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Mild and efficient copper sulphate catalyzed synthesis of bis-indolylmethanes

Uttam B.More[1]*, Bapurao S.Sonawane[1], Pramod P.Mahulikar[2]

[1]Post-Graduate and Research Centre, Department of Chemistry, R.B.N.B College, Shrirampur-413 709, Dist-Ahmednagar, (M .S.), (INDIA)

[2]School of Chemical Sciences, North Maharashtra University, Jalgaon-425001, (M. S.), (INDIA)

Fax : (02347) 222347

E-mail : uttambmore@rediffmail.coml.com

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ABSTRACT

A mild and efficient electrophilic substitution reaction of indole with various aldehydes and ketones in presence of copper sulphate as catalyst, afforded bis-indolylmethanes in good yields. The simple isolation of product is additional feature of the methodology.

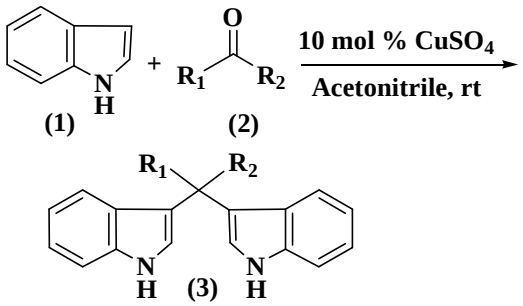
KEYWORDS

Indole;
Aldehydes and ketones;
Copper sulphate;
Electrophilic substitutions;
Bis-indolylmethanes.

1. INTRODUCTION

Indoles and their derivatives are used as antibiotics in the field of pharamaceuticals[1]. The bis-indolylmethanes and their derivatives are found in important bioactive metabolites of terrestrial and marine origin[2]. A large number of bis-indolylmethanes have been isolated from terrestrial and marine natural sources, such as parasitic bacteria, tunicates, and sponges and some of these possess significant biological activities. Vibrindole A was demonstrated for the first time to exhibit antibacterial activity against S*taphylococcus aureus*, *S.albus* and *B.subtillis* species[3].

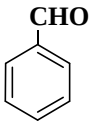
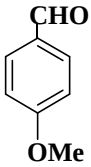
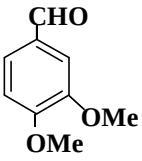
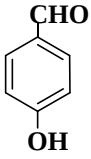
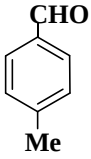
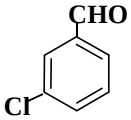
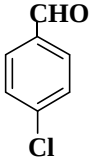
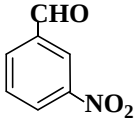
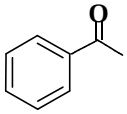
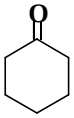
Therefore, there is a great deal of interest in the synthesis of this class of bis-indolylmethane compounds. The condensation of indoles with carbonyl compound using protic acids[4] and Lewis acids[5] as catalysts have been known to form bis-indolylmethanes, however, most of these methods require rather harsh acidic conditions, which are often incompatible with other sensitive functions present in the substrates. Recently many milder procedures based upon the use of catalytic amount of Lewis acid have been reported. Particularly, the electrophilic substitution reactions of indoles with various aldehyde and ketones have been carried out using ionic liquids, montmorillonite K10, NBS, Zeolite, $LiClO_4$ and rare earth catalysts[6] such as Ln $(OTf)_3$. However, it requires longer reaction times for nitro substituted aromatic aldehydes giving the corresponding bis-indolylmethanes in moderate yields whereas reactions with aromatic ketones arevery slow resulting in poor yield of the products. Recently bis-indolylmethanes have also been synthesized using amberlyst[7], hexamethylene-tetramine-bromine[8], sulphonic acid[9] and tetrabutylam monium tribromide[10].



SCHEME 1

Short Communication

TABLE 1 : Copper sulphate catalyzed synthesis of bis-indolylmethanes

Entry	Carbonyl compound 2	Time (min)	Yield (%)	M.p.^{0}C [lit.m.p.][8]
a		65	85	90-91 [88-90]
b		60	87	186-187 [187-189]
c		60	85	198-199 [199-200]
d		60	83	121-122 [122-124]
e		50	82	94-95 [95-97]
f		60	80	153-154 [152-154]
g		60	80	75-76 [76-77]
h		50	78	220-221 [218-220]
i		60	85	189-190 [190-192]
j		65	78	120-121 [118-120]

In the view of potent bioactivity of bis-indolyl methanes and the major problems with their synthetic routes, we here report the simple, mild and rapid synthetic approach using copper sulphate as catalyst (SCHEME 1).

2. EXPERIMENTAL

All chemicals were of AR grade. Solvent, aldehydes and ketones were distilled before use. Melting points were taken by open capillary method and are uncorrected.

General procedure for the synthesis of bis-indolyl methanes (3)

The reaction of aldehyde or ketone with indole in acetonitrile solvent was carried by using 10 mole % of copper sulphate as a catalyst. For this indole (10 mmol), aldehyde or ketone (5 mmol) and 10 mol % copper sulphate (0.249 g) were taken in acetonitrile (25 ml). The mixture was stirred for 45 min. to 65 min. at room temperature until the completion of reaction. The reaction was monitored by silica gel thin layer chromatography (hexane: ethyl acetate, 9:1). Then reaction contents were washed with distilled water followed by sodium carbonate and dried with sodium sulphate. The solvent was evaporated to obtain the crude products (TABLE 1), which were recrystallised from ethyl acetate.

Spectral data

(3a): ^{1}H NMR: ($CDCl_3$, δ ppm): 5.79 (s, 1H), 6.59(d, 2H), 7.01(m, 2H), 7.18-7.32(m, 5H), 7.33-7.36(m, 4H), 7.38(d, 2H), 8.08(bs, 2H, NH)., IR (KBr, cm^{-1}): 3420, 1635, 1380, 734.

(3b):, ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 3.72(s, 3H), 5.76(s, 1H), 6.57(d, 2H), 7.02(t, 2H), 7.19(t, 2H), 7.20-7.34(m, 8H), 7.9(bs, 2H, NH)., IR (KBr, cm^{-1}): 3400, 2929, 1620, 1515, 1451, 1412, 735.

3. RESULTS AND DISCUSSION

A facile syntheses of bis-indolylmethanes through the copper sulphate catalyzed electrophilic substitution reaction of indole with different aldehydes and ketones have been developed. The reaction was completed at room temperature under mild conditions within 45-65 min. according to the reactivity of aldehydes and ketones. Simple isolation of product is additional feature of the methodology.

4. ACKNOWLEDGMENTS

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