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Cupric acetate catalysed alkylation of indoles in water: A comparative study between conventional heating and microwave irradiation

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ABSTRACT

A green and facile method for the synthesis of bis(indolyl)methanes (BIMS) and Michael addition of indoles to α-β-unsaturated carbonyl compounds using cupric acetate in water as the catalytic medium is reported. The substitution of indoles occurred exclusively at C-3 and products of N-alkylation have not been observed. In case of C-3 substituted indoles, reactions occur at the C-2. The catalytic medium can be reused upto 3 times without losing its activity. A Comparative study between conventional and microwave heating is also reported.

KEYWORDS

Cupric acetate;
Water;
Microwave;
Michael addition;
Bis(indolyl)methanes.

INTRODUCTION

The development of new environmentally friendly reaction is a challenging goal for organic chemists[1-3]. Due to its low cost, reduced pollution, simplicity in process, and easy handling, the reaction in water has attracted attention in recent years. Many reactions which were thought to be impossible in water have been successfully carried out in the recent past[4a-b]. Besides being a green solvent, reactions in water are also clean and sustainable and can be easily extracted by organic solvents once the reaction is completed.

Owing to the great structural diversity of pharmacologically and biologically active indoles[5,6], it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents[7a-h]. For well over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed[8a-c]. In the context of medicinal chemistry the convergent synthesis of C-3 functionalized indoles became a priority. There are many methods to functionalize the C-3 position of the indole nucleus[9a-d] but very few of them have reported the alkylation at the C-2 position. Numerous methods for the preparation of BIMs employing protic acids or Lewis acids as catalysts have been reported in the literature, but there are still some drawbacks in these catalytic systems, such as the requirement for a large quantity of catalyst, long reaction times, poor yield of products, drastic conditions for catalyst preparation, or tedious workup that leads to the generation of large amounts of toxic waste[10-20]. In particular, the replacement of toxic, harmful solvents with less toxic and harmless solvents or green solvents is of interest from the viewpoint of safety of chemical processes. Moreover, the use of ubiquitous metals instead of rare metals is desirable because the availability of rare metals is limited, and their exhaustion is also a serious problem. Numerous reports have been pub-

lished over the last 40 years on the synthesis of bis(indolyl)methanes and its derivatives. Michael addition is one of the most important tools for the synthesis of 3-substituted indole derivatives[21-23]. However, from our literature survey, cupric acetate as a model catalyst has so far been unexplored. Hence, we turned our attention to the effective catalysis of cupric acetate in water as the reaction medium for the direct and conjugate alkylation of indole/substituted indoles. A comparative study between the conventional heating and microwave irradiation was also carried out in view of the significance of microwave irradiations in saving time which is fast developing as a convenient and eco-friendly mode of synthesis.

EXPERIMENTAL

Microwave reactions were carried out in a CEM Discover Benchmate microwave digester. Melting points were determined in open capillary tubes with Kumar's apparatus and are uncorrected. Infrared spectra were recorded on a BOMEM DA-8 FTIR instrument and the frequencies are expressed in cm^{-1}. ^1H and ^{13}C NMR (400 MHz) spectra were recorded on a Bruker Avance II-400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm downfield from internal tetramethylsilane and are given on the δ scale. Mass spectral data were obtained with a JEOL D-300 (EI) mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. All compounds give satisfactory elemental analyses within 0.4% of the theoretical values. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 254 0.2 mm thickness) and developed in an iodine chamber or under UVGL-15 mineral light 254 lamp. Column chromatographic separations were carried out using ACME silica gel (60–120 mesh).

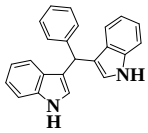
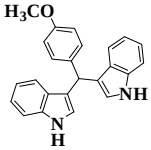
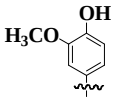
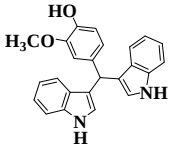
General procedure for conventional method

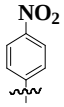
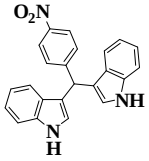
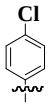
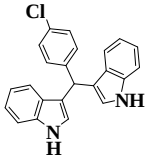
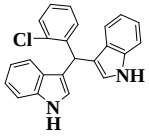
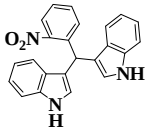
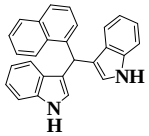
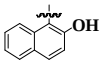
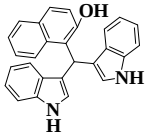
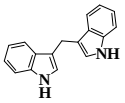
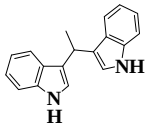
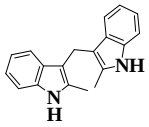
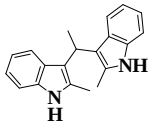
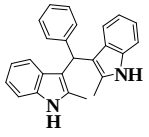
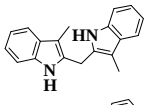
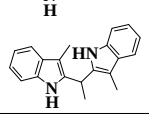
To a stirring mixture of indole (6.83 mmol) and benzaldehyde/ketone (4.27 mmol)/chalcone (6.83 mmol) in water, cupric acetate (0.2 mmol) was added. The reaction mixture was then refluxed at 100°C for 3-5 hrs (TABLE 1 & 2). After the completion of the reaction (monitored by TLC), it was extracted with ethyl acetate and the solvent distilled off under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford pure products in good to excellent yields.

General procedure for microwave assisted method

A mixture of the indole (6.83 mmol), benzaldehyde/ acetophenone (4.27 mmol) / chalcone (6.83 mmol) and cupric acetate (0.2 mmol) in water was irradiated in a microwave digester at 5-10 bar, 80-120 W, 180-250 seconds. After the reaction was completed (monitored by TLC) the resultant mixture was purified by column chromatography to afford the pure compound.

TABLE 1 : Comparative study of formation of bis-indolyl compounds from different aldehydes and indole/substituted indoles under reflux and microwave conditions.

Entry	R_1	R_2	R_3	R_4	Products	Reflux condition		Microwave condition	
						Time (hr)	Yield (%)	Time (s)	Yield (%)
3a	H	H		H		2	86	120	91
3b	H	H		H		2	84	120	91
3c	H	H		H		2	85	120	90

Entry	R_1	R_2	R_3	R_4	Products	Reflux condition		Microwave condition	
						Time (hr)	Yield (%)	Time (s)	Yield (%)
3d	H	H		H		1.5	88	60	94
3e	H	H		H		1.5	86	60	92
3f	H	H		H		1.5	86	60	90
3g	H	H		H		1.5	87	60	92
3h	H	H		H		2	87	120	90
3i	H	H		H		2	86	120	91
3j	H	H	H	H		2	85	120	92
3k	H	H	CH_3	H		2	86	120	90
3l	H	CH_3	H	H		1.5	78	120	85
3m	H	CH_3	CH_3	H		1.5	78	120	84
3n	H	CH_3		H		1.5	79	120	86
4a	CH_3	H	H	H		3	77	180	84
4b	CH_3	H	CH_3	H		3	79	180	85

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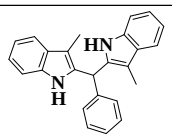
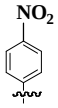
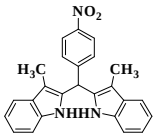
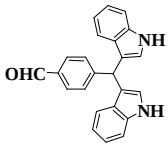
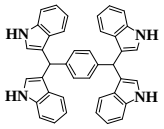
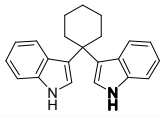
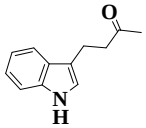
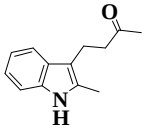
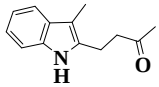
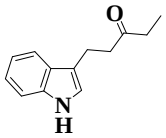
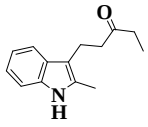
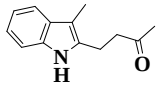
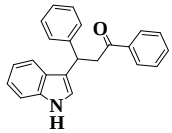
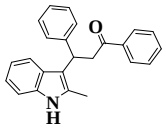
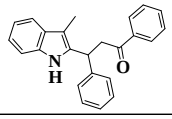
Entry	R_1	R_2	R_3	R_4	Products	Reflux condition		Microwave condition	
						Time (hr)	Yield (%)	Time (s)	Yield (%)
4c	CH_3	H		H		3	78	180	86
4d	CH_3	H		H		2	75	120	88
3o	H	H		H		1	46	120	50
3p	H	H		H		2	87	240	94
3q	H	H		---		2	81	220	90

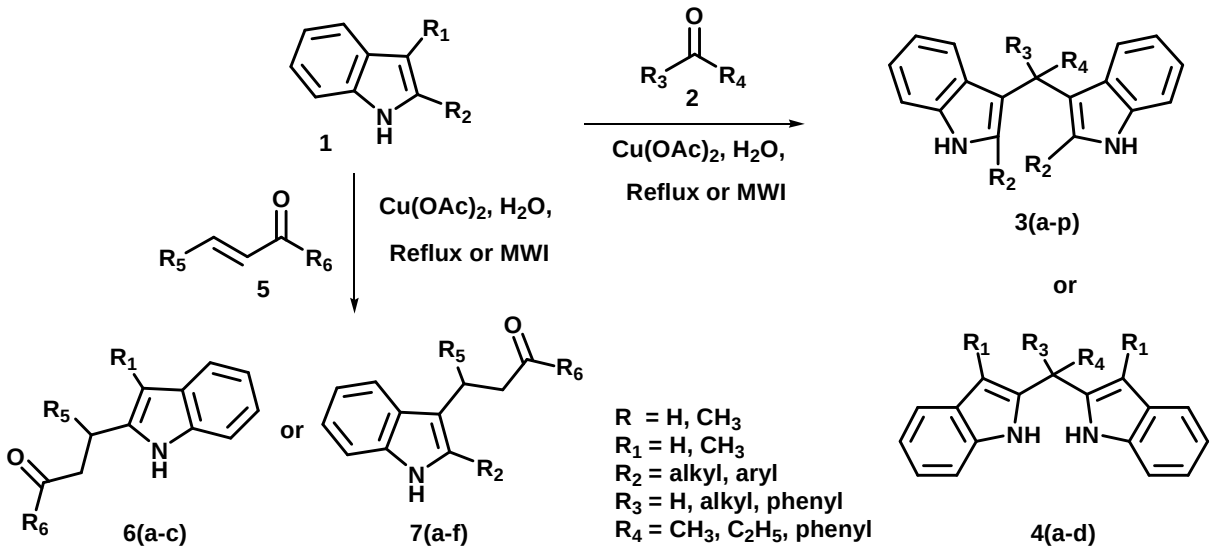
TABLE 2 : Comparison of reaction of indole/substituted indole with α,β-unsaturated ketones under reflux and microwave condition

Entry	R_1	R_2	R_5	R_6	Products	Reflux condition		Microwave condition	
						Time (hr)	Yield (%)	Time (s)	Yield (%)
7a	H	H	H	CH_3		1.5	89	120	93
7b	H	CH_3	H	CH_3		1.20	87	100	92
6a	CH_3	H	H	CH_3		2.5	82	240	87
7c	H	H	H	C_2H_5		1.5	88	120	92
7d	H	CH_3	H	C_2H_5		1.20	88	100	91
6b	CH_3	H	H	CH_3		2.5	82	240	87
7e	H	H				1.5	91	120	94

Entry	R_1	R_2	R_5	R_6	Products	Reflux condition		Microwave condition	
						Time (hr)	Yield (%)	Time (s)	Yield (%)
7f	H	CH_3				1.20	89	100	92
6c	CH_3	H				2.5	81	240	86

RESULTS AND DISCUSSION

Our present study mainly focuses on the synthesis of 2- and 3-substituted bis-indoles and 2- or 3-alkylation of indoles in water and their relative comparison with microwave assisted synthesis. ^1H and ^{13}C NMR spectra show that the products were obtained in good purity. For these one pot reactions of indole/substituted indoles and aldehydes/substituted benzaldehydes/ketones, it is noteworthy that these types of reactions have been mostly carried out in acetonitrile[24a,b] and since acetonitrile is a polar solvent miscible in water, we came to the generalization that it should work in water also. And true to our proposition, the reactions were not only successful in water (Scheme 1) but clean, easy to handle and most importantly increased the yield to a good extent. The conventional synthesis was carried out in refluxing condition in one pot till the completion of the reaction is observed in TLC. The reactants at first were not properly miscible in water but as the reaction progressed, it was found that the miscibility increased up to a favorable extent.

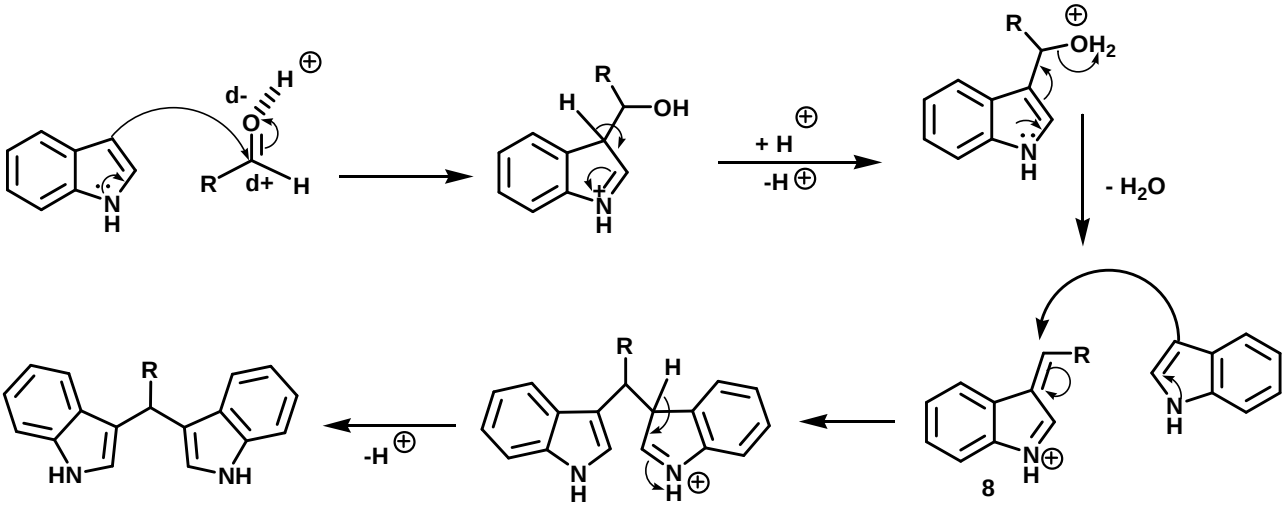


Scheme 1 : Alkylation of indole/substituted indole at the 2-position and 3-position

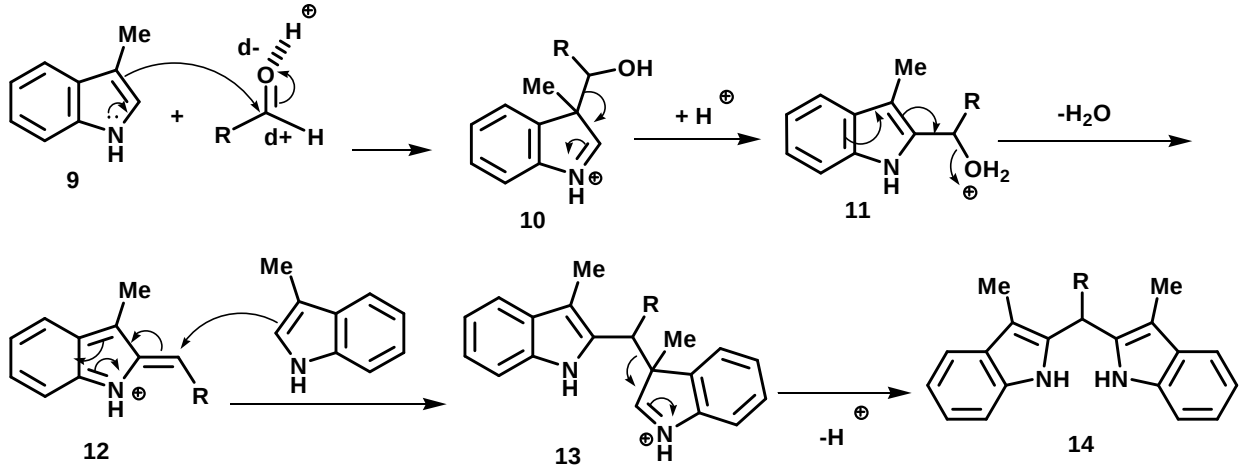
The mechanism (Scheme 2) has been proposed where, in the presence of cupric ions, the reaction seems to first forms azafulvenium salt **(8)**. **(8)** then undergo further reaction with a second molecule of indole to produce bis(indolyl)methanes. For the reaction of indole with α,β-unsaturated ketones, the reaction proceed by simple Michael type mechanism aided by the catalyst.

Same mechanism applies to the 2-substituted indoles in both direct addition to aldehydes and conjugate addition to α,β-unsaturated ketones, however when the 3-position of the indole moiety is blocked, attack first occurred at the 3-position followed by subsequent shift to the 2-position (Scheme 3). Formation of **(10)** and its rearrangement to **(11)** is followed by elimination of water to yield the cation intermediate **(12)**. **(12)** re-

act again with 3-substituted indole which leads to the formation of **(13)**. A final rearrangement of **(13)** gave the 2,22 - bis(indolyl)methanes **(14)**[25]. It was also observed that reactions of indoles and 2-substituted indoles gave predominantly 3-alkylated products (Scheme 1) without any N-alkylation, however, when the 3-position of indole is blocked, 2-alkylated products are obtained, and no N-alkylation product was observed.



Scheme 2 : Mechanism of BIM formation *via* azafulvenium salt 8



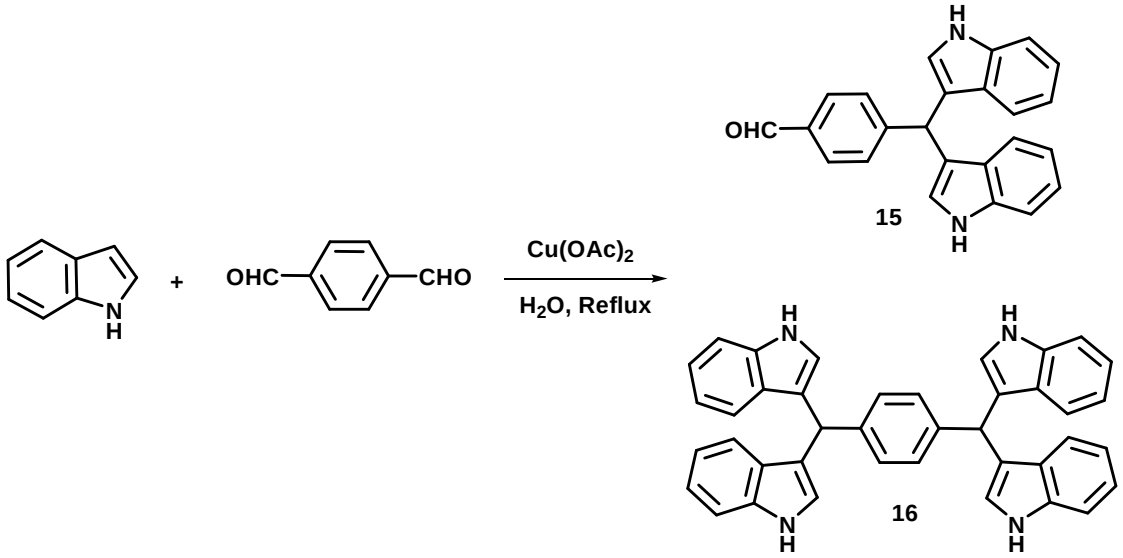
Scheme 3 : Rearrangement of indole substituents from position 3 to position 2

Mention may be made regarding the stoichiometry of the catalyst and the reactants for the formation of BIMs in our present strategy. Only a catalytic amount (0.25 equiv.) of cupric acetate has been used to standardize our reaction conditions. The reaction requires an excess of indole (2 equiv.), but at the end of the reaction, a small quantity of indole was always left out. The left over indole was recovered by column chromatography. In order to avoid this, the methodology was optimized by using only 1.6 equiv. of indole instead of 2 equiv. and these conditions proved to be general for a variety of indoles.

As shown in TABLE 1, aromatic aldehydes underwent smooth direct addition to the corresponding bis(indolyl)methanes in good to excellent yield in relatively short reaction times. It has been observed that the electronic properties of the aromatic ring have an effect on the rate of the reaction. In the conventional method, presence of electron-withdrawing groups (NO_2,Cl) in aldehydes (entries **(3d)** and **(3e)**) enhances the electrophillic substitution reaction with a lesser reaction time than electron donating groups, but in the microwave induced method, the effect of substituents has no significant effect on the reaction yields

and time. This indicated that the cupric acetate catalytic system has wide functional group tolerance. To prove the generality of this protocol, the reaction was then extended to a variety of ketones (TABLE 1) and also to aliphatic and aromatic α,β-unsaturated ketones (TABLE 2).

In this category of reactions, 2-methylindole was found to be more reactive than indole, giving the corresponding products in good to excellent yields. As shown in TABLE 2, the required reaction time for the reaction of aldehydes and ketones with 2-methylindole is shorter as compared to indole under the same reaction condition. But the reaction time required for the reaction of 3-methyl indole is a little more as compared to the other indoles. As expected, due to the steric crowding in corresponding BIMS, aliphatic and aromatic ketones (TABLE 2, entries **(6a)**, **(6b)** and **(6c)**) reacted with longer reaction times and their yields was lower. However, in microwave synthesis the presence of electron-withdrawing or electron-donating group did not affect much to the rate of conversion. As shown in Scheme 4, reaction of terephthalaldehyde with indole gave the corresponding products **(15)** and **(16)**. It was found that the reaction of 2 equiv. of indole with 1 equiv. terephthalaldehyde gave the corresponding BIM **(15)** with high selectivity (entry **(3o)**) while by using 4 equiv. of indole the corresponding product **(16)** was obtained with comparable yield (entry **(3p)**).

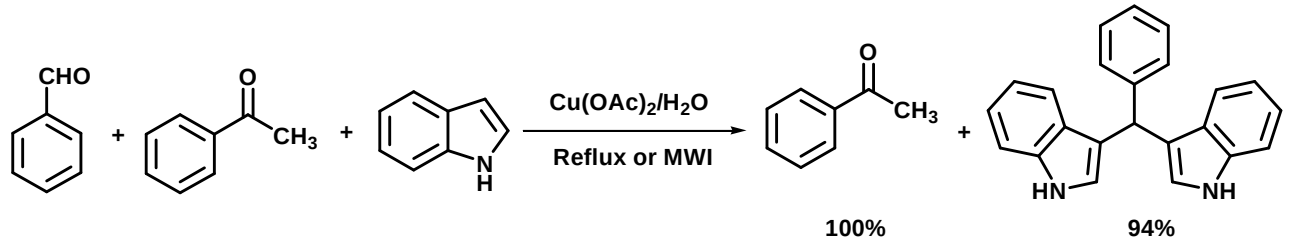


Scheme 4 : Reaction of indole with terepthaladehyde

During the past two decades many papers have described the successful combination of microwave irradiation as a nonclassical energy source with alternative reaction media. In continuation of our previous works[26] on unconventional means of organic reactions, we have carried out the microwave reactions under solvent free condition. It was successful but with some drawbacks like charring of the reaction mixture and danger of combustion of the starting materials when heated too strongly. Here water was used as the medium for refluxing as well as microwave irradiation. Both conventional heating as well as microwave irradiation showed similar observations except in the reaction time and yields.

The outstanding feature of this protocol is its high chemoselectivity for aldehydes. For example, when a 1:1 mixture of benzaldehyde and acetophenone was treated with indole in the presence of cupric acetate, only phenyl-3,3'-bis(indolyl)methane was obtained, while acetophenone was recovered in 100% (Scheme 5).

The reusability of the catalyst was also studied where after the reaction was completed, the products were extracted from the reaction mixture by ethyl acetate and the remaining aqueous part was reused without further treatment. As shown in Figure 1, the catalytic activities gradually decreased. However, even after three cycles, it still has moderate yields. It implied that the cupric acetate/water catalytic system can be reused at least three times without significant loss of activity.



Scheme 5 : Chemoselectivity of aldehyde in reaction with indole in the presence of a ketone

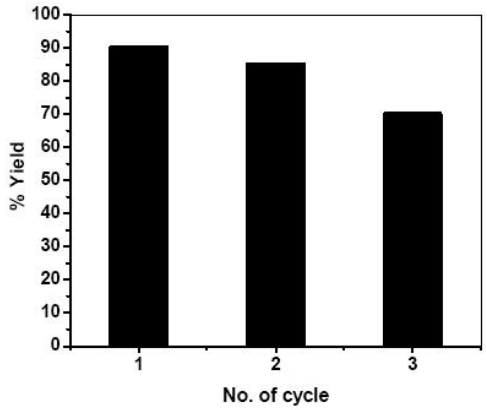


Figure 1 : Reusability studies of catalyst for synthesis of 3-((1*H*-indol-3-yl)(4-nitrophenyl)methyl)-1*H*-indole (TABLE 1, entry 3d)

SPECTROSCOPIC AND ANALYTICAL DATA

3-((1*H*-indol-3-yl)(phenyl)methyl)- 1*H*-Indole (3a)

m.p. 124–125ºC; IR(KBr) νcm^{-1}: 3390 (NH), 3100 (ArC-H), 2927, 1699, 1341; ^{1}H NMR (TMS) δ ppm : 7.84 (s, 2H, NH), 6.92-7.43 (m, 13H, Phenyl), 6.85 (s, 2H, N-CH=C), 5.81 (s, 1H, CH); ^{13}C NMR (TMS) δ ppm : 137.1, 136.5, 129.1, 128.4, 126.3, 124.9, 122.87, 121.9, 120.0, 118.9, 112.6, 111.4 and 40.7; MS (ESI): m/z 323 [M+1]; Anal. Calcd. for $C_{23}H_{18}N_2$ are: C, 85.68; H, 5.63; N, 8.69; Found: C, 85.58; H, 5.78; N, 8.49.

4-(di(1*H*-indol-3-yl)methyl)-2-methoxy phenol (3c)

m.p. 108–111°C; IR(KBr) νcm^{-1}: 3625 (OH), 3429 (NH), 2853, (ArC-H), 1613, 1341, 1096; ^{1}H NMR (TMS) δ ppm: 7.84 (s, 2H, NH), 6.70-7.33 (m, 11H, Phenyl), 6.57 (s, 2H, N-CH=C), 5.73 (s, H, CH), 5.43 (s, H, OH), 3.68 (s, 3H, OCH_3); ^{13}C NMR (TMS) δ ppm: 145.2, 142.7, 136.6, 135.0, 126.0, 122.5, 120.8, 120.2, 118.9, 118.1, 112.1, 110.3, 109.9, 54.8 and 38.8; MS (ESI): m/z 369 [M+1]; Anal. Calcd. for $C_{24}H_{20}N_2O_2$ are: C, 78.24; H, 5.47; N, 7.60; Found: C, 78.24; H, 5.47; N, 7.69.

3-(1-(1*H*-indol-3-yl)ethyl)-1*H*-indole (3k)

m.p. 137-142°C; IR(KBr) νcm^{-1}: 3387 (NH), 3001 (ArC-H), 2928, 1603, 1348; ^{1}H NMR (TMS) δ ppm: 7.74 (s, 2H, NH), 6.80-7.50 (m, 8H, Phenyl), 6.80 (s, 2H, N-CH=C), 4.61 (q, 1H, CH), 1.73 (d, 3H, CH_3); ^{13}C NMR (TMS) δ ppm: 136.5, 126.9, 122.3, 121.0, 120.7, 119.0, 118.8, 110.5, 28.1 and 21.1; MS (ESI): m/z 261 [M+1]; Anal. Calcd. for $C_{18}H_{16}N_2$ are: C, 83.04; H, 6.19; N, 10.76; Found: C, 83.13; H, 6.29; N, 10.46.

4-(di(1*H*-indol-3-yl)methyl)benzaldehyde (3o)

m.p. 205-207°C; IR(KBr) νcm^{-1}: 3387 (NH), 3111 (ArC-H), 2956, 1715 (C=O), 1683, 1342; ^{1}H NMR (TMS) δ ppm: 9.89 (s, 1H, CHO), 7.93 (s, 2H, NH), 6.92-7.73 (m, 12H, Phenyl), 6.59 (s, 2H, N-CH=C), 5.89 (s, 1H, CH); ^{13}C NMR (TMS) δ ppm: 190, 142.9, 135.1, 132.8, 129.5, 129.1, 126.8, 122.1, 121.8, 119.8, 117.0, 112.1, 110.8 and 45.1; MS (ESI): m/z 351 [M+1]; Anal. Calcd. for $C_{24}H_{18}N_2O$ are: C, 82.26; H, 5.18; N, 7.99; Found: C, 82.39; H, 4.93; N, 7.87.

3-((4-(di(1*H*-indol-3-yl)methyl)phenyl)(1*H*-indol-3-yl)methyl)-1*H*-indole (3p)

m.p. 197-200°C; IR(KBr) νcm^{-1}: 3389 (NH), 3189 (ArC-H), 2930, 1558, 1342; ^{1}H NMR (TMS) δ ppm: 7.44 (s, 2H, NH), 6.92-7.34 (m, 20H, Phenyl), 6.27 (s, 4H, N-CH=C), 5.70 (s, 2H, CH); ^{13}C NMR (TMS) δ ppm: 141.5, 136.6, 129.0, 128.5, 127.0, 123.6, 122.0, 121.7, 119.9, 118.1, 111.9, 110.9 and 45.1; MS (ESI): m/z 567 [M+1]; Anal. Calcd. for $C_{40}H_{30}N_4$ are: C, 84.78; H, 5.34; N, 9.89; Found: C, 84.48; H, 5.46; N, 9.72.

3-(1-(1*H*-indol-3-yl)cyclohexyl)-1*H*-indole (3q)

m.p. 137-142°C; IR(KBr) νcm^{-1}: 3890 (NH), 3201 (ArC-H), 2935, 1603; ^{1}H NMR (TMS) δ ppm:

7.82 (s, 2H, NH), 7.48-6.81 (m, 8H, Phenyl), 6.79 (s, 2H, N-CH=C), 1.56 (t, 4H, CH_2), 1.16 (t, 6H, CH_2); ^{13}C NMR (TMS) δ ppm: 135.2, 125.9, 122.0, 121.2, 119.0, 118.9, 112.0, 110.1, 42.1, 41.9, 25.6 and 20.8; MS (ESI): m/z 315 [M+1]; Anal. Calcd. for $C_{22}H_{22}N_2$ are: C, 84.04; H, 7.05; N, 8.91; Found: C, 84.14; H, 6.76; N, 9.06.

3-methyl-2-((3-methyl-1*H*-indol-2-yl)(phenyl)methyl)-1-*H*-indole (4c)

m.p. 123–125°C; IR(KBr) νcm^{-1}: 3320 (NH), 2919 (ArC-H), 1453, 1325; ^{1}H NMR (TMS) δ ppm: 7.52 (s, NH, 2H), 7.03-7.49 (m, 13H, Phenyl), 5.92 (s, 1H, CH), 2.09 (s, 6H, CH_3); ^{13}C NMR (TMS) δ ppm: 139.0, 134.2, 132.3, 133.4, 128.0, 127.4, 126.3, 120.6, 118.4, 117.4, 109.8, 107.6, 28.6 and 7.5; MS (ESI): m/z 351 [M+1]; Anal. Calcd. for $C_{25}H_{22}N_2$ are: C, 85.68; H, 6.33; N, 7.99; Found: C, 85.80; H, 6.23; N, 7.88.

3-methyl-2-((3-methyl-1*H*-indol-2-yl)(4-nitrophenyl)methyl)-1*H*-indole (4d)

m.p. 130-134°C; IR(KBr) νcm^{-1}: 3345 (NH), 3058 (ArC-H), 2919, 1453, 1325; ^{1}H NMR (TMS) δ ppm: 8.12 (s, 2H, NH), 7.06-8.10 (m, 12H, Phenyl), 6.01 (s, 1H, N-CH=C), 2.10 (s, 6H, CH_3); ^{13}C NMR (TMS) δ ppm: 144.1, 143.0, 135.5, 134.3, 129.8, 126.9, 121.2, 120.8, 119.5, 118.7, 109.9, 106.5, 33.3 and 9.5; MS (ESI): m/z 396 [M+1]; Anal. Calcd. for $C_{25}H_{21}N_3O_2$ are: C, 75.93; H, 5.35; N, 10.63; Found: C, 75.63; H, 5.48; N; 10.77.

1-(1*H*-indol-3-yl)pentan-3-one (7c)

m.p. 82-85°C; IR(KBr) νcm^{-1}: 3374 (NH), 2919 (ArC-H), 1706 (C=O), 1400; ^{1}H NMR (TMS) δ ppm: 7.87 (s, 2H, NH), 7.03-7.53 (m, 4H, Phenyl), 6.92 (s, 1H, N-CH=C), 2.99 (t, 2H, CH_2CO), 2.75 (t, 2H, CH_2), 2.35 (q, 2H, $\underline{C}H_2CH_3$), 2.99 (t, 3H, $CH_2\underline{C}H_3$); ^{13}C NMR (TMS) δ ppm: 210.4, 135.2, 126.1, 120.9, 120.4, 118.2, 117.6, 114.3, 110.1, 41.7, 35.0, 28.6 and 6.7; MS (ESI): m/z 202 [M+1]; Anal. Calcd. for $C_{13}H_{15}NO$ are: C, 77.58; H, 7.51; N, 6.96; Found: C, 77.33; H, 7.60; N, 7.07.

3-(1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (7e)

m.p. 130-133°C: IR(KBr) νcm^{-1}: 3350 (NH), 1672 (C=O), 1593, 1354; ^{1}H NMR (TMS) δ ppm: 7.89 (s, 2H, NH), 7.05-7.46 (m, 14H, Phenyl), 6.93 (s, 1H, N-CH=C), 4.99 (t, 1H, CH), 3.76 (dd, 1H, CH_2), 3.64 (dd, 1H, CH_2); ^{13}C NMR (TMS) δ ppm: 198.5, 144.2, 137.1, 136.6, 133.0, 128.5, 128.4, 127.8, 126.6, 126.2, 122.1, 121.4, 119.4, 119.3, 119.3, 111.1, 45.2 and 38.2; MS (ESI): m/z 326 [M+1]; Anal. Calcd. for $C_{23}H_{19}NO$ are: C, 84.89; H, 5.89; N, 4.30; Found: C, 84.76; H, 5.70; N, 4.50.

CONCLUSIONS

In summary, this paper demonstrates the versatility of the condensation of indoles with aldehydes and other aliphatic as well as aromatic α,β-unsaturated ketones with reasonable yields.

This method also offers several significant advantages such as green and sustainable, high conversions, easy handling, cleaner reaction profiles, and short reaction times in case of microwave irradiation, which makes it a useful and attractive process for the rapid synthesis of substituted indoles. A true test of the utility of a synthetic method is in its application to the synthesis of natural products or complex molecules. Due to the versatile application possibilities of BIMs and indole derivatives, there is a continuous quest for more efficient synthetic methods of indole derivatives and we believe to have provided a clean and green strategy.

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REFERENCES

[1] B.M.Trost; Science, **254**, 1471-1477 **(1991)**.
[2] B.M.Trost; Angew Chem.Int.Ed Engl., **34**, 259-281 **(1995)**.
[3] C.J.Li, B.M.Trost; Proc.Natl.Acad.Sci.USA, **105**, 13197-13202 **(2008)**.
[4] **(a)** F.Fringuelli, F.Pizzo, L.Vaccaro; J.Org.Chem., **66**, 4719-4722 **(2001)**; **(b)** B.Das, G.Satyalakshmi, K.Suneel, K.Damodar; J.Org.Chem., **74**, 8400-8402 **(2009)**.

[5] R.J.Sundberg; In the Chemistry of Indoles, Academic: New York, 113 **(1996)**.

[6] R.Livingstone; In Rodd's Chemistry of Carbon Compounds, M.F.Ansell, (Ed); Elsevier, Oxford, **(1984)**.

[7] **(a)** R.J.Sundberg; The Chemistry of Indoles, Academic Press: New York, **(1970)**; **(b)** R.J.Sundberg; Heterocyclic Chemistry, A.R.Katritzky, C.W.Rees, (Eds); Pergamon: Oxford, U.K, **4**, 313-376 **(1984)**; **(c)** R.J.Sundberg; In Best Synthetic Methods, Indoles, Academic Press: New York, 7-11 **(1996)**; **(d)** J.A.Joule; Indole and its Derivatives. Science of synthesis: Houben-Weyl methods of molecula transformations, E.J.Thomas, (Ed); George Thieme Verlag: Stuttgart, Germany, **(2000)**; **(e)** R.K.Brown; Indoles, W.J.Houlihan, (Ed); Wiley-Interscience: New York, **(1972)**; **(f)** R.J.Sundberg; Comprehensive Heterocyclic Chemistry II, A.R.Katritzky, C.W.Ress, E.F.V.Scriven, C.W.Bird, (Eds); Pergamon Press: Oxford, 119 **(1996)**; **(g)** G.W.Gribble; Comprehensive Heterocyclic Chemistry II, A.R.Katritzky, C.W.Ress, E.F.V.Scriven; C.W.Bird, (Eds); Pergamon Press: Oxford, 207 **(1996)**; **(h)** R.J.Sundberg; Indoles, Ed., Academic Press: London, **(1996)**.

[8] **(a)** G.W.Gribble; J.Chem.Soc.Perkin Trans 1, 1045-1075 **(2000)**; **(b)** U.Pindur, R.J.Adam; J.Heterocycl.Chem., **25**, 1-8 **(1988)**; **(c)** T.L.Gilchrist; J.Chem.Soc.Perkin Trans 1, 2491-2515 **(2001)**.

[9] **(a)** R.J.Sundberg; Indoles, Academic Press: San Diego, CA, 105-118 **(1996)**; **(b)** D.L.Comins, E.D.Stroud; Tetrahedron Lett., **27**, 1869-1872 **(1986)**; **(c)** V.G.Matassa, T.P Maduskuie, H.S.Shapiro, B.Hesp, D.W.Snyder, D.Aharony, R.D.Krell, R.A.Keith; J.Med.Chem., **33**, 1781-1790 **(1990)**; **(d)** A.R.Katritzky, X.Lan, J.N.Lam; J.Org.Chem., **6**, 4397-4403 **(1991)**.

[10] G.Babu, N.Sridhar, P.T.Perumal; Synth.Commun., **30**, 1609-1614 **(2000)**.

[11] D.Chen, L.Yu, P.G.Wang; Tetrahedron Lett., **37**, 4467-4470 **(1996)**.

[12] R.Nagrajan, P.T.Perumal; Chem.Lett., **33**, 288-290 **(2004)**.

[13] M.Chakrabarty, N.Ghosh, R.Basak, Y.Harigaya; Tetrahedron Lett., **43**, 4075-4078 **(2002)**.

[14] A.V.Reddy, K.Ravinder, V.L.N.Reddy, T.V.Goud, V.Ravikant, Y.Venkateswarlu; Synth.Commun., **33**, 3687-3694 **(2003)**.

[15] L.Wang, J.Han, H.Tian, J.Sheng, Z.Fan, X.Tang; Synlett., **2**, 337-339 **(2005)**.

[16] C.Ramesh, J.Banerjee, R.Pal, B.Das; Adv.Synth. Catal., **345**, 557-559 **(2003)**.

[17] P.R.Singh, D.U.Singh, S.D.Samant; Synth. Commun., **35**, 2133-2138 **(2005)**.

[18] W.J.Li, X.F.Lin, J.Wang, G.L.Li, Y.G.Wang; Synth. Commun., **35**, 2765-2769 **(2005)**.

[19] J.T.Li, H.G.Dai, W.Z.Xu, T.S.Li; Ultrason. Sonochem., **13**, 24-27 **(2006)**.

[20] Z.H.Zhang, L.Yin, Y.M.Wang; Synthesis, **12**, 1949-1954 **(2005)**.

[21] S.Y.Wang, S.J.Ji, T.P.Loh; Synlett., **15**, 2377 **(2003)**.

[22] S.J.Ji, S.Y.Wang; Synlett., **15**, 2074 **(2003)**.

[23] V.V.Perekalin, E.S.Lipina, V.M.Berestovitskaya, D.A.Efremov; Nitroalkenes, Wiley, Chichester, **(1994)**.

[24] **(a)** L.Mo, Z.Ma, Z.Zhang; Synth.Commun., **35**, 1997-2004 **(2005)**; **(b)** H.Firouzabadi, N.Iranpoor, A.A.Jafari; J.Mol.Catal.A: Chemical, **244**, 168-172 **(2006)**.

[25] K.M.Biswas, A.H.Jackson; Tetrahedron, **25**, 227 **(1969)**.

[26] S.Tumtin, I.T.Phucho, A.Nongpiur, R.Nongrum, J.N.Vishwakarma, B.Myrboh, R.L.Nongkhlaw; J.Heterocycl.Chem., **47**, 125-130 **(2010)**.