Potassium Hydrogen Sulfate-Catalyzed Reactions of Indoles: A Mild, Expedient Synthesis of Bis-indolylmethanes

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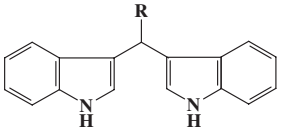
Biologically important bis-indolylmethanes and their derivatives were prepared in good yields by the electrophilic substitution of indole with aldehydes catalyzed by potassium hydrogen sulfate.

Bis-indolylmethanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin.[1] A large number of bis-indolylmethanes have since been reported to be isolated from terrestrial and marine natural sources, viz. parasitic bacteria, tunicates and sponges,[1] and some of these possess significant biological activities.

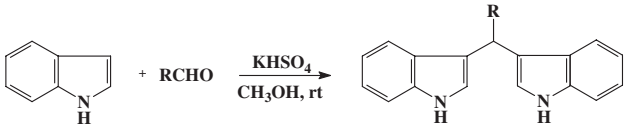


1: R = H
2: R = CH_3
3: R = CH_2OAc
4: R = $CH(OH)CH_2OH$

Three toxic indolic metabolites were isolated from the fungus, *Balansia epichloe*, a parasite to pasture grasses which were known to elicit ergot-type syndrome in cattle grazing on these infected grasses.[1a] One of these compounds is 3,3′-bis(3′-indolyl)propane-1,2-diol **4**, the first diindolylmethane reported from a natural source. Streptindole **3** is the first bacterial diindolylmethane metabolite possessing genotoxicity and DNA-damaging activities which are reparable in *Basillus subtilis* cells.[1b] The diindolylmethane, vibrindole A **2** was demonstrated for the first time to exihibit antibacterial activity against *Staphylococcus aureus*, *S. albus*, and *B. subtilis*, where gentamycin is used as the standard drug. 3,3′-Diindolylmethane **1** has been gaining increasing importance in recent years because of its potent anticarcinogenic properties.[2]

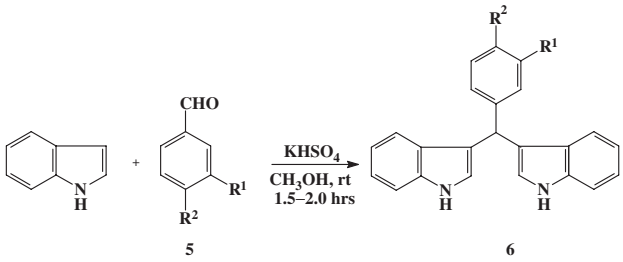
The principal synthetic avenues to the bis-indolylmethanes comprise the protic or Lewis acid-catalyzed reaction of indoles or indolyl Grignard reagents with aldehydes, ketones, α-keto acids, imines, iminium salts, or nitrones.[3] Most of these methods suffer from various disadvantages such as long reaction time (e.g. 10 days[4]), use of expensive Lewis acids (e.g. dysprosium triflate[5]) or preformed reagents (e.g. oxazolidines/tetrahydrooxazines,[6a,b] nitrones[7]) etc., yet furnishing the *bis*-indolymethanes in extremely low (e.g. 2%[1b]) or unspecified[6b] yields in some cases. Recently several efficient methods were developed using $InCl_3$,[8] I_2,[9] NBS,[10] Montmorillonite,[11] and $LiClO_4$.[12]

In this report we wish to introduce $KHSO_4$ as a mild and efficient catalyst for the synthesis of bis-indolylmethanes in high yields for the first time. The method is highly efficient and free from aforesaid drawbacks. The electrophilic substitution reactions of indole with aldehydes proceeded smoothly at room temperature to afford the corresponding bis-indolylmethanes[13] in high yields in shorter reaction times. The reaction is general and applicable to various aromatic as well as aliphatic aldehydes. The lower yield of the vibridole A is due to the self condensation of acetaldehyde under acidic condition. The catalyst is not affected by the presence of water was evidenced by the reaction of aqueous formaldehyde with indole (Scheme 1, Entry 1).



1, R = H, 2.5 hrs, 83%
2, R = CH_3, 2.0 hrs, 43%
3, R = C_3H_7, 3.0 hrs, 79%
4, R = C_5H_{11}, 3.5 hrs, 73%

Scheme 1.



Scheme 2.

Table 1. Synthesis of bis-indolyl(aryl)methanes catalyzed by $KHSO_4$

Entry	Substituents		Time /h	Yield[a,b] /%
	R^1	R^2		
1	H	H	2.5	90
2	OCH_3	OH	1.5	87
3	H	Cl	2.0	92
4	H	CH_3	2.0	93
5	H	OCH_3	2.0	95
6	H	NO_2	2.0	96

[a]All the products were thoroughly characterized by IR, NMR, Mass, and elemental analysis.
[b]Yield is based on isolation by column chromatography.

In conclusion, we have developed a mild, expedient, $KHSO_4$ catalyzed synthesis of diindolylmethane derivatives. The catalyst is mild and better dehydrating agent may be due to the slow and controlled release of sulfuric acid generated in situ in protic solvent such as methanol. Direct use of sulfuric acid leads to oli-

gomerisation of indole as reported in the literature. Even though Lewis acids and other protic acids are known to catalyze this reaction, this is the first report using a mineral salt. The use of other mineral salts is yet to be explored. The catalyst is mild, cheap, commercially available and also offers several advantages including cleaner reactions, higher yields of the products as well as simple experimental and isolation procedures which makes it a useful and attractive process for the synthesis of bis-indolylmethanes.

References and Notes

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13 To a mixture of indole (2.5 mmol) and substituted benzaldehydes (1.25 mmol) in methanol (10 mL), $KHSO_4$ (1.25 mol) was added and stirred at room temperature for the appropriate time. When the reaction was complete, water (10 mL) was added to quench the reaction and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried using anhydrous Na_2SO_4, filtered and the solvent evaporated. The crude products were purified by column chromatography and eluted with ethyl acetate and petroleum ether mixture to afford the products. 3,3′-Bis-indolyl(phenyl)methane **6a**: Pink coloured solid; mp 125–126 °C (Lit.,[14] 124–125 °C); IR (KBr) 3416, 1634, 1378, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (brs, 2H), 7.45–7.18 (m, 13 H), 6.51 (s, 2H), 5.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 134.3, 133.7, 130.2, 130.1, 130.0, 127.1, 125.1, 123.0, 119.4, 118.9, 114.3, 21.5; MS m/z 322 (M^+); Anal Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69; Found : C, 85.59; H, 5.68; N, 8.54%.

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