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Tetrabutylammonium Tribromide as Efficient Catalyst in the Synthesis of Bis(indolyl)methanes*

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Abstract—An efficient procedure has been developed for the synthesis of bis(indolyl)methane derivatives by condensation of aldehydes with indole in the presence of tetrabutylammonium tribromide as catalyst.

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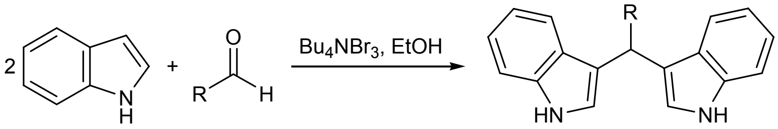
Indoles and their derivatives are important as pharmacologically and biologically active compounds [1]. Bis(indolyl)methanes and their derivatives are widely recognized as bioactive metabolites of terrestrial and marine origin [2–6]. Significant efforts have been made to synthesize such compounds. They are usually prepared by condensation of indole with carbonyl compounds in the presence of a protic [7] or Lewis acid [8]. However, the problem in using Lewis acids is their sensitivity to moisture, and in many cases more than stoichiometric amount is required due to trapping by nitrogen-containing substrate. This problem may be avoided to some extent by using lithium perchlorate [9], but the latter is expensive, and the reaction time is longer. Some other reagents like $NaHSO_4$–SiO_2, I_2, NBS, and K-10 montmorillonite were also used to catalyze the above reaction [10]. Some syntheses in the presence of rare earths, such as $LnCl_3$, $Ln(OTf)_3$, and $Re(PFO)_3$, were recently reported as alternative of conventional Lewis acid catalysis [11, 12]. However, many of these procedures require long reaction time and large amounts of the catalyst. Ionic liquid [13] and surfactant [14] were used very recently to catalyze synthesis of bis(indolyl)methanes, but ionic liquids are expensive and the use of surfactant makes the experimental procedure very tedious.

Taking the above stated into account, development of a mild and efficient alternative procedure for the synthesis of bis(indolyl)methanes seems to be important. Our continuous studies in this line [15–21] showed that tetrabutylammonium tribromide (TBATB) effectively catalyzes formation of bis(indolyl)methanes in the condensation of various aldehydes with indoles in ethanol at room temperature (Scheme 1). The experimental procedure is very simple. It involves mixing equimolar amounts of aldehyde and indole and 8 mol % of TBATB in ethanol at room temperature and allowing the reaction to go to completion (the progress of the reaction being monitored by thin-layer chromatography). The results are summarized in table. It is seen that the reaction is general: various aliphatic, aromatic, heterocyclic, and α,β-unsaturated carbonyl compounds reacted with indole in the presence of TBATB to produce the corresponding bis(indolyl)methane derivatives in good yields. The conditions were so mild that no other transformations, e.g., isomerization of double bond, occurred. The yields of the condensation products from aromatic aldehydes with electron-withdrawing substituents were compared with those obtained from other aliphatic and aromatic aldehydes containing electron-donating groups, the reaction time being 2–4 h.

Scheme 1.



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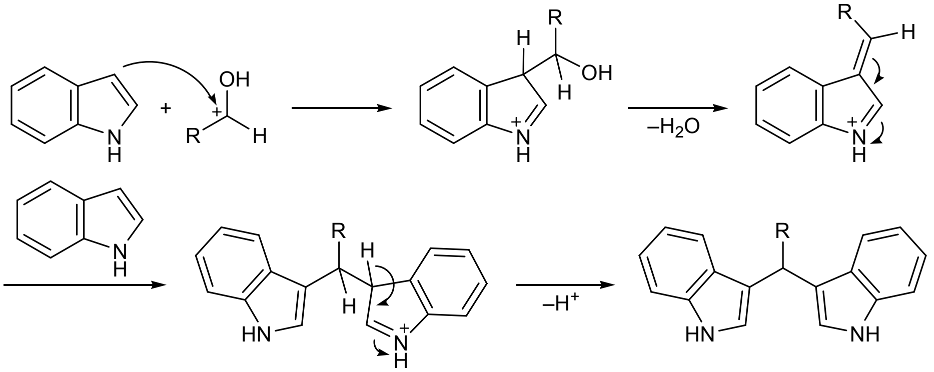
[*] The text was submitted by the authors in English.

Scheme 2.

$Bu_4NBr_3 + EtOH \longrightarrow HBr + BrOEt + Bu_4NBr$



A probable reaction mechanism is shown in Scheme 2. Tetrabutylammonium tribromide is an excellent source of anhydrous hydrogen bromide, and the acidity of the medium can be tuned by choosing an appropriate solvent. In our case, anhydrous HBr liberated in the reaction of TBATB with ethanol catalyzes addition of indole to carbonyl compounds.

To conclude, the proposed procedure ensures highly efficient synthesis of bis(indolyl)methane derivatives at room temperature. It is advantageous due to operational simplicity, mild conditions, ecological safety, compatibility with various functional groups, high yields, and the use of easily accessible and inexpensive reagent as catalyst.

EXPERIMENTAL

3,3′-Benzylidenedi(1*H*-indole) (*typical procedure*)**.** A mixture of 106 mg (1 mmol) of benzaldehyde, 234 mg (2 mmol) of indole, and 40 mg (8 mol %) of tetrabutylammonium tribromide in 3 ml of ethanol was stirred for 2.5 h at room temperature. When the reaction was complete (TLC), the mixture was evaporated, and the residue was extracted with diethyl ether. The extract was dried over Na_2SO_4 and concentrated, and the crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (9 : 1) as eluent. Yield 231 mg (72%). The product was identified by spectral data and comparison with an authentic sample. The other compounds were synthesized in a similar way.

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Yields of bis(1*H*-indol-3-yl)methanes in reactions of indole with aldehydes

R	Time, h	Yield,[a] %
Ph	2.5	72
1-Naphthyl	3.5	70
2-$O_2NC_6H_4$	2	80
4-HOC_6H_4	3	65
4-ClC_6H_4	3	60
4-MeC_6H_4	6	60
4-$MeOC_6H_4$	3	65
3,4,5-$(MeO)_3C_6H_2$	4	65
2,4-$(MeO)_2C_6H_3$	3	75
2-Furyl	15	70
2-Thienyl	1	75
Pr	4	60
C_7H_{15}	5	60
PhCH=CH	4	60
C_9H_{19}	6	65

[a] Preparative yield after purification; the products were characterized by IR and ^1H NMR spectra.

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