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An efficient and clean synthesis of bis(indolyl)methanes in a protic solvent at room temperature

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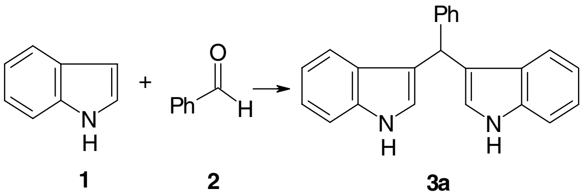
Abstract—Electrophilic substitution reactions of indoles with various aldehydes were carried out in a protic solvent at room temperature in the absence of any other catalyst to afford bis(indolyl)-methanes in excellent yields.

The importance of indoles and their derivatives is well recognized by synthetic as well as biological chemists.[1] Bis(indolyl)methanes, which contain two indole or substituted indole units in a molecule, feature widely in bioactive metabolites of terrestrial and marine origin.[2] Therefore, significant efforts have been directed towards the synthesis of these molecules. Synthetically, these compounds are obtained from the condensation of indoles with aldehydes and ketones in the presence of protic (e.g., HCl)[3] or Lewis acids (e.g., $AlCl_3$, BF_3).[4] Generally, traditional Lewis acid catalysts are moisture sensitive and are easily decomposed or deactivated in the presence of even a small amount of water. In many reactions, more than stoichiometric amounts of Lewis acids are required[5] because these acids are trapped by the nitrogen-containing reactants. These problems can be solved to some extent by using expensive lithium perchlorate but this also requires long reaction times.[6] $NaHSO_4$–SiO_2, I_2 and NBS have been used to catalyze these reactions.[7] Recently, rare earth catalysts have been recognized as possible environmentally friendly alternatives to conventional Lewis acids in many organic reactions. Hence, $LnCl_3$, $Ln(OTf)_3$ and $Re(PFO)_3$ have been successfully used in the synthesis of bis(indolyl)methanes.[8] Similarly, the use of ionic liquids is of interest for such organic synthesis.[9]

In our continued interest in the development of a highly expedient methodology[10] for the synthesis of fine chemicals and heterocyclic compounds of biological importance, we report here the first example of the synthesis of bis(indolyl)methanes from the condensation of various aldehydes and indoles in a protic solvent at room temperature in the absence of any added catalyst. In fact, we concentrated our study on the effect of solvents on condensation processes of aldehydes and indoles. The reactions were studied in various aprotic, protic, polar and non-polar solvents. Remarkably, we found that the condensation of aldehydes and indoles to bis(indolyl)methanes required no catalyst when performed in a suitable protic solvent, for example, methanol or water (in the presence of surfactants). Moreover, the reactions occur at room temperature giving good to excellent yields of the desired products.

First, we examined the reaction using methanol as a solvent. In a simple experimental procedure,[11] equimolar amounts of indole **1** and benzaldehyde **2** in methanol were allowed to react with stirring at room temperature for 12 h, to give, after workup, a 70% yield of compound **3a** (Scheme 1). The structure of **3a** was confirmed from spectroscopic data and by comparison with an authentic sample. Similarly, compounds **3b–o** were synthesized



Scheme 1.

Keywords: Indoles; Bis(indolyl)methanes; Aldehydes; Protic solvent; Aqueous medium.

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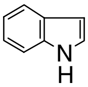
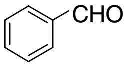
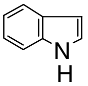
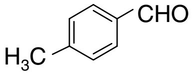
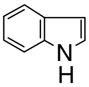
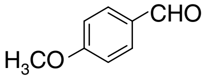
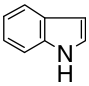
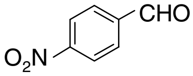
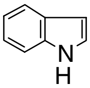
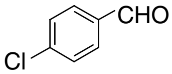
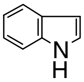
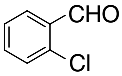
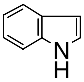
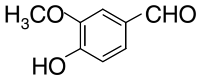
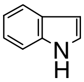
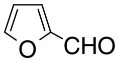
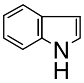
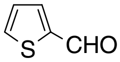
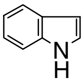
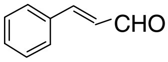
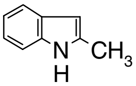
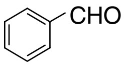
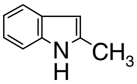
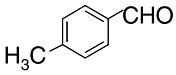
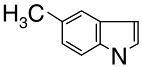
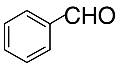
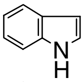
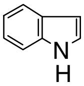
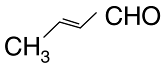
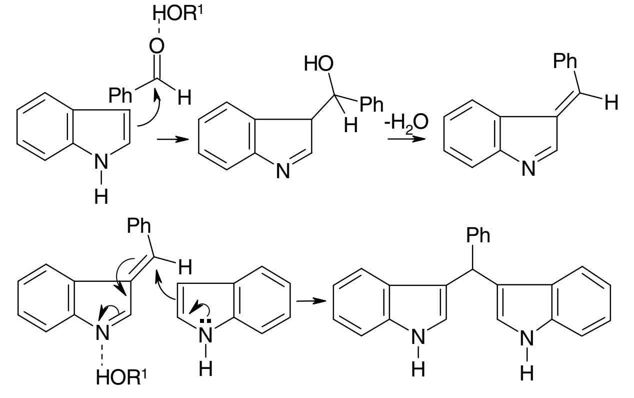
and characterized (Table 1). 2-Methylindole was found to be the most reactive giving the product in excellent yields in 2.5 h. 3-Methylindole on the other hand did not react under these reaction conditions. Interestingly, when the condensation reaction was carried out using acetonitrile, chloroform, THF or toluene as the solvent, no reaction occurred at all.

Encouraged by the effect of a protic solvent and to reduce the reaction time, we studied the reaction using water as the solvent. Unfortunately, it was observed that indoles were insoluble in water and no reaction occurred even after stirring the reaction mixture for a long time. Presuming the insolubility of the reactant was the problem, we considered the use of SDS (sodium dodecylsulfate) as a surfactant, since it forms micelles in water and can solubilize organic compounds, which are otherwise insoluble in water. Accordingly, we studied the reaction by utilizing equimolar amounts of the indoles and aldehydes in water in the presence of a small amount of SDS.[12] The indoles dissolved in a very short time and it was exciting to observe that the reaction occurred immediately on stirring the reaction mixture at room temperature and was complete in 2.5–5 h giving 55–96% yields of bis(indolyl)methanes. Our observations are recorded in Table 1.

Table 1. Synthesis of bis(indolyl)methanes from the condensation of aldehydes and indoles

Entry	Indole	Aldehyde	Product	Mp (°C)	Reaction time (h)		Yield (%)	
					MeOH	H_2O	MeOH	H_2O
1			**3a**	149–150[13]	12	2.5	70	95
2			**3b**	93–94[14]	12	2.5	65	96
3			**3c**	185–187[15]	18	5	78	80
4			**3d**	217–220[15]	20	5	60	60
5			**3e**	76–77[14]	18	5	75	55
6			**3f**	70–71[14]	17	4	72	60
7			**3g**	126–127	16	4	65	60
8			**3h**	>300[15]	18	—	61	—
9			**3i**	150–153[14]	20	—	50	—
10			**3j**	98–99[15]	14	2	60	65
11			**3k**	247–248	2.5	1	90	94
12			**3l**	174–175	3.5	1	70	60
13			**3m**	195–196	12	1	70	88
14		CH_3CHO	**3n**	148–150[15]	16	—	65	—
15			**3o**	123–126[15]	17	—	60	—



Scheme 2.

We studied the reaction by utilizing a variety of aromatic, heterocyclic and aliphatic aldehydes with a number of substituted indoles in both solvents (Table 1). Both solvents had their own advantages in terms of reaction simplicity, time required, workup and overall yields. The reactivity increased with increasing order of acidity of the solvents ($H_2O > CH_3OH$). However, the reaction was highly chemoselective and applicable only to aldehydes and not to ketones.

A reasonable mechanism for the reaction is outlined in Scheme 2, which is applicable for both solvents in the present study.

In conclusion, we have demonstrated a simple, efficient and clean synthesis of bis(indolyl)methanes from the condensation of indoles and aldehydes in a protic solvent at room temperature. The results demonstrate that the effect of solvent on this condensation process is remarkable.

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11. Experimental procedure: Indole **1** (0.234 mg, 2 mmol) and benzaldehyde **2** (0.106 mg, 1 mmol) were taken in methanol (10 ml) and stirred at rt for 12 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using hexane–chloroform (5:2) as eluent. Product **3a**: Solid, mp 149–150 °C (lit.,[13] 150–152 °C), yield 70% (225 mg).
12. Experimental procedure: Indole **1** (0.234 mg, 2 mmol) and benzaldehyde **2** (0.106 mg, 1 mmol) were taken up in water (10 ml). A small amount of surfactant (sodium dodecyl sulfate) was added to the reaction mixture, which was stirred for 2.5 h. at rt. The organic material was extracted with ethyl acetate and the surfactant was precipitated by the slow addition of $CaCl_2$ to the vigorously stirred mixture of the micellar solution and ethyl acetate. The solvent was removed under reduced pressure and the product was purified by column chromatography using hexane–chloroform (5:2) as eluent. Product **3a**: yield 95% (306 mg).
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