was diluted with diethyl ether and filtered over a sintered funnel. The filtrate was concentrated and the resulting product was purified by column chromatography. Procedure with solvent (acetonitrile): To a mixture of aldehyde (1 mmol), *N*-methyl aniline (2 mmol) in acetonitrile (5 mL) was added PMA–$SiO_2$ (5 mol%) and the reaction mixture was stirred at rt for 1 h. To this was added indole (1 mmol) and the reaction mixture was stirred till the completion of the reaction. The reaction mixture was filtered over a sintered funnel. The filtrate was concentrated and the resulting product was purified by column chromatography.
10. *Analytical data for few representative compounds*: **[***(1H-Indol-3-yl)-phenyl-methyl]-methyl-phenyl-amine* (**1a**): Brown solid, mp = 145–147 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.76 (s, 3 H), 5.54 (s, 1H), 6.51(d, *J* = 8.3 Hz, 3H), 6.09–7.04 (m, 3H), 7.09–7.38 (m, 9H), 7.81(s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 29.66, 47.91, 110.93, 112.37, 119.17 120.48, 121.86, 123.92,125.89, 127.03,128.11, 128.88, 129.65, 132.91, 136.65, 144.67, 147.52. IR (KBr): 453, 600, 738, 1450, 1611, 2855, 2923, 3417, 3361 $cm^{-1}$. ESIMS:*m/z* 313($M^+$+H). HRMS. calcd for $C_{22}H_{21}N_2$: 313.1704. Found 313.1701. *[(Cyclohexyl-(1H-indol-3-yl)-methyl]-methyl-phenyl-amine* (**6a**): Brown solid mp = 110–112 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$.819–1.02 (m, 2 H), 1.05–1.32 (m, 3H), 1.47–1.80 (m, 4H), 2.65 (s, 3H), 3.65 (d, *J* = 9.5 Hz, 1H), 4.05 (dd, *J* = 7.3, 13.9 Hz, 1H), 6.36 (d, *J* = 8.8 Hz, 2H), 6.76 (m, 2H), 6.88–7.07 (m, 6H), 7.44–7.55 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 48.89, 26.59, 30.81, 31.99, 32.46, 42.51, 48.89, 110.89, 118.80, 119.35, 119.82, 127.54, 128.91, 133.82, 147.01. IR (KBr): 422, 745, 1452, 1571, 1614, 2850, 2923, 3051, 3414 $cm^{-1}$. ESIMS: *m/z* 319($M^+$+H) HRMS calcd for $C_{22}H_{27}N_2$,329.2174. Found 329.1644. *[(1H-Indol-3-yl)-naphth-2-yl-methyl]-methyl-phenyl)-amine* (**8a**): Brown solid mp = 75–80 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.81 (s, 3 H), 6.27 (s, 1H), 6.41 (d, *J* = 2.1 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 2H), 6.87- 7.17 (m, 4H), 7.20–7.42 (m, 6H), 7.65–7.86 (m, 3H), 8.05 (d, *J* = 7.9 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 50.38, 63.30, 130.47, 131.94, 138.75, 139.39, 139.96, 141.44, 143.93, 144.09, 144.72, 144.88, 145.31, 146.14, 146.40, 146.54, 148.06, 149.40, 151.40, 151.97, 153.39, 156.81, 159.79, 167.06. IR (KBr): 486, 743, 788, 1092, 1453, 1515, 1612, 2922, 3048, 3412 $cm^{-1}$. ESIMS: *m/z* 362($M^+$+H). HRMS calcd for $C_{26}H_{23}N_2$,363.1861 Found 363.1850. *[(4-Chlorophenyl)-(5-methyloxy-1H-indol-3-yl)-methyl]-methyl-phenyl)-amine* (**14a**): Brown solid mp = 129–131 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.82 (s, 3H), 3.65 (s, 3H), 5.43 (s, 1H), 6.45–6.52 (m, 4H), 6.72–6.76 (m, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 7.10–7.24 (m, 6H), 7.27 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 21.21, 31.10, 47.70, 55.98, 102.28, 111.78, 112.01, 112.57, 120.55, 124.86, 127.71, 135.48, 128.96, 129.02, 129.81, 132.03, 133.30, 141.84, 147.71, 153.77. IR (KBr): 467, 818, 926, 1091, 1206, 1459, 1616, 1745, 2855, 2924, 3189, 3369 ESIMS: *m/z* 377($M^+$+H). HRMS calcd for $C_{23}H_{22}ClN_2O$ 377.1420 Found 377.1410.
11. Cinnamaldehyde gave mixture of unidentified spots with no desired product, whereas both *n*-octanal and *n*-butyraldehyde gave the corresponding bisindolyl alkanes in 60% yield.
12. Excess amine was used for allowing the complete consumption of aldehyde to give iminium ion leading to the formation of the desired product rather than the bisindolyl alkanes which may result from the free aldehyde if present.