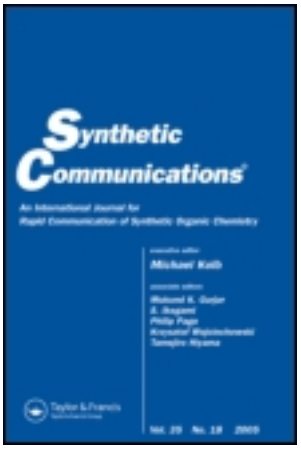

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$KHSO_4$-Assisted Michael Addition-Elimination Reactions of Indole with 3-Dimethylamino-1-phenylprop-2-en-1-ones in Water: An Environmentally Friendly Synthesis of Novel 3-Indolylchalcones

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$KHSO_4$-ASSISTED MICHAEL ADDITION–ELIMINATION REACTIONS OF INDOLE WITH 3-DIMETHYLAMINO-1-PHENYLPROP-2-EN-1-ONES IN WATER: AN ENVIRONMENTALLY FRIENDLY SYNTHESIS OF NOVEL 3-INDOLYLCHALCONES

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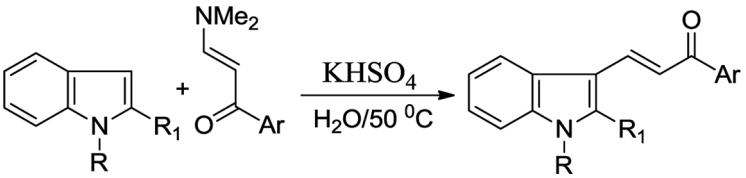
GRAPHICAL ABSTRACT



Abstract *$KHSO_4$-assisted Michael addition–elimination reactions of 2-methylindoles and 1,2-dimethylindoles with 3-dimethylamino-1-phenylprop-2-en-1-ones (**2**) in water, leading to the formation of 3-(2-methyl-1*H*-indol-3-yl)-1-arylpropenones (**3a–e**) and 3-(1,2-dimethy-1*H*-lindol-3-yl)-1-arylpropenones (**3f–j**) respectively in good to excellent yields have been reported. However, cyclodehydration of adducts **3a–f** to give carbazoles **4** failed to take place under the reaction conditions.*

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Keywords Enaminones; indoles; $KHSO_4$; Michael addition–elimination reactions

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Dedicated to Rev. Fr. Dr. Stephen Mavely, SDB, on his 60th birthday.

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INTRODUCTION

Water plays an essential role in life processes; however, its use as a solvent has been limited in organic synthesis. Despite the fact that it is the cheapest, safest, and most nontoxic solvent in the world, its presence is generally avoided through the dehydrative drying of substrates and solvents. The use of water as a medium for organic reactions is therefore one of the latest challenges for modern organic chemists. An excellent review about stereoselective organic reactions in water has been recently published.[1] A number of reports on the use of water as solvent for organic reactions have appeared in the recent past.[2–16]

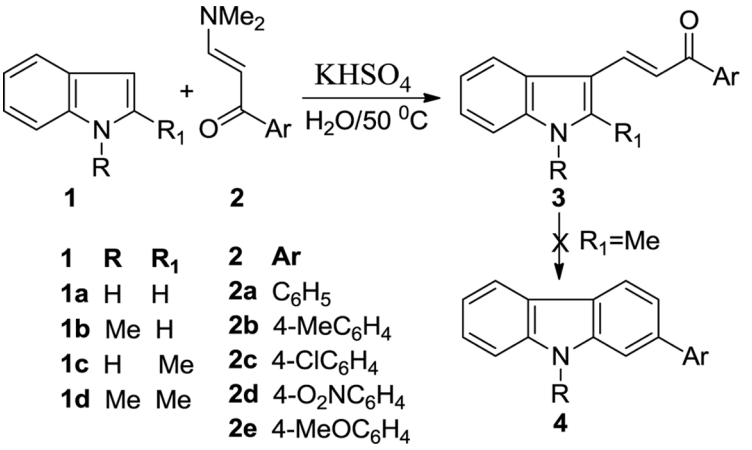
The indole scaffold is a prominent and privileged structural motif found in numerous natural products and various synthetic compounds. Recently, a number of indole-containing compounds have revealed remarkable pharmacological activity and their utility as therapeutic agents has attracted considerable attention from chemists.[17,18] Libraries based on the indole scaffold have been developed to address the need for novel drugs with increased potency.[19,20] Subsequently, the development of efficient methods that allow rapid access to functionalized indoles with different substitution patterns (at C-2, C-3, N-atom, and aromatic ring) constitutes an emerging area.[21]

Michael addition of indoles to electron-deficient olefins has been promoted by several Lewis acids such as $Yb(OTf)_3 \cdot 3H_2O$,[22] zirconium triflate,[23] samarium triiodide,[24] and $CeCl_3 \cdot 7H_2O$-NaI.[25] Catalytic asymmetric Lewis acid–mediated addition reactions with indoles have been reported.[26,27] However, the majority of Lewis acids cannot play their desired role in water because of the basic character of water molecules. Recently, aluminiumdodecylsulfate[28] and $KHSO_4$[29,30] have been shown to substitute for Lewis acids in water.

Our literature survey at this stage revealed that the reactions of indole with enaminones of type **2** have not been reported in the literature to the best of our knowledge, and hence as a part of our interest in the synthetic applications[31–33] of enaminones **2**,[34] we report herein the results of our studies on the reactions of indoles with enaminones **2** assisted by $KHSO_4$ in water, envisaging that addition–elimination product **3** formed in the case of 2-methylindoles could undergo cyclodehydration under the reaction conditions, leading to carbazoles **4**.

RESULTS AND DISCUSSION

The reaction of unsubstituted indole (**1a**) was taken up as a test case to evaluate the feasibility of addition and the optimum reaction conditions. The addition–elimination reaction of **1a** with **2a** assisted by $KHSO_4$ in water showed encouraging signs as an oily product started floating on water soon after starting the reaction. After the disappearance of the staring material (monitored by thin-layer chromatography, TLC), the crude product obtained was found to be a complex mixture from which no product could be isolated. All attempts to arrive at isolable products by varying the reaction conditions failed. We then turned our attention to the reaction of N-methylindole **1b** with **2a** under similar conditions. In this case, too, the result was equally discouraging as no product could be isolated from the complex reaction mixture formed.



Scheme 1. Reaction of indole with enaminone.

The reaction of 2-methylindole (**1c**) with **2a** was then undertaken under similar conditions. Thus, when an equimolar mixture of 2-methylindole (**1c**) and **2a** was treated with $KHSO_4$ in water, a solid product could be isolated in 81% yield, which was characterized as (*E*)-3-(2-methyl-1*H*-indol-3-yl)-1-phenylpropenone (**3a**) on the basis of spectral and analytical data. The reaction **1c** with enaminones **2b–e** was found to follow similar trend, giving adducts **3b–e** in 86–88% overall yields. The structures of **3a–e** were established with the help of spectral and analytical data (Scheme 1, Table 1). Thus, the infrared (IR) spectra showed strong peaks around 3200 cm^{-1} and 1640 cm^{-1} for NH and carbonyl groups respectively. The ^1H NMR spectra exhibited singlet in the vicinity of 8.6 ppm due to the N-H proton. The methyl protons at C-2 of indole resonated between 2.45 and 2.60 ppm. The signals due to vinylic protons appeared as doublets near 7.60 and 8.20 ppm with coupling constants close to 15 Hz, thereby confirming the *trans* geometry of the product (Fig. 1). We expected **3a** to undergo intramolecular cyclodehydration giving **4a**

Table 1. Synthesis of 3-(2-methyl-1*H*-indol-3-yl)-1-arylpropenones and 3-(1,2-dimethy-1*H*-lindol-3-yl)-1-arylpropenones

Product	R	R_1	Ar	Time (h)	Yield (%)	Mp (°C)
3a	H	Me	C_6H_5	5	81	183 (lit.[35] 183–184)
3b	H	Me	4-MeC_6H_4	3	88	210
3c	H	Me	4-ClC_6H_4	5	88	215
3d	H	Me	4-$O_2NC_6H_4$	3	86	237
3e	H	Me	4-$MeOC_6H_4$	3.5	86	170 (lit.[36][a])
3f	Me	Me	C_6H_5	5	90	115
3g	Me	Me	4-MeC_6H_4	4.5	80	139
3h	Me	Me	4-ClC_6H_4	3	80	158
3i	Me	Me	4-$O_2NC_6H_4$	4	90	180–181
3j	Me	Me	4-$MeOC_6H_4$	4.5	90	158–160

[a]Melting point not reported.

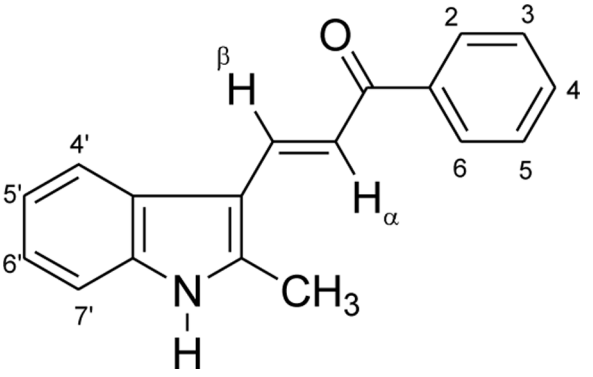
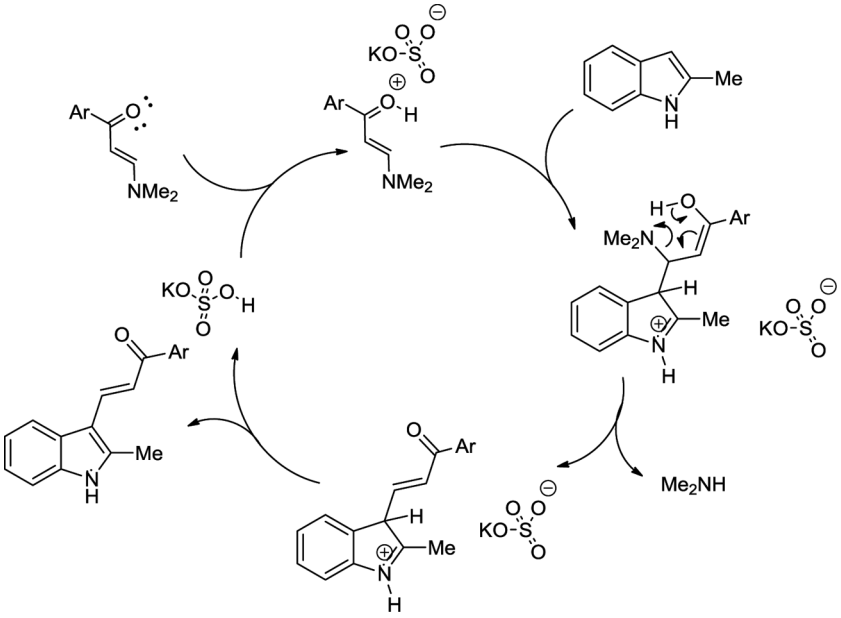


Figure 1. Stereochemistry of indolylchalcone.

under the reaction conditions but it failed, probably because of the presence of the enolizable NH proton.

At this stage, it was envisaged that if a methyl group replaces the NH proton, the protons of the 2-CH_3 group will attain a good degree of acidity and hence the chance of cyclodehydration leading to carbazole would be increased. Thus, when 1,2-dimethylindole (**1d**) was reacted with **2a** in the presence of $KHSO_4$ in water, the product isolated (90%) was found to be the usual addition–elimination product (**3f**) and no trace of the envisaged carbazole was formed. The reactions of **1d** with other enaminones **2b–e** were found to be equally facile under identical conditions, giving the corresponding addition-elimination products **3g–j** in 80–90% overall



Scheme 2. Plausible mechanism for the reaction of indole with enaminone.

yields. The structures of **3f–j** were also established with the help of spectral and analytical data. Our attempts, however, to cyclodehydrate **3** to yield the corresponding carbazoles **4** under various conditions are in progress. A plausible mechanism for the formation of **3a–j** has been rationalized in Scheme 2.

In summary, we have developed a facile and environmentally friendly strategy for the Michael addition–elimination reaction of indoles with formylated acetophenones in water as solvent. This methodology eliminates the use of hazardous organic solvents and involves a simple workup and isolation procedure.

EXPERIMENTAL

Melting points were recorded by the open capillary method and are uncorrected. The IR spectra were recorded on a BOMEM DA-8 FTIR instrument. High-resolution ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and two-dimensional (2D) NMR ^{1}H-^{1}H correlation spectrometry (COSY) and ^{1}H-^{13}C heteronuclear single quantum coherence (HSQC) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to tetramethylsilane (TMS) as internal reference. Fast atom bombardment (FAB)–mass spectra (MS) were measured on a Jeol 3SX102/DA-6000 mass spectrometer using argon as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Heraeus CHN-O-Rapid analyzer. Formylated acetophenones **2** were synthesized by our previously reported procedure.[34]

Reaction of 2-Methyl/1,2-dimethylindole with 3-Dimethylamino-1-arylpropenone

$KHSO_4$ (2 mmol) was added to a mixture of indole **1c** or **1d** (1 mmol) and enaminone **2** (1 mmol) suspended in water (4 mL), and the resulting mixture was stirred at 50 °C for 3–5 h. After the completion of the reaction (monitored by TLC), the oily product formed was extracted with dichloromethane (3 × 2 mL). The combined organic extract was washed with water (3 × 2 mL) and dried (Na_2SO_4), and the solvent was distilled off to give a viscous mass, which on trituration with hexane yielded a practically pure product. Further purification for analytical purposes was achieved by column chromatography over silica gel using 10% EtOAc–hexane for elution. Spectral and analytical data of two representative products are presented and the rest are given in the Supplementary Information, available online.

(*E*)-3-(2-Methyl-1*H*-indol-3-yl)-1-phenylpropenone (3a)

Pale yellow solid, mp 183 °C; IR (KBr): 3264, 1636, 1578 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 7.28 (m, 2H, 2H-indole), 7.38 (m, 1H, H-indole), 7.57 (m, 3H, 3H-phenyl), 7.62 (d, 1H, $J = 15$ Hz, H_α), 7.99 (m, 1H, H-indole), 8.10 (m, 2H, 2H-phenyl), 8.20 (d, 1H, $J = 15$ Hz, H_β), 8.76 (s, 1H, NH);^{13}C NMR ($CDCl_3$): δ 12.4 (CH_3), 110.7 (Cq), 111.2 (CH-indole), 116.4 (CH-α), 120.3 (CH-indole), 121.7 (CH-indole), 122.7 (CH-indole), 126.3 (Cq), 128.3 (2 CH-phenyl), 128.5 (2 CH-phenyl), 132.2 (CH-phenyl), 135.9 (Cq), 138.3 (CH-β), 139.3 (Cq), 142.2

(Cq), 190.9 (CO); MS: m/z 262 (MH^+). Anal. calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.62; H, 5.82; N, 5.34%.

(*E*)-3-(1,2-Dimethyl-1*H*-indol-3-yl)-1-phenylpropenone (3f)

Yellow solid, mp 115 °C; IR (KBr): 1643, 1556 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.62 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 7.33 (m, 3H, 3H-indole), 7.53 (m, 3H, 3H-phenyl), 7.62 (d, 1H, $J = 15$ Hz, H_α), 8.02 (m, 1H, H-indole), 8.09 (m, 2H, 2H-phenyl), 8.25 (d, 1H, $J = 15$ Hz, H_β); ^{13}C NMR ($CDCl_3$): δ 10.9 (CH_3), 30.1 (CH_3), 109.6 (CH-indole), 110.2 (Cq), 115.8 (CH-α), 120.4 (CH-indole), 121.7 (CH-indole), 122.4 (CH-indole), 125.7 (Cq), 128.2 (2 CH-phenyl), 128.5 (2 CH-phenyl), 132.0 (CH-phenyl), 137.8 (Cq), 138.3 (CH-β), 139.43 (Cq), 143.7 (Cq), 190.7 (CO); MS: m/z 276 (MH^+). Anal. calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.71; H, 6.19; N, 5.13%.

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