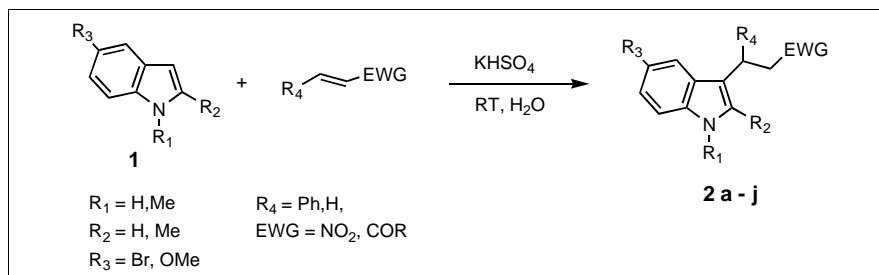


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The Michael addition of indoles to various electron deficient olefins was performed in water using potassium hydrogen sulphate as catalyst at room temperature.

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Introduction.

Indole is omnipresent in nature as constituent of many biologically active molecules. For example, the analgesic pravadoline and antiemetic ramoseton both have indole moiety in their structure. The hapalindole alkaloids represent a series of 20 compounds isolated from the blue green algae *Hapalosiphon fontinalis* by Moore and co-workers [1], incorporates indole moiety in their structure. They exhibit significant antibacterial and antimycotic activity and have attracted the interest of both synthetic and pharmaceutical chemists.

The major reason for regarding chemical industry as one of the causes for environmental pollution is attributed to ubiquitous use of organic solvents such as methanol, toluene, xylene, methyl ethyl ketone and methylene chloride [2]. Organic solvents because of their high vapour pressure and toxic nature is hazardous to the environment. Hence there is always a need for alternative to organic solvents. In this context, media such as water [3,4], ionic liquids [5], a low melt of sugar, urea and salt [6] are reported. Water on account of its ready availability, environmental friendly nature, low cost and non-toxic nature is certainly superior to all other alternatives. The notion of the special nature of water as a solvent for organic reactions began with the early examples of Diels-Alder reaction more than fifty years ago [6]. But there was no substantial progress in such reactions till last decade. The foremost reason why organic chemist refrained from using water as solvent is the poor solubility of the reactants in water and the venerable assumption that "substances do not interact unless dissolved". Hence a series of modification to enhance the solubility are attempted such as, (i) by the use

of surfactant [7], (ii) by ionic derivatisation [8] (iii) by the use of hydrophilic auxiliaries such as carbohydrates [9]. However these strategies detract from the simplicity and advantages sought from the use of water as perfect solvent.

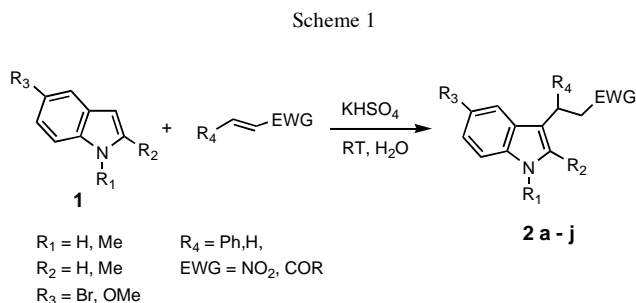
Michael addition of indoles to electron deficient olefins promoted by several Lewis acids such as, $\text{Yb}(\text{OTf})_3 \cdot 3\text{H}_2\text{O}$ [10], zirconium triflate [11], samarium triiodide [12], $\text{CeCl}_3 \cdot 7\text{H}_2\text{O} \cdot \text{NaI}$ [13]. Catalytic asymmetric Lewis acid mediated addition reactions with indoles have been reported by Jørgensen [14] and Umani-Ronchi [15]. However most of the Lewis acids cannot be used in water because water too has a Lewis basic site and therefore competes with the reactant for the Lewis acid especially when present in large excess as solvent. Aluminium dodecylsulphate [16] is recently shown to catalyse Michael addition of indoles in water. Recently the commonly available KHSO_4 is used as catalyst as a substitute for Lewis acids by us [17]. In continuation of our interest in the development of simple catalytic systems we successfully attempted yet another application of potassium hydrogen sulphate as catalyst for the Michael addition of indoles to various electron deficient olefins in water.

Results and Discussion.

Reaction involves stirring a heterogenous mixture of olefin and indole in water containing the catalyst at room temperature. With nitrostyrene, 2-methyl indole gives 94% yield of adduct and with methyl vinyl ketone, 5-methoxy indole gives maximum yield of 96% of the adduct.

It is worth mentioning that when the reaction was performed in methanol, where reactants are completely

soluble, the yield dropped substantially due to polymerizations of starting material in the acidic medium. However in water because of heterogeneity of the reaction mixture such polymerization does not take place and the desired reaction proceeds smoothly giving the Michael adduct in good to excellent yields.



In summary we have developed a simple and environmental friendly protocol for the Michael addition of indoles using water as solvent. This protocol eliminates the use of hazardous organic solvents and is operationally simple since the product can be easily isolated by a simple phase separation and the aqueous solution containing the catalyst can be reused.

EXPERIMENTAL

Representative Experimental Procedure.

To 0.260 g (1.74 mmol) of ω -nitrostyrene in water (10 mL) was added $KHSO_4$ 0.07 g (30 mol%) and the mixture stirred for 5 min and then 2-methylindole 0.256 g (1.74 mmol) was added and the stirring was continued and the progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was extracted with ethyl acetate (3x10mL) and ethylacetate was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure and the residue was column chromatographed over silica gel using ethylacetate / pet-ether (9.5/0.5) as eluent to get the pure product 0.45g (94%) yield.

Spectral Data for Selected Compounds.

(2a): Viscous oil; IR 3400, 3050, 1550, 1373 cm^{-1} ; 1H NMR (500MHz, $CDCl_3$): δ 8.08 (brs, NH, 1H), 7.46(d, J = 8.05 Hz, 1H.), 7.34-7.31(m, 5H), 7.28-7.27(m, 1H), 7.21(t, J = 8.05 Hz, 1H), 7.09(t, J = 8.0Hz, 1H.), 6.98(d, J = 2.25Hz, 1H.), 5.19(t, J = 8.0Hz, 1H.), 5.01(dd, J = 7.45, 12.6Hz, 1H.), 4.94(dd, J = 8.05, 12.6Hz, 1H.). ^{13}C NMR (125MHz, $CDCl_3$): δ 41.7, 77.4, 111.5, 114.4, 119.0, 120.0, 121.7, 122.7, 126.2, 127.6, 127.8, 129.0, 136.5, 139.3.

(2b): Colourless solid, m.p 72 $^{\circ}C$; IR 3058, 2918, 1551, 1469 cm^{-1} ; 1H NMR (500MHz, $CDCl_3$): δ 7.48(d, J = 8.0Hz, 1H.), 7.37-7.25(m, 7H), 7.09(d, J = 8.0Hz, 1H), 6.87(s, 1H), 5.20(d, J = 8.05, 1H), 5.05(dd, J = 8.05, 12.6Hz, 1H), 4.94(dd, J = 8.55, 12.6Hz, 1H.), 3.74(s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ

Table 1

S.No	Indole	Olefin	Michael adduct	Time(h)	Yield(%)
1				1.0	65
2				2.0	76
3				1.5	94
4				2.5	75
5				10.0	60
6				3.0	85
7				3.0	90
8				3.0	96
9				24	50 ^b
10				24	80 ^b

^a Isolated yields after column chromatography; ^b 20mol % of catalyst is used.

32.9, 41.6, 77.4, 109.6, 112.8, 119.1, 119.6, 122.3, 126.5, 126.6, 127.6, 127.8, 129.0, 137.3, 139.4

(2f): Pale orange solid m.p. 71– 73 $^{\circ}C$; IR 3014, 2880, 1695 1412 cm^{-1} ; 1H NMR (500MHz, $CDCl_3$): δ 8.12(brs, NH, 1H), 7.60(d, J = 8.4Hz, 1H), 7.34(d, J = 8.4 Hz, 1H), 7.23-7.13(m, 2H), 6.95(brs, 1H.), 3.07(t, J = 7.65 Hz, 2H), 2.85 (t, J = 7.65 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 209.2, 136.4, 127.2, 122.1, 121.6, 119.3, 118.7, 115.1, 111.3, 44.2, 30.1, 19.4.

(2j): Viscous oil; IR 3380, 2860, 1704, 1473 cm^{-1} ; 1H NMR (500MHz, $CDCl_3$): δ 7.89(brs, NH, 1H), 7.59(d, J = 7.65Hz, 1H), 7.25(d, J = 7.60Hz, 1H), 7.12-7.06(m, 2H), 3.44(t, J = 12.2Hz, 1H), 3.15(t, J = 12.2Hz, 1H), 2.66-2.64(m, 3H), 2.35(s, 3H), 2.18-2.04 (m, 4H.). ^{13}C NMR (125MHz, $CDCl_3$): δ 214.7,

146.9,135.4,129.4,126.8,120.9,119.0,116.5,110.6,50.5,44.1,37.9, 34.7,29.9,24.5, 12.2. Anal calcd for C₁₆H₁₉NO: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.65; H, 7.91; N, 5.78.

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