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A simple and efficient procedure for the synthesis of 3-substituted indoles catalyzed by methane sulphonic acid

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ABSTRACT

A three component one-pot synthesis of 3-substituted indole derivatives by a coupling reaction between indole, aldehydes and amines catalyzed by methane sulphonic acid, under ambient conditions to afford 3-substituted indole in excellent yields, with short reaction time, simple procedure, easy work-up and ecofriendly reaction condition.

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KEYWORDS

Multicomponent reaction;
Methane sulphonic acid;
3-Substituted indole derivatives;
Green synthesis;
Iminium ion.

INTRODUCTION

In recent years, much interest has been attracted to the synthetic methods leading to indole derivatives, such as 3-substituted indoles due to their numerous biologically significant activities^[1]. These are common components of drugs and are also usually found to be of pharmaceutical importance in a variety of therapeutic areas^[2]. The feasibility of their 3-position for electrophilic substitution makes these 3-substituted indole derivatives as versatile intermediates in organic synthesis^[3]. The reaction of indoles with aldehydes, primary and secondary amines as electrophiles is, however, only sparsely reported^[4]. Green chemistry have focused significant interest on multicomponent reaction (MCR)^[5], where in at least three partners are added together to result in a single diverse complex structure which allow formation of several new bonds. The utility of MCR is well represented in the synthesis of privileged medicinal scaffolds.

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^[6], the development of simple, efficient and environmentally benign approaches for indole derivatives are highly desirable. In continuation of our efforts for exploring methane sulphonic acid (MSA) as an acid catalyst for multicomponent condensation reaction of indole with aldehydes and primary and secondary amines to form a skeleton of 3-substituted indoles (Scheme 1&2).

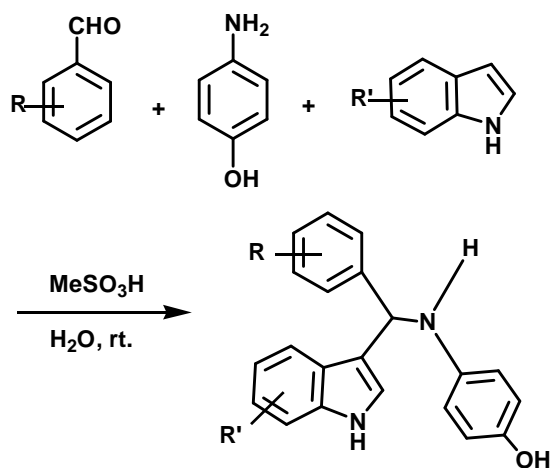
EXPERIMENTAL

Chemicals were purchased from Sigma-Aldrich, Merck and Lancaster, used as such without further purification. All solvents used for spectroscopy and other physical studies were reagent grade and were further purified by literature methods. Melting points (m.p.) were

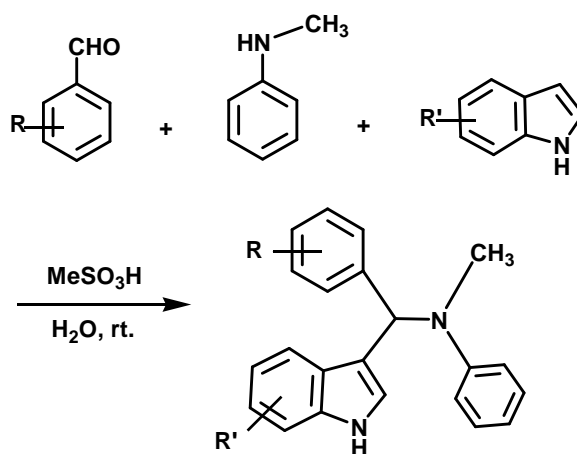
determined using a calibrated thermometer by Guna Digital Melting Point apparatus. Infrared spectra (IR) were recorded on a Nicolet 380 FT-IR spectrophotometer. Samples were recorded as potassium bromide (KBr) discs. Absorptions are reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded in $\text{DMSO}-d_6$ on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^1H , 100 MHz for ^{13}C NMR. The ^1H and ^{13}C chemical shifts are expressed in parts per million (ppm) with reference to tetramethylsilane (TMS). LC mass spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer.

RESULTS AND DISCUSSION

In the present method, we describe a mild, efficient, less reaction timing, high yielding efficient process for condensation reaction of various aromatic aldehydes, indole, and amines in the presence of MSA as a catalyst in water at room temperature (Scheme 1). Using this methodology these reactions were completed in shorter reaction times (2 to 3 min) with good yields (85-94%). It is noteworthy to mention that the green route method require simple workup procedures i.e. simple filtration to isolate the products as they are insoluble in water and the desired products were obtained with satisfactory yields without any further purification. Considering the reaction time, water as solvent and yield of products, this process was selected as green, environmental benign, clean and safe to promote the synthesis at room temperature of various 3-substituted indoles (TABLE 1).



Scheme 1



Scheme 2

This acceleration has been attributed to many factors, including the hydrophobic effect^[7], enhanced hydrogen bonding in the transition state^[8] and the high cohesive energy density of water ($550.2 \text{ cal}\cdot\text{mL}^{-1}$ at 25°C)^[9]. From previous studies^[10], above three effects are as follows, the first involves the motion that enforced hydrophobic interactions^[11] destabilize the initial state relative to the activated complex, thereby increasing the rate of the reaction in water. Secondly, hydrogen bonding of water to the activating group(s) stabilizes the polarized activated complex, leading to a significant rate enhancement. This is due to the small size of water molecule which allows efficient interaction with hydrogen bond acceptors by forming more hydrogen bonds than protic organic solvents. Hence, the rate of the reaction was increased in water. Thirdly, the cohesive energy density of water is high ($550.2 \text{ cal}\cdot\text{mL}^{-1}$ at 25°C) as it is able to form four hydrogen bonds with four other water molecules in a tetrahedral configuration, where as it is not possible in the case of organic solvents like methanol ($204 \text{ cal}\cdot\text{mL}^{-1}$ at 25°C), benzene ($85 \text{ cal}\cdot\text{mL}^{-1}$ at 25°C), tetra chloromethane ($74 \text{ cal}\cdot\text{mL}^{-1}$ at 25°C). This facilitates the water reactions faster. Recent computer simulations by Jorgensen et al^[12] strongly support these suggestions.

To find out the optimum quantity of MSA, the reaction of indole, benzaldehyde, and *para* hydroxy aniline/*N*-methyl aniline was carried out using different quantities of MSA in water medium (TABLE 1). A slight excess of the *para* hydroxy aniline was advantageous; therefore the molar ratio of indole, benzaldehyde, and *para* hydroxy aniline/*N*-methyl aniline was kept at 1:1:1.5, respectively. The reaction proceed through the

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in situ formation of iminium ion intermediate and indole acted as a nucleophile which reacted further, in the presence of a catalyst, with primary/secondary amine via conjugate addition to give 3-substituted indoles.

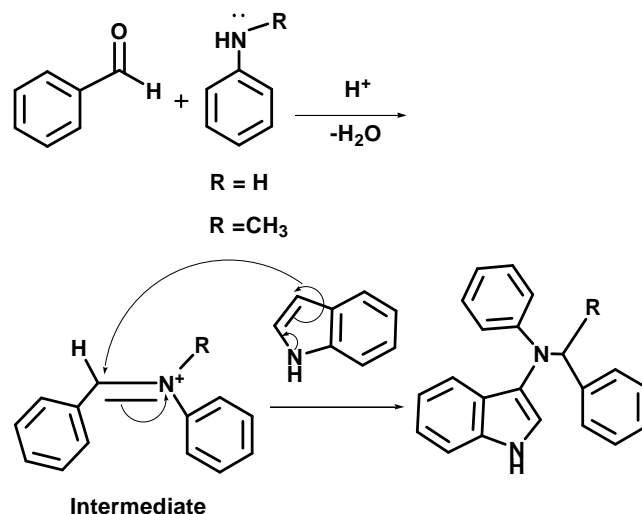
In order to understand the reaction scope and generality of the catalyst, a series of 3-substituted indoles were prepared in high yields using various aldehydes and primary/secondary amine. This catalyst worked excellently with aromatic aldehydes bearing electron-donating substituents as well as electron-withdrawing

groups. It was found that all the reactions proceeded well and produced the corresponding products in good yields (TABLE 1). No significant changes in yields were observed when either substituted indoles or substituted aromatic aldehydes were used. Surprisingly, aliphatic aldehydes did not work under the present protocol.

TABLE 1 : The effect of amount of MSA on the reaction of indole, amine and aldehyde^a

Entry	Catalyst (mol %)	Time (min)	Yield (%) ^b
1	0.25	50	46
2	0.5	35	59
3	0.75	20	77
4	1.0	10	86
5	1.25	5	90
6	1.5	2	94
7	2.0	2	94

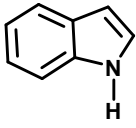
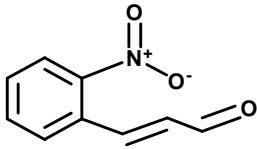
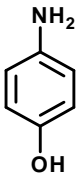
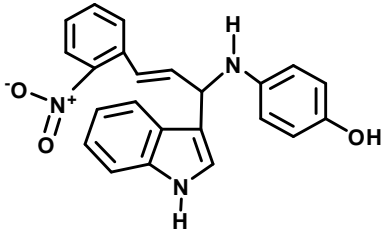
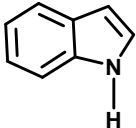
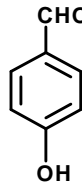
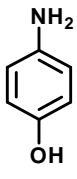
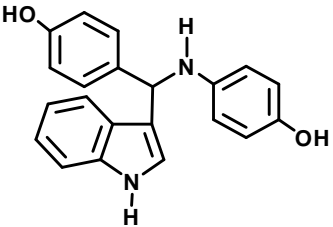
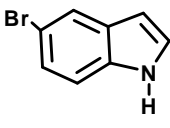
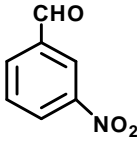
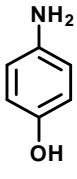
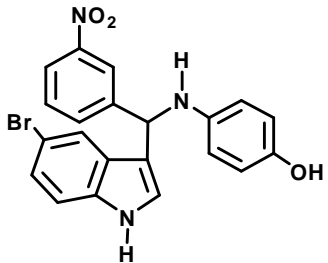
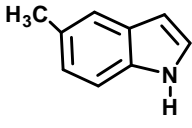
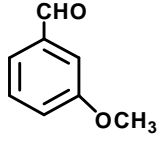
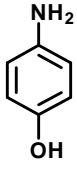
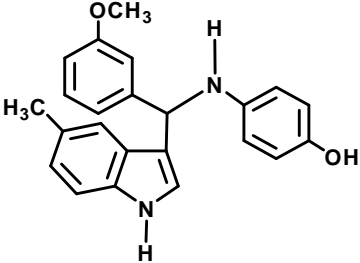
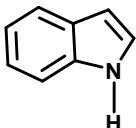
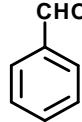
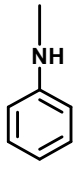
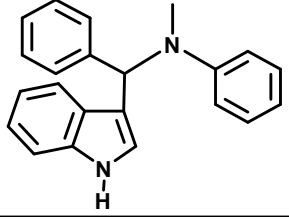
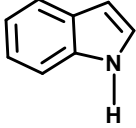
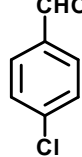
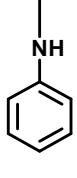
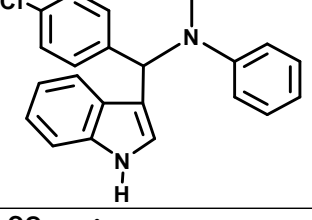
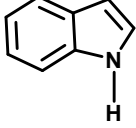
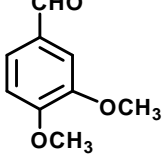
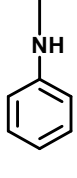
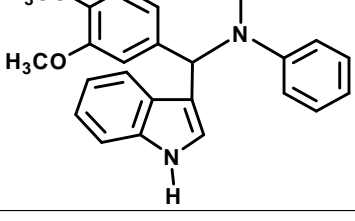
^aIndole (2 mmol), amine (2.5 mmol), aldehyde (2 mmol), reaction temp. 28-30 °C; ^bIsolated yield.



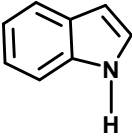
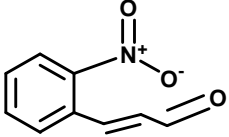
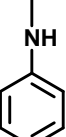
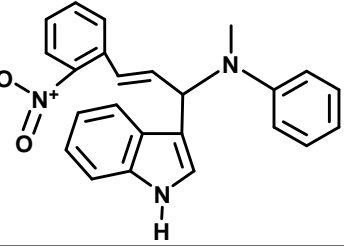
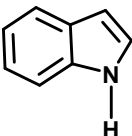
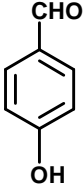
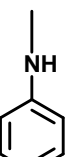
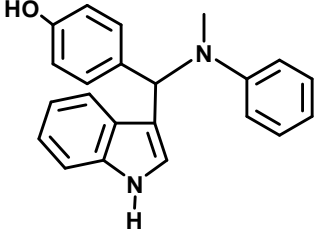
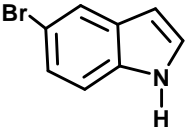
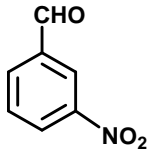
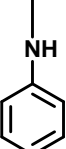
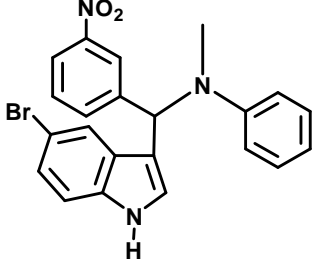
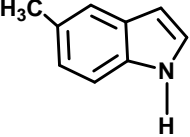
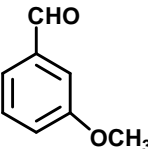
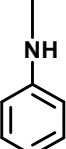
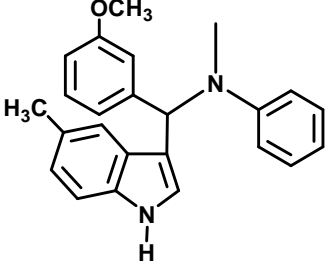
Scheme 3 : Suggested mechanism for the preparation of 3-substituted indole derivatives

TABLE 2 : Synthesis of 3-substituted indoles via multicomponent coupling reaction in the presence of MSA^a

Entry	Indole	Aldehyde	Amine	Product	Yield (%) ^b	Time (min)
1					92	2.0
2					91	3.0
3					89	3.0

Entry	Indole	Aldehyde	Amine	Product	Yield (%) ^b	Time (min)
4					87	3.0
5					92	2.0
6					94	2.0
7					92	2.0
8					93	2.0
9					90	3.0
10					87	3.0

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Entry	Indole	Aldehyde	Amine	Product	Yield (%) ^b	Time (min)
11					85	3.0
12					94	2.0
13					92	2.0
14					90	2.0

^aIndole (2 mmol), amine (2.5 mmol), aldehyde (2 mmol), reaction temp 28-30 °C; ^bIsolated yield.

General procedure for multicomponent coupling reaction

A mixture of indole (2 mmol), aldehydes (2 mmol), amine (2.5 mmol), and MSA (1.5ml) and water (5ml) were taken in round bottom flask (10ml). The reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the precipitated product was washed with water (4 x 10ml).

4-((1H-indol-3-yl)(phenyl)methylamino)phenol (1, C₂₁H₁₈N₂O)

Brown solid. Yield: 88%, m.p.: 132-134 °C; IR (KBr) ν cm⁻¹: 3475, 3380, 3023, 2922, 2855, 2361, 1730, 1662, 1612, 1564, 1470, 1353, 1310, 1243, 1216, 1176, 1045, 971, 919, 873, 820, 670, 625,

542, 505 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.89 (s, 1H), 8.14-8.23 (m, 5H), 8.02 (s, 1H), 7.92 (s, 1H), 7.76 (d, 1H), 7.63 (d, 1H), 7.53-7.62 (m, 8H) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 156.5, 147.6, 136.5, 134.7, 129.5, 128.3, 127.4, 123.0, 121.7, 120.8, 119.8, 118.8, 115.7, 113.5, 112.1, 111.1, 65.5; LCMS m/z: 315 [M+H]⁺.

4-((4-Hydroxyphenyl)(1H-indol-3-yl)methylamino)phenol (5, C₂₁H₁₈N₂O₂)

Brown solid. Yield: 88%, m.p.: 152-154 °C; IR (KBr) ν cm⁻¹: 3425, 3396, 3062, 3026, 2922, 2856, 2360, 1730, 1599, 1491, 1456, 1406, 1367, 1296, 1269, 1216, 1179, 1157, 1088, 1041, 1012, 969, 930, 881, 825, 666, 508; ¹H NMR (400 MHz, DMSO-*d*₆) δ : 10.85 (s, 1H), 10.0 (s, 1H), 7.69 (s, 1H), 7.30-

7.36 (m, 4H), 7.26 (d, 1H), 7.04 (d, 1H), 6.82-6.88 (m, 8H), 5.84 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 156.2, 146.8, 141.2, 136.8, 135.4, 128.5, 127.4, 123.2, 121.7, 119.8, 118.4, 117.5, 116.4, 114.8, 112.1, 111.1, 66.5 ppm; LCMS m/z: 331 [M+H] $^+$.

N-((1H-indol-3-yl)(phenyl)methyl)-N-methylaniline (8, C₂₂H₂₀N₂)

Brown solid. Yield: 88%, m.p.: 145-147 °C; IR (KBr) ν cm $^{-1}$: 3425, 3108, 2923, 2851, 2638, 2438, 2360, 2232, 2135, 1715, 1616, 1593, 1512, 1486, 1444, 1386, 1342, 1249, 1169, 1086, 1009, 896, 857, 804, 759, 738, 642, 616, 552; ^1H NMR (400 MHz, DMSO- d_6) δ : 7.76 (s, 1H), 7.70-7.72 (m, 5H), 7.67 (s, 1H), 7.47 (d, 1H), 7.25-7.32 (m, 8H), 5.70 (s, 1H), 2.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 149.5, 137.8, 136.6, 129.2, 128.5, 128.3, 127.8, 127.5, 123.6, 122.7, 121.3, 120.1, 118.9, 114.3, 112.1, 76.0, 36.1; LCMS m/z: 311 [M-H] $^+$.

4-((1H-indol-3-yl)(methyl(phenyl)amino)-methyl)-phenol (12, C₂₂H₂₀N₂O)

Brown solid, Yield: 88%, m.p.: 152-154 °C; IR (KBr) ν cm $^{-1}$: 3394, 3108, 2986, 2948, 2673, 2490, 2360, 1716, 1646, 1592, 1513, 1486, 1393, 1341, 1168, 1022, 892, 858, 759, 549; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.85 (s, 1H), 7.56 (s, 1H), 7.28-7.39 (m, 5H), 7.19 (d, 1H), 7.0 (d, 1H), 6.81-6.87 (m, 7H), 5.76 (s, 1H), 2.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 155.8, 149.5, 136.5, 130.6, 129.4, 129.2, 127.4, 122.9, 121.7, 115.3, 114.3, 118.8, 119.8, 112.1, 111.1, 76.0, 36.1. LCMS m/z: 329 [M+H] $^+$.

CONCLUSIONS

In summary, a reliable, simple, rapid, efficient and environmentally benign method for synthesis of 3-substituted indoles has been achieved by a one-pot three-component coupling reaction of aldehydes, primary and secondary amines and indole using 1.5 mol% MSA as a catalyst in aqueous medium at room temperature.

Some of the major advantages of this protocol are the ambient conditions, high yields, short reaction times, simple work-up procedure, single product

formation, use of water as a desirable solvent for chemical reaction for reasons of cost, safety and environmental concerns and employment of cheap catalyst MSA make this an attractive protocol over the existing procedures.

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