Silica Supported Sodium Hydrogen Sulfate and Amberlyst-15: Two Efficient Heterogeneous Catalysts for Facile Synthesis of Bis- and Tris(1*H*-indol-3-yl)methanes from Indoles and Carbonyl Compounds[1]

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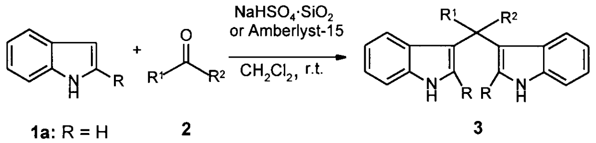
Abstract: Bis- and tris(1*H*-indol-3-yl)methanes are synthesized in high yields by an electrophilic substitution reaction of indoles with carbonyl compounds under mild reaction conditions using two efficient heterogeneous catalysts, silica supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) and amberlyst-15. The second catalyst can be reused.

Keywords: aldehydes; amberlyst-15; bisindolylmethanes; indoles; ketones; $NaHSO_4 \cdot SiO_2$; trisindolylmethanes

Indoles are known to possess various biological properties including antibacterial, cytotoxic, antioxidative and insecticidal activities.[2] Some indole derivatives are used as antibiotics in pharmaceuticals.[2b] The preparation of different indole compounds and evaluation of their bioactivity are now highly essential. Indoles can readily undergo electrophilic substitution reactions with carbonyl compounds in the presence of a suitable catalyst to form bis- and tris(1*H*-indol-3-yl)methanes. Different protic acids[2a,3] and Lewis acids [4] are known to catalyze this reaction and most of these catalysts work under homogeneous conditions. The protic acids (e.g., HCl and H_2SO_4) and Lewis acids (e.g., BBr_3 and BF_3) which are generally used are hazardous and difficult to handle and remove from the reaction mixture. Some of the reported catalysts may decompose the indoles or disturb the functionalities. Several catalysts are also not readily available or expensive.

In recent years different heterogeneous catalysts have successfully been applied to carry out various chemical transformations. Environmental and economical considerations prompt an urgent need to redesign the important chemical processes using suitable heterogeneous catalysts.[5] The electrophilic substitution reaction of indoles with carbonyl compounds has been achieved with Montmorrilonite clay[6] and with Yb-amberlyst XN-1010.[7] More recently, the formation of bisindolylmethanes from indoles and carbonyl compounds has been reported in ionic liquids without additional catalyst.[8]



1a: R = H
1b: R = Me
2
3

Scheme 1.

We have recently observed that silica supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) and amberlyst-15 are two different heterogeneous catalysts for the electrophilic substitution reaction of indoles with carbonyl compounds (Scheme 1). We have found that indole and 2-methylindole when reacted with carbonyl compounds in the presence of $NaHSO_4 \cdot SiO_2$ or amberlyst-15 at room temperature produced bisindolylmethanes in high yields (Table 1).

When 3-formylindole was used as a carbonyl compound the corresponding trisindolylmethanes are formed. The reaction proceeded at room temperature and the time required for the conversion was short. The structures of all the products were settled from their spectral (IR, ^1H-NMR and mass) data.

The bisindolylmethanes have been prepared by using both the aromatic and aliphatic carbonyl compounds. The long-chain aliphatic aldehydes (entries n and o) also worked well to form the products in high yields. The reactions of indoles with cyclohexanone (entry q) and cyclopentanone (entry r) took a slightly longer time. The ether (entry c) and ester linkages (entry g) present in the carbonyl compounds were unaffected. The activity of indole and 2-methylindole was found to be almost similar towards the reaction. The scope and generality of the present method has been shown with respect to various carbonyl compounds and indoles (Table 1).

Both the catalysts, $NaHSO_4 \cdot SiO_2$ and amberlyst-15, are heterogeneous and can conveniently be applied,

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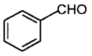
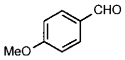
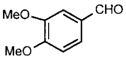
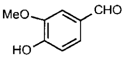
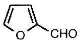
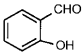
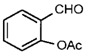
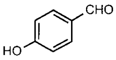
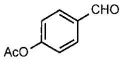
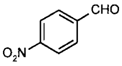
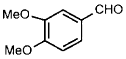
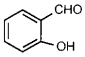
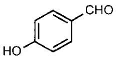
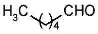
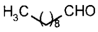
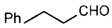
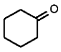
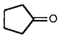
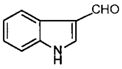
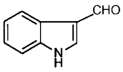
Table 1. Synthesis of bis- and tris(1*H*-indol-3-yl)methanes[a]

Entry	Indole	Carbonyl compound (**2**)	Catalyst	Time [h]	Yield [%]
a	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	2.5 2.5	89 91
b	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	2.5 2.5	91 90
c	**1a**		NaHSO4 · SiO2 Amberlyst-15	2.5 2.5	93 89
d	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	2.5 2.0	87 90
e	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	85 87
f	**1a**		NaHSO4 · SiO2 Amberlyst-15	3.0 3.0	82 86
g	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	2.5 2.5	89 91
h	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	87 89
i	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	2.5 2.5	94 95
j	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	100 97
k	**1b**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	2.5 2.5	96 87
l	**1b**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	89 87
m	**1b**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	85 85
n	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	86 87
o	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	84 86
p	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	2.5 2.5	74 75
q	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	78 82
r	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	72 76
s	**1a**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	87 92
t	**1b**		$NaHSO_4 \cdot SiO_2$ Amberlyst-15	3.0 3.0	87 90

[a] The structures of all the products were deduced from their spectral (IR, ^{1}H- NMR and mass) data.

involving simple experimental procedures for the reaction of indoles with carbonyl compounds. The first catalyst can easily be prepared[9] from the readily available $NaHSO_4$ and silica gel while the second catalyst is commercially available. Both the catalysts are inexpensive and non-hazardous. Amberlyst-15 can be recovered by filtration and reused after activation.

In conclusion, we have developed a highly convenient and efficient method for the preparation of bis- and tris(1*H*-indol-3-yl)methanes in high yields through the electrophilic substitution reaction of indoles with carbonyl compounds using $NaHSO_4 \cdot SiO_2$ and amberlyst-15. We feel the present process is an attractive alternative to the existing methodologies for the synthesis of bis- and tris(1*H*-indol-3-yl)methanes.

Experimental Section

Typical Experimental Procedure

To a stirred solution of indole (2 mmol) and carbonyl compound (1 mmol) in CH_2Cl_2 (5 mL) at room temperature $NaHSO_4 \cdot SiO_2$ (100 mg) or amberlyst-15 (100 mg) was added.

Stirring was continued. After completion of the reaction as indicated by TLC, the catalyst was filtered off and washed with EtOAc (2 × 5 mL). The filtrate and washings were combined and the solvents were removed under vacuum. The residue was purified by column chromatography over silica gel using mixtures of hexane and EtOAc as eluent to afford the bis- and tris(1*H*-indol-3-yl)methanes.

Spectroscopic Data of Representative Bis- and Tris(1*H*-indol-3-yl)methanes

3 g: IR (KBr): ν = 3403, 1747, 1484, 1456 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ = 7.86 (2H, br s), 7.44 – 7.02 (12H, m), 6.62 (2H, d, J = 2.4 Hz), 5.98 (1H, s), 1.98 (3H, s); EIMS: m/z = 380 ($M^{+\cdot}$), 338, 221, 156, 142.

3 m: IR (KBr): ν = 3403, 1599, 1509, 1458 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ = 7.56 (4H, m), 7.24 – 7.02 (8H, m), 6.78 (2H, d, J = 8.0 Hz), 5.88 (1H, s), 4.64 (1H, br s), 2.17 (6H, s); EIMS: m/z = 366 ($M^{+\cdot}$), 351, 257, 235, 220, 183.

3p: IR (KBr): ν = 3416, 1612, 1456 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ = 7.62 (2H, br s), 7.24 (2H, d, J=8.0 Hz), 7.35 – 6.83 (11H, m), 6.78 (2H, d, J = 2.4 Hz), 4.42 (1H, t, J = 7.0 Hz), 2.76 – 2.58 (2H, m), 2.46 (2H, t, J = 7.0 Hz); EIMS: m/z = 350 ($M^{+\cdot}$), 245, 232, 155, 141.

3 s: IR (KBr): ν = 3430, 3400, 1620, 1470 cm^{-1}; ^{1}H NMR (CDCl$_3$ + DMSO-d_6): δ = 9.89 (3H, br s), 7.39 (3H, d, J = 8.0 Hz), 7.24 (3H, d, J = 8.0 Hz), 6.98 (3H, t, J = 8.0 Hz), 6.82 (3H, t, J = 8.0 Hz), 6.69 (3H, d, J = 2.4 Hz), 6.40 (1H, s); EIMS: m/z = 361($M^{+\cdot}$), 243, 216, 117.

Acknowledgements

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References and Notes

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