Efficient Conjugate Addition of 1*H*-Indoles to Electron-Deficient Olefins Catalyzed by Silica-Supported Sodium Hydrogen Sulfate ($NaHSO_4 \cdot SiO_2$)[1])

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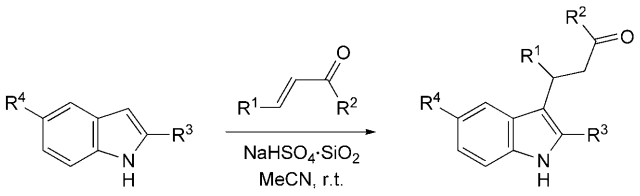
A simple, mild, rapid, and highly efficient method for the conjugate addition of 1*H*-indoles to electron-deficient olefins has been developed using $NaHSO_4 \cdot SiO_2$ as heterogeneous catalyst. The conversion proceeds at room temperature, and the corresponding *Michael* adducts are formed in good-to-excellent yields.

Introduction. – Indole moieties are frequently found in pharmaceuticals and biologically active compounds [1], and 3-substituted congeners are important building blocks for the synthesis of different therapeutic agents and natural products [2]. The general method for the synthesis of 3-alkylated indoles involves conjugate addition to electron-deficient olefins in the presence of H^+ [3] or *Lewis* acids [4]. However, acid-catalyzed reactions of indoles require precise control of acidity to avoid side reactions such as dimerization or polymerization. Moreover, harsh reaction conditions, expensive reagents, long reaction times, low yields, and tedious experimental procedures are disadvantages of many reported methods.

Results and Discussion. – In continuation of our work on the development of useful synthetic methodologies [5], we recently observed that silica-supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) efficiently catalyzes the conjugate addition of 1*H*-indoles to electron-deficient olefins to form the corresponding *Michael* adducts at room temperature (*Scheme*). A variety of indoles and activated olefins were, thus, tested to elucidate the scope of the reaction.

Scheme



[1]) Part 120 in the series 'Studies on Novel Synthetic Methodologies'; IICT Communication No. 070108.

As can be seen from the *Table*, good-to-excellent yields were obtained for the condensation of various 1*H*-indoles and olefinic substrates. Both unsubstituted 1*H*-indoles as well as indoles carrying a substituent at C(2) or at the benzene ring readily underwent the reaction, giving rise to 3-substituted *Michael* adducts in yields of 79–98%. In the case of 3-methyl-1*H*-indole (*Entries 3* and *6*), 2- instead of 3-substituted indole adducts were obtained, and the yields were somewhat lower (67–69%). As activated olefins, a series of α,β-unsaturated ketones and nitro compounds were used. With aliphatic enones (acyclic or cyclic) and α,β-unsaturated nitro compounds, the reactions were complete within 2–15 min. In the case of α,β-unsaturated carbonyl compounds carrying a conjugated aromatic ring, the reaction time was 30–35 min (*Entries 8–12*).

Most of the earlier reported methods for the preparation of 3-substituted 1*H*-indoles by conjugate addition require much longer reaction times [3][4]. Also, our synthetic protocol is very simple, and inert atmospheric conditions are not needed. As a further advantage, the indole N-atom does not have to be protected, since no *N*-alkylation [6] takes place under the reaction conditions.

The catalyst, $NaHSO_4 \cdot SiO_2$, works under heterogeneous conditions. In recent years, heterogeneous catalysts have gained importance in various organic transformations due to their reactivity as well as for economic and environmental reasons. $NaHSO_4 \cdot SiO_2$ has been found to be highly efficient in the present conversion. It can easily be prepared [7] from inexpensive, readily available, and non-toxic $NaHSO_4$ and silica gel (SiO_2), and it can conveniently be removed from the reaction mixture by simple filtration. In the present reaction, no product was formed in the absence of catalyst.

In conclusion, we have developed a method for the conjugate addition of 1*H*-indoles to electron-deficient olefins in the presence of $NaHSO_4 \cdot SiO_2$. Our protocol has the advantages of being mild, fast, simple, inexpensive, and high-yielding.

We wish to thank *CSIR* and *UGC*, New Delhi, for financial assistance.

Experimental Part

General. ^{1}H-NMR Chemical shifts δ and coupling constants J are given in ppm (rel. to Me_4Si) and in Hz, resp. Mass-spectrometric (MS) data are reported in m/z. Elemental-analyses data are reported in %.

General Procedure. To a mixture of an 1*H*-indole (1 mmol) and an electron-deficient olefin (1 mmol) in MeCN (1 ml) is added $NaHSO_4 \cdot SiO_2$ (30 mg) [7], prepared by addition of silica gel (200–400 mesh, 10 g) to a soln. of $NaHSO_4 \cdot H_2O$ (4.14 g) in H_2O (20 ml) followed by gently heating on a hot plate for 0.5 h to make a free-flowing white solid, which was further dried in an oven at 120° for 48 h prior to use. The mixture is stirred at r.t., the progress of the reaction being monitored by TLC. After completion, the catalyst is separated by filtration, the solvent is removed under reduced pressure, and the residue is subjected to column chromatography (SiO_2; hexane/AcOEt) to afford the pure *Michael* adduct. The anal. data of some representative products are given below.

*1-(1*H*-Indol-3-yl)pentan-3-one* (*Table*, *Entry 5*). Solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.89 (br. *s*, 1 H); 7.52 (*d*, J = 8.0, 1 H); 7.28 (*d*, J = 8.0, 1 H); 7.16–7.04 (*m*, 2 H); 6.91 (*d*, J = 1.5, 1 H); 3.02 (*t*, J = 7.0, 2 H); 2.78 (*t*, J = 7.0, 2 H); 2.36 (*q*, J = 7.0, 2 H); 1.01 (*t*, J = 7.0, 3 H). FAB-MS: 201 ($[M+H]^+$). Anal. calc. for $C_{13}H_{15}NO$: C 77.61, H 7.46, N 6.96; found: C 77.56, H 7.41, N 6.90.

Table. *Conjugate Addition of 1H-Indoles to Activated Olefins in the Presence of $NaHSO_4 \cdot SiO_2$ as Catalyst in MeCN at Ambient Temperature*

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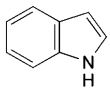
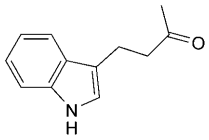
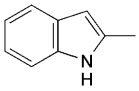
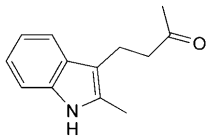
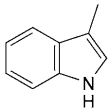
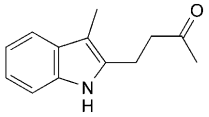
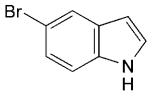
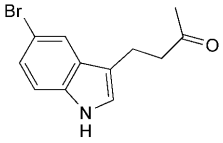
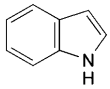
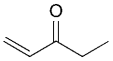
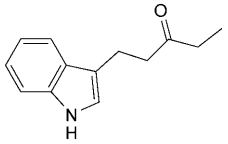
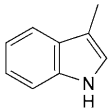
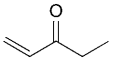
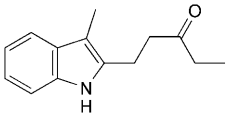
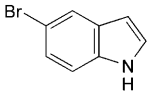
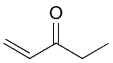
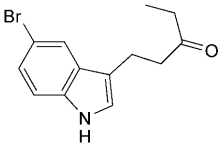
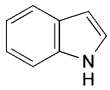
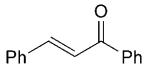
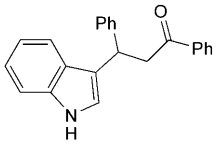
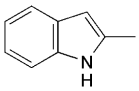
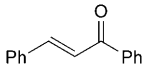
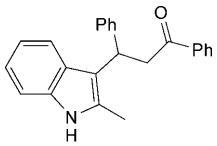
1				5	98
2				5	94
3				15	69
4				5	89
5				5	88
6				15	67
7				5	85
8				30	84
9				30	82

Table (cont.)

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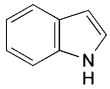
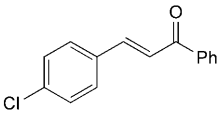
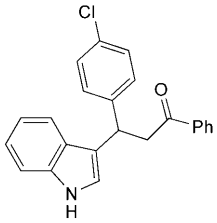
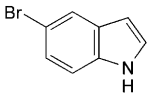
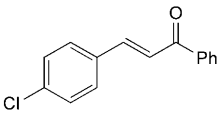
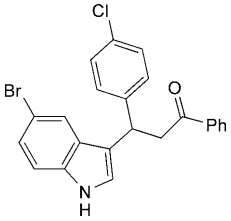
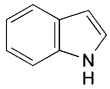
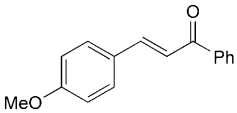
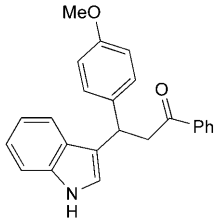
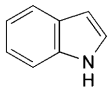
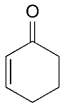
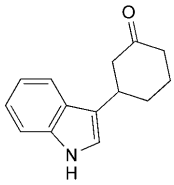
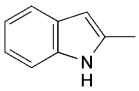
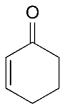
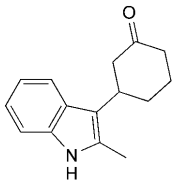
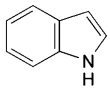
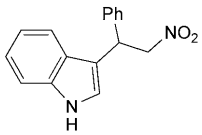
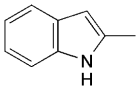
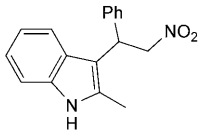
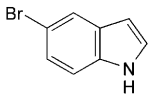
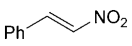
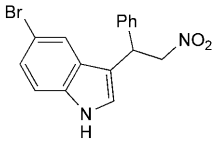
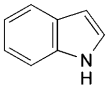
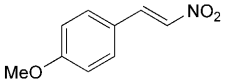
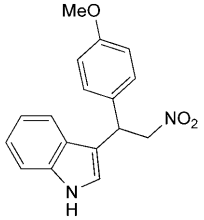
10				35	79
11				35	76
12				30	81
13				5	82[b])
14				5	80[b])
15				2	92
16				2	90

Table (cont.)

Entry	Indole	Olefin	Product	Time [min]	Yield [%][a])
17				2	88
18				5	91

[a]) After column-chromatographic purification. [b]) Some 10% of the corresponding higher adduct was also obtained.

*1-(5-Bromo-1*H*-indol-3-yl)pentan-3-one* (*Table*, *Entry 7*). Solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.04 (br. *s*, 1 H); 7.70 (*s*, 1 H); 7.31–7.22 (*m*, 2 H); 7.00 (*d*, $J=1.5$, 1 H); 3.02 (*t*, $J=7.0$, 2 H); 2.81 (*d*, $J=7.0$, 2 H); 2.42 (*q*, $J=7.0$, 2 H); 1.08 (*t*, $J=7.0$, 3 H). FAB-MS: 282/280 ($[M+H]^+$). Anal. calc. for $C_{13}H_{14}BrNO$: C 55.17, H 5.00, N 5.00; found: C 55.22, H 5.08, N 5.12.

*3-(4-Chlorophenyl)-3-(1*H*-indol-3-yl)-1-phenylpropan-1-one* (*Table*, *Entry 10*). Solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.98 (br. *s*, 1 H); 7.90 (*d*, $J=8.0$, 1 H); 7.59–7.05 (*m*, 11 H); 7.03–6.90 (*m*, 2 H); 5.01 (*dd*, $J=7.0$, 5.5, 1 H); 3.78 (*dd*, $J=12.5$, 5.5, 1 H); 3.62 (*dd*, $J=12.5$, 7.0, 1 H). FAB-MS: 362/360 ($[M+H]^+$). Anal. calc. for $C_{23}H_{18}ClNO$: C 76.77, H 5.01, N 3.89; found: C 76.63, H 5.12, N 3.91.

*3-(5-Bromo-1*H*-indol-3-yl)-3-(4-chlorophenyl)-1-phenylpropan-1-one* (*Table*, *Entry 11*). Solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.99 (br. *s*, 1 H); 7.89 (*d*, $J=8.0$, 1 H); 7.56–7.40 (*m*, 4 H); 7.26–7.13 (*m*, 7 H); 6.92 (*d*, $J=1.5$, 1 H); 4.97 (*dd*, $J=7.0$, 5.5, 1 H); 3.71 (*dd*, $J=12.0$, 5.5 1 H); 3.61 (*dd*, $J=12.0$, 7.0, 1 H). FAB-MS: 442/440/438 ($[M+H]^+$). Anal. calc. for $C_{23}H_{17}BrClNO$: C 62.97, H 3.88, N 3.19; found: C 62.91, H 3.82, N 3.23.

*5-Bromo-3-(2-nitro-1-phenylethyl)-1*H*-indole* (*Table*, *Entry 17*). Solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.28 (br. *s*, 1 H); 7.50 (*d*, $J=1.5$, 1 H); 7.45–7.18 (*m*, 7 H); 7.03 (*d*, $J=1.5$, 1 H); 5.11 (*dd*, $J=7.0$, 5.5, 1 H); 5.01–4.79 (*m*, 2 H). FAB-MS: 347/345 ($[M+H]^+$). Anal. calc. for $C_{16}H_{13}BrN_2O_2$: C 55.65, H 3.76, N 8.11; found: C 55.58, H 3.81, N 8.17.

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