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PEG_{1000}-Based Dicationic Acidic Ionic Liquid/Solvent-Free Conditions: An Efficient Catalytic System for the Synthesis of Bis(Indolyl)methanes

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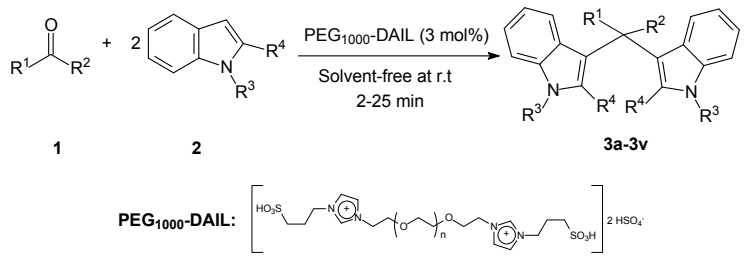
Abstract: An efficient procedure has been researched for the solvent-free synthesis of bis(indolyl)methanes via a one-pot reaction of indoles and aldehydes or ketones promoted by PEG_{1000}-based dicationic acidic ionic liquid (PEG_{1000}-DAIL). The catalyst PEG_{1000}-DAIL could be reused seven times with excellent results. Furthermore, through this method, a highly chemoselective reaction of benzaldehyde and acetophenone with indole could be achieved.

Keywords: bis(indolyl)methanes; ionic liquids; solvent-free conditions

1. Introduction

Numerous indoles occur in many active medicine compounds for human health [1,2]. In particular, bis(indolyl)methanes possess a wide range of pharmaceutical activities, such as serving as anti-bacterial and anti-fungal agents [3–6]. Due to their important role in medicine chemistry, many synthetic routes for the bis(indolyl)methanes have been researched by synthetic chemists. The simplest method for the preparation of bis(indolyl)methanes is the reaction of indoles with carbonyl compounds [7–11]. However, most of these synthetic routes require longer reaction times and a toxic organic solvent. Hence, it is desirable to develop improved reaction systems for the synthesis of these compounds.

Nowadays, ionic liquids (ILs) have attracted a great deal of interest because of their special performance including excellent heat stability, ease of operation, unique dissolution properties, and a wide liquid range [12–18]. Among all the types of developed ILs, PEG-DAILs [19–28] have been researched as excellent and powerful catalysts for various organic synthetic reactions. To the best of our knowledge, there have been no reports on the application of PEG_{1000}-DAIL as acid catalysts for the synthesis of bis(indolyl)methanes. As part of our ongoing interest in PEG_{1000}-DAIL [23–28], we now report, herein, an efficient and simple method for the synthesis of bis(indolyl)methanes using PEG_{1000}-DAIL as a reusable catalyst under solvent-free conditions (Scheme 1).



Scheme 1. PEG_{1000}-based dicationic acidic ionic liquid (PEG_{1000}-DAIL) catalyzed synthesis of bis(indolyl)methanes.

2. Results and Discussion

2.1. Effects of Different Reaction Conditions

To establish the optimum conditions for this reaction, various ratios of PEG_{1000}-DAIL were examined using indole and bezaldehyde as a model reaction. At room temperature, the mixture was ground together in a mortar with a pestle. We found that excellent results were obtained within 3 min when using 3 mol % PEG_{1000}-DAIL (Table 1, entry 4), and there was no superiority to using added PEG_{1000}-DAIL (Table 1, entries 5 and 6).

The recycling performance of PEG_{1000}-DAIL was researched in a condensation reaction of bezaldehyde and indole. The experimental data listed in Table 1 showed that PEG_{1000}-DAIL could be reused seven times with good results (Table 1, entry 4), and only a 6% loss of weight of PEG_{1000}-DAIL was observed after recycling seven times.

Table 1. Optimizing reaction conditions.

Entry	PEG_{1000}-DAIL (mol %)	t (min)	Yield (%) [a]
1	0	20	trace
2	1	20	75
3	2	12	85
4 [b]	3	3	98, 98, 97, 97, 95, 94, 90
5	4	3	98
6	5	3	98

[a] Isolated yields; [b] PEG1000-DAIL was used for seven consecutive cycles.

2.2. Effects of Different Substrates

To show the efficiency of this method, we researched the versatility of our approach via the reaction of various aromatic aldehydes with several kinds of indoles (Table 2). For all the corresponding reactions, the products of bis(indolyl)methanes (**3a–3x**) were obtained in excellent yields at room temperature after 25 min. The benzaldehydes with electron-donating groups require longer reaction times than those with electron-withdrawing groups. However, acetophenones and alkyl ketones required longer reaction times (Table 2, entries 21–24), the most likely cause being the steric effects of the -CH_3.

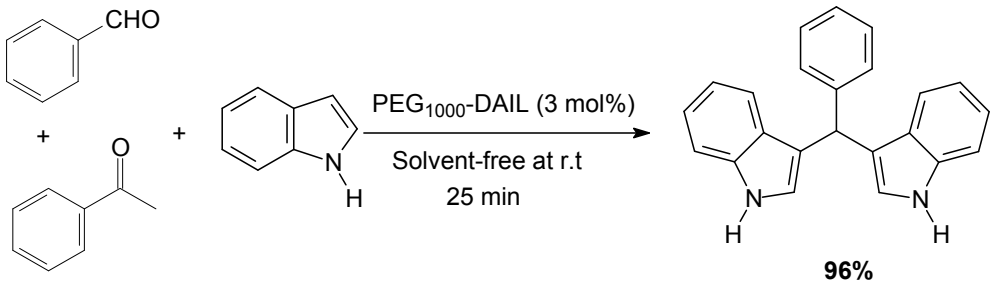
Table 2. PEG_{1000}-DAIL-catalyzed synthesis of bis(indolyl)methanes (**3a–3x**).

Entry	R^1	R^2	R^3	R^4	t (min)	Product	Yield (%) [a]
1	C_6H_5	H	H	H	3	**3a**	98
2	4-ClC_6H_4	H	H	H	2	**3b**	98
3	2-ClC_6H_4	H	H	H	2	**3c**	98
4	4-$CH_3C_6H_4$	H	H	H	10	**3d**	96
5	4-$CH_3OC_6H_4$	H	H	H	10	**3e**	95
6	2-$CH_3OC_6H_4$	H	H	H	8	**3f**	93

7	4-$NO_2C_6H_4$	H	H	H	2	**3g**	98
8	3-$NO_2C_6H_4$	H	H	H	3	**3h**	94
9	4-BrC_6H_4	H	H	H	2	**3i**	95
10	4-HOC_6H_4	H	H	H	10	**3j**	96
11	C_6H_5	H	CH_3	H	3	**3k**	94
12	4-ClC_6H_4	H	CH_3	H	2	**3l**	96
13	4-$CH_3C_6H_4$	H	CH_3	H	10	**3m**	95
14	3-$NO_2C_6H_4$	H	CH_3	H	3	**3n**	95
15	4-$NO_2C_6H_4$	H	CH_3	H	2	**3o**	97
16	C_6H_5	H	H	CH_3	4	**3p**	96
17	4-$NO_2C_6H_4$	H	H	CH_3	3	**3q**	98
18	4-$CH_3C_6H_4$	H	H	CH_3	10	**3r**	96
19	$CH_3(CH_2)_3$	H	H	H	15	**3s**	92
20	C_6H_5CH=CH	H	H	H	5	**3t**	95
21	C_6H_5	CH_3	H	H	25	**3u**	95
22	4-$NO_2C_6H_4$	CH_3	H	H	18	**3v**	97
23	CH_3	CH_3	H	H	50	**3w**	73
24	$(CH_2)_5$		H	H	40	**3x**	81

[a] Isolated yields.

In Table 2, we can see that the acetophenones (Table 2, entries 21 and 22) that react with iodine require longer reaction times than the aldehydes. This provides us a hint that our procedure could be used in the chemoselective reaction of aldehydes and acetophenones. Thus, a mixture of benzaldehyde and acetophenone (mole ratio of 1:1) was allowed to react with indole under the same reaction conditions. The results show that only 3,3′-bisindolyl-phenylmethane was obtained, and the acetophenone did not react with indole and recovered quantitatively (Scheme 2). This result indicates that the presented route is potentially applicable for the chemoselective reaction of aldehyde groups and ketone groups in multi-functional compounds to the desired bis(indolyl)methanes.



Scheme 2. Chemoselective reactions of carbonyl groups with indole.

2.3. Effects of Different Catalysts

In order to show the virtues of PEG_{1000}-DAIL in comparison with other previously reported catalysts, we summarized some of the results in Table 3 (the reaction of benzaldehyde with indole). The results showed that PEG_{1000}-DAIL was a more efficient catalyst with respect to reaction time and yield than other previously reported catalysts at room temperature. For example, in an EtOH solution, the product, 3,3′-bisindolyl-phenylmethane, was obtained in only a 72% yield, in 2.5 h, using Bu_4NBr_3 as a catalyst (Table 3, entry 5).

Table 3. Comparison of the condensation of benzaldehyde with indole with other catalysts.

Entry	Catalysts	Amount (mmol)	Solvents	T (°C)	t (h)	Yield (%)
1	PEG_{1000}-DAIL	0.03	No	r.t.	0.05	98
2	Ascorbic Acid	0.14	EtOH	r.t.	0.5	89 [7]
3	Sulfated Zirconia	0.30	No	r.t.	24	97 [29]
4	$BF_3{\cdot}Et_2O$	0.15	Et_2O	r.t.	2	90 [30]
5	Bu_4NBr_3	0.08	EtOH	r.t.	2.5	72 [31]
6	Cyclic phosphoric acid	0.01	CH_2Cl_2	r.t.	2.5	97 [32]

3. Experimental Section

3.1. Materials and Methods

PEG_{1000}-DAIL was synthesized using the route provided in a previously report [19]. All other chemicals are bought from companies (Aladdin Company, Shanghai, China). NMR spectra were recorded on a Bruker Advance DMX400 (Bruker Corporation, Karlsruhe, Germany). All corresponding bis(indolyl)methanes were known compounds and were identified using NMR and mp.

3.2. Typical Procedure for the Synthesis of Bis(indolyl)methanes

At room temperature, a mixture of indole (4 mmol), carbonyl compound (2 mmol), and PEG_{1000}-DAIL (0.092 g, 0.06 mmol) were ground together in a mortar with a pestle for a given amount of time and was monitored using TLC (Aladdin Company, Shanghai, China) (Table 2). After completion of the reaction, the reaction mixture was extracted with Et_2O or EtOAc (15 mL). The upper organic extracts were then washed with water (3 × 5 mL) to remove PEG_{1000}-DAIL. The organic layer was dried over Na_2SO_4. The organic solvent (Et_2O or EtOAc) was evaporated, and the crude product was purified using plate chromatography on silica gel eluted with ethyl acetate/petroleum ether (Aladdin Company, Shanghai, China). After the removal of H_2O under reduced pressure, the PEG_{1000}-DAIL was reused in the next reaction.

4. Conclusions

In conclusion, we have successfully researched an efficient route to synthesize bis(indolyl)methanes. The merits of the present method using PEG_{1000}-DAIL as a catalyst consist in short times, an elimination of metals, high yields of products, and an ease of handing. Furthermore, PEG_{1000}-DAIL can be reused easily for several subsequent cycles, thus making this route more environmentally acceptable.

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Author Contributions: Yi-Ming Ren contribute to the experimental design. Xiong Wang contribute to all the experimental data collection. Yi-Ming Ren and Mao-Dong Xu analyzed the data. Mao-Dong Xu wrote the first draft of the manuscript that was then extensively improved by Yi-Ming Ren.

Conflicts of Interest: The authors declare no conflict of interest.

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