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1-Carboxymethyl-3-methylimidazolium chloride {[cmmim]Cl} as an efficient catalyst for the solvent-free synthesis of bis(indolyl)methanes

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Abstract

1-Carboxymethyl-3-methylimidazolium chloride {[cmmim]Cl} is utilized as an efficient catalyst for the synthesis of bis(indolyl)methanes by the condensation reaction of indole with arylaldehydes under solvent-free conditions at room temperature.

Keywords: 1-Carboxymethyl-3-methylimidazolium chloride {[cmmim]Cl}; imidazolium salt; bis(indolyl)methane; indole; arylaldehyde; solvent-free.

Introduction

The exploitation of imidazolium salts as solvents as well as catalysts in organic transformations have been reported extensively during the past decade. The most useful properties of these salts are high thermal stability, recyclability, non-flammability, very low vapor pressure, safety and the fact that they can be stored for a long time without decomposition [1-4]. Among the imidazolium salts, Brønsted acidic ones have offered a possibility for development of environmental friendly acid catalysts in organic transformations because of their operational simplicity, efficacy and selectivity coupled with their green natures [2-4].

Meanwhile, bis(indolyl)methanes are of importance as they show different pharmaceuticals and biological activities [5-8]. For example, they are useful cruciferous substances in promoting beneficial estrogen metabolism for men and women [6]. They are also effective in preventing cancer due to their ability to modulate certain cancer causing estrogen metabo-

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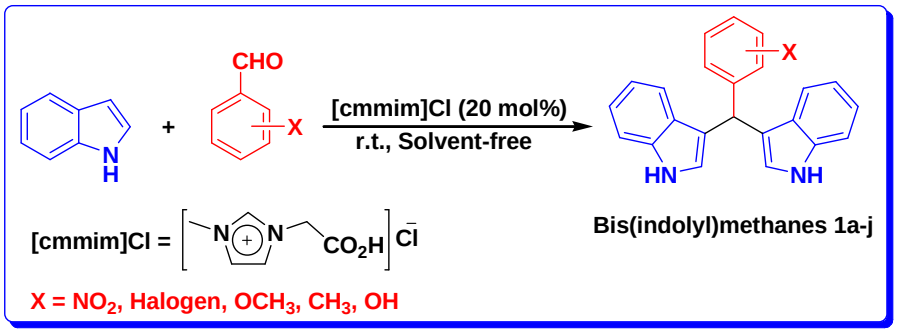
lites [7]. Moreover, these compounds may normalize abnormal cell growth associated with cervical dysplasia [8]. The best synthetic route towards bis(indolyl)methanes is the condensation reaction between indoles and carbonyl compounds using different catalysts [2,5,9-12]. Although several methods and catalysts for the preparation of bis(indolyl) methanes are known, considering the high importance of these compounds, search for finding efficient catalysts and methods for their synthesis are still of significance. In this paper, we report an efficient method for the preparation of bis(indolyl)methanes via the condensation of indole with arylaldehydes using Brønsted acidic imidazolium salt namely 1-carboxymethyl-3-methylimidazolium chloride {[cmmim]Cl} at room temperature in the absence of solvent (Scheme 1).

Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. The catalyst was prepared according to the reported procedure [13]. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Bruker Avance DPX, FT-NMR spectrometer (δ in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.



Scheme 1. The preparation of bis(indolyl)methanes using [cmmim]Cl

General procedure for the synthesis of bis(indolyl)methanes

A mixture of indole (0.24 g, 2 mmol), aromatic aldehyde (1 mmol) and [cmmim]Cl (0.035 g, 0.2 mmol) in a mortar, was vigorously ground at room temperature. After completion of the reaction, as monitored by TLC, warm H_2O (5 mL) was added to the reaction mixture, stirred for 2 min, and filtered (the imidazolium salt is soluble in warm H_2O; but, the product is insoluble in this solvent). The precipitate (crude product) was purified by recrystallization from EtOAc/petroleum ether (1:2) or plate chromatography on silica gel eluted with EtOAc/petroleum ether (1:2). The filtrate was washed with CH_2Cl_2 (2×5 mL), and the solvent (H_2O) was evaporated under reduced pressure to give recycled [cmmim]Cl.

Selected spectral data of the products

3-[(1H-Indol-3-yl)(phenyl)methyl]-1H-indole (1a)

^{1}H NMR ($CDCl_3$): δ 5.86 (s, 1H, ArCH), 6.66 (s, 2H), 7.11 (t, *J* = 6.9 Hz, 2H), 7.14-7.22 (m, 3H), 7.28-7.31 (m, 2H), 7.35-7.42 (m, 6H), 7.93 (br, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 31.6, 110.9, 111.9, 118.4, 119.5, 121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2.

3-[(2-Chlorophenyl)(1H-indol-3-yl)methyl]-1H-indole (1e)

^{1}H NMR ($CDCl_3$): δ 6.32 (s, 1H, ArCH), 6.67 (s, 2H), 7.02 (t, *J* = 7.8 Hz, 2H), 7.10-7.22 (m, 6H), 7.38-7.43 (m, 4H), 7.98 (br, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 37.1, 110.4, 111.6, 119.2, 120.0, 122.4, 123.9, 126.8, 127.3, 128.5, 130.5, 131.4, 135.6, 136.8, 141.5.

Results and discussion

Obtaining the optimized reaction conditions, as a model reaction, the condensation of indole (2 mmol) with 4-nitrobenzaldehyde (1 mmol) was studied in the presence of different molar ratios of [cmmim]Cl at room temperature in the absence of solvent. The results showed that 20 mol% of the imidazolium salt was sufficient to catalyze the reaction efficiently; in the mentioned conditions, the corresponding bis(indolyl)methane (**1d**) was obtained in 98% yield after 15 min. Increment of the catalyst amount up to 25 mol% didn't significantly affect on the reaction results (Table 1).

Optimizing the reaction conditions, indole was reacted with different arylaldehydes. The results are summarized in Table 2. As it can be seen in Table 1, all aldehydes, including benzaldehyde and

arylaldehydes possessing electron-withdrawing substituents, electron-releasing substituents and halogens on their aromatic ring, afforded the desired bis(indolyl)methanes **1a-j** in high to excellent yields and in short reaction times. Thus, the catalyst was efficient and general for the reaction.

Table 1. The condensation of of indole (2 mmol) with 4-nitrobenzaldehyde using different amounts of [cmmim]Cl at room temperature.

Entry	Catalyst Amount (mol%)	Time (min)	Yield[a] (%)
1	10	40	64
2	15	35	85
3	20	15	98
4	25	15	98

[a]Isolated yield

Table 2. The solvent-free preparation of bis(indolyl)methanes from indole and arylaldehydes using [cmmim]Cl at room temperature (Scheme 1).

X	Product	Time (min)	Yield[a] (%)	M.p. °C (Lit.)
H	**1a**	12	94	137-139 (139-141) [2]
2-NO_2	**1b**	15	93	141-143 (139-141) [14]
3-NO_2	**1c**	8	93	219-221 (219-221) [2]
4-NO_2	**1d**	15	98	215-217 (217-219) [14]
2-Cl	**1e**	15	87	75-77 (74-76) [2]
4-Cl	**1f**	8	93	78-80 (78-80) [14]
4-Br	**1g**	8	95	113-115 (112-116) [15]
4-OCH_3	**1h**	13	91	184-186 (186-188) [14]
4-CH_3	**1i**	12	93	96-98 (95-97) [2]
4-OH	**1j**	13	94	121-123 (119-121) [2]

[a]Isolated yield

Conclusion

In summary, we have developed a new method for the synthesis of bis(indolyl)methanes, with the following advantages: simplicity, low cost, generality, efficiency, clean reaction profile, high yield, short reaction time, ease of product isolation, and good agreement with the green chemistry protocols.

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