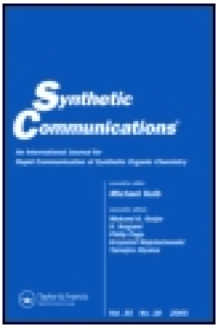

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Facile Synthesis of Bis(indolyl)methanes Using $LaCl_3 \cdot 7H_2O$ as a Mild and Efficient Catalyst in Molten Salt Media

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Abstract: Efficient electrophilic substitution reaction of indole with various carbonyl compounds were carried out using a catalytic amount of $LaCl_3 \cdot 7H_2O$ in molten tetraethylammonium chloride as an ionic liquid to afford the corresponding bis(indolyl)methanes in excellent yields.

Keywords: Bis(indolyl)methane, lanthanum chloride, molten salt, tetraethylammonium chloride

INTRODUCTION

Indole fragment is featured widely in a wide variety of pharmacologically and biologically active compounds.[1] For example, bis(indolyl)alkanes and their derivatives are found in bioactive metabolites of terrestrial and marine origin.[2]

The acid-catalyzed condensations of indole with carbonyl compounds have been a useful route for preparation of bis(indolyl)methanes. The protic acids[3] and Lewis acids[4] usually have been used in excess, and drastic conditions are required. To decrease the environmental pollution of the disposal of the excess acids and improvement of the condensation reactions of indole and carbonyl compounds, a number of catalytic systems such as $NaHSO_4 \cdot SiO_2$,[5] 12-tungstophosphoric acid,[6] $AlPW_{12}O_{40}$,[7]

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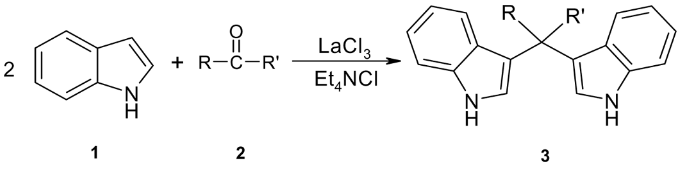


Scheme 1. Synthesis of bis(indolyl)methanes using $LaCl_3 \cdot 7H_2O$.

zeolites,[8] ionic liquids,[9] and I_2[10] have been successfully utilized. These methods have their own advantages and disadvantages, but it is always interesting to develop a new method with desirable features such as efficiency, short reaction time, easy workup, and ecofriendly catalyst for the organic transformation.

Recently, catalytic reactions using ionic liquids have attracted considerable interest[11] because they possess unique advantages of negligible vapor pressure, excellent thermal stability, and interesting intrinsic physicochemical characteristics. Ionic liquids have been used as effective solvents for clean chemical reactions, namely as replacements for volatile organic and dipolar aprotic solvents. They may provide a medium for clean reactions with minimal waste and efficient product extraction. It has been found that catalytic activity and product selectivity are accelerated when they are used. However, the high cost of most conventional room-temperature ionic liquids has led us to explore the use of more benign salts in the molten state as practical alternatives. Previously, molten tetraalkylammonium halides were used as cost-effective ionic liquids in a number of useful synthetic transformations.[12,13]

In the context of developing environmentally friendly green chemistry and on the basis of our previous work on lanthanum chloride,[14] we decided to look at the use of this salt in a one-pot synthesis of bis(indolyl)methanes in molten tetraethylammonium chloride as an ionic liquid (Scheme 1).

RESULTS AND DISCUSSION

First, the reaction of benzaldehyde with indole was carried out with 1:2 molar ratios to optimize the reaction conditions with respect to temperature, time, and the molar ratios of lanthanum chloride and tetraethylammonium chloride with respect to the substrate. We found that 10 mol% of $LaCl_3 \cdot 7H_2O$ and 2:1 molar ratio of tetraethyl ammonium chloride was sufficient to obtain the desired bis(indolyl)methane in 92% yield within 30 min at 100 °C.

These optimized conditions have been applied successfully for the condensation of a variety of aldehydes with indole. The results are summarized in Table 1.

The influence of electron-withdrawing and electron-donating substituents on the aromatic ring of aldehydes upon results of the reaction was investigated. Surprisingly, the results showed that both electron-withdrawing and electron-donating substituents had no significant effect on the reaction times and the yields (Table 1, entries 2–4 and 7). The presence of a substituent on the ortho position of aromatic aldehydes caused an increase in the reaction times (Table 1, entries 5, 6, and 10). In the case of aliphatic aldehydes such as butyraldehyde, the reaction took a longer time and lower yield was produced in comparison with aromatic aldehydes (Table 1, entry 12). To extend the scope of this method, the rate of the reaction of several ketones such as cyclohexanone and acetophenone was also investigated. Because of the lower reactivity of ketones relative to the aldehydes, longer reaction times and greater amounts of catalyst were used for the reaction of cyclohexanone with indole in comparison with the aliphatic and aromatic aldehydes (Table 1, entry 13). Attempts to bring indole into a reaction with acetophenone in the presence of this catalyst were mostly unsuccessful, and after a prolonged reaction time, most of the starting materials were recovered (Table 1, entry 14).

Table 1. Synthesis of bis(indolyl)methanes via the condensation of indole with carbonyl compounds using $LaCl_3 \cdot 7H_2O$ in molten tetraethylammonium chloride

Entry	Product[ref.]	R	R′	Catalyst (mol%)	Time (min)	Yield (%)
1	**3a**[15]	C_6H_5	H	10	30	92
2	**3b**[16]	$4\text{-}CH_3O\text{-}C_6H_4$	H	10	30	92
3	**3c**[16]	$4\text{-}CH_3\text{-}C_6H_4$	H	10	20	93
4	**3d**[16]	$4\text{-}Cl\text{-}C_6H_4$	H	10	20	93
5	**3e**[17]	$2\text{-}CH_3O\text{-}C_6H_4$	H	10	40	90
6	**3f**[18]	$2\text{-}Cl\text{-}C_6H_4$	H	10	30	88
7	**3g**[16]	$4\text{-}NO_2\text{-}C_6H_4$	H	10	20	93
8	**3h**[18]	$3\text{-}NO_2\text{-}C_6H_4$	H	10	30	93
9	**3i**[19]	1-Naphthyl	H	10	30	84
10	**3j**[20]	$2, 4\text{-Di-}Cl\text{-}C_6H_3$	H	10	40	88
11	**3k**[21]	$2\text{-}HO\text{-}C_6H_5$	H	10	15	91
12	**3l**[19]	$CH_3CH_2CH_2$	H	10	40	70
13	**3m**[15]	$\text{-}(CH_2)_5\text{-}$		30	120	60
14	**3n**	C_6H_5	CH_3	30	180	00

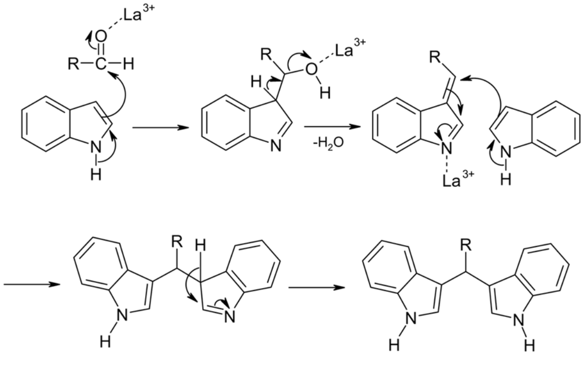
Table 2. Comparative results of condensation of indole with benzaldehyde using the reported methods versus the present method

Entry	Catalyst	Solvent	Time (min)	Yield(%)[ref.]
1	$LaCl_3 \cdot 7H_2O$	Molten Et_4NCl	30	92
2	$PPh_3 \cdot HClO_4$	CH_3CN	30	61[22]
3	$ZrOCl_2 \cdot 8H_2O$	Solventfree	40	84[23]
4	$In(OTf)_3$	CH_3CN	25	71[24]
5	$H_3PW_{12}O_{40}$	Water	120	84[20]

To assess the capability of the present method with respect to the reported methods for the preparation of bis(indolyl)methanes from indoles and carbonyl compounds, the synthesis of compound **3a** was compared with some of the reported methods (Table 2). As is clear from Table 2, the present method is more efficient.

The following sequence of reactions appears to afford a satisfactory explanation of the mode of formation of products for the synthesis of bis(indolyl)methanes catalyzed by $LaCl_3 \cdot 7H_2O$ from carbonyl compounds (Scheme 2). The carbonyl group was first activated by La^{3+} and carried out an electrophilic substitution reaction at C-3 of indole. After loss of water, an intermediate was generated. The intermediate was further activated by La^{3+} and served as an electrophile to attack a second molecule of indole to form the final product.

In conclusion, we have demonstrated a simple, convenient, and efficient protocol for the synthesis of a wide range of bis(indolyl)methane in molten salt media. The simplicity, efficiency, mild reaction conditions, high yields of products, easy workup procedure, lack of waste produced,



Scheme 2. Mechanism of $LaCl_3 \cdot 7H_2O$-catalyzed reaction indole with carbonyl compounds.

water as the only by-product, good generality, and use of a small amount of catalyst make it the preferred procedure for the preparation of different kinds of bis(indolyl)methanes. Other important features of this methodology are the use of molten tetraethylammonium chloride as a low-cost ionic liquid and the avoidance of hazardous organic solvent.

EXPERIMENTAL

All products are known compounds and were characterized by comparison of thier physical properties and spectral data with authentic samples. All reagents were purchased from Merck Chemical Company and were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer in dimethyl sulfoxide (DMSO-d_6).

Typical Experimental Procedure

A mixture of 1 mmol of appropriate aldehyde, 2 mmol indole, 2 mmol Et_4NCl, and 10 mol% of $LaCl_3$ was heated at 100 °C for the appropriate time. After the completion of the reaction (monitored by thin-layer chromatography, TLC) the mixture was dissolved in ethanol and poured in water. The resulting precipitate was recrystallized by ethanol to give pure product **3**.

Spectral Data for Selected Compounds

2-((1*H*-Indol-2-yl)(phenyl)methyl)-1*H*-indole (**3a**)

^{1}H NMR: δ (ppm) 5.94 (s, 1H, CH), 6.68 (d, $J = 1.6$ Hz, 2H), 7.06 (t, $J = 7.2$ Hz, 4H), 7.21–7.46 (m, 9H, arom), 7.89 (s, br, 2H, NH). ^{13}C NMR: δ (ppm) 40.7, 111.4, 119.8, 120.3, 122.3, 123.8, 126.3, 127.5, 127.7, 128.4, 128.6, 137.1, 144.4.

2-((1*H*-Indol-2-yl)(4-methoxyphenyl)methyl)-1*H*-indole (**3b**)

^{1}H NMR: δ (ppm) 3.84 (s, 3H, OCH_3), 5.90 (s, 1H, CH), 6.64 (d, $J = 1.6$ Hz, 1H), 6.88 (d, $J = 8.6$ Hz, arom), 7.07 (t, $J = 7.4$ Hz, arom), 7.23 (t, $J = 7.2$ Hz, arom), 7.30 (t, $J = 6.7$ Hz, arom), 7.37 (d, $J = 8.1$ Hz, arom), 7.45 (d, $J = 7.9$ Hz, arom), 7.82 (s, br, 2H, NH). ^{13}C NMR: δ (ppm): 39.7, 55.6, 111.5, 114.0, 119.6, 120.4, 120.4, 122.3, 123.9, 127.5, 130.0, 136.7, 137.1, 158.3.

2-((1*H*-Indol-2-yl)(*p*-tolyl)methyl)-1*H*-indole (**3c**)

^{1}H NMR: δ (ppm) 2.37 (s, 3H, CH_3), 5.90 (s, 1H, CH), 6.70 (t, $J = 1.4$ Hz, 2H), 7.05 (t, $J = 7.5$ Hz, 2H, arom), 7.44 (d, $J = 7.9$ Hz, 2H, arom), 7.90 (s, br, 2H, NH). ^{13}C NMR: δ (ppm): 21.5, 40.2, 111.4, 119.6, 120.3, 120.4, 122.3, 123.9, 127.5, 128.9, 129.3, 135.9, 137.1, 141.4.

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