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Prolinium Triflate: a protic ionic liquid which acts as water-tolerant catalyst in the alkylation of indoles

Morteza Shiri

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Abstract Prolinium triflate (ProTf) was easily prepared by addition of triflic acid to an aqueous solution of L-proline. The latter is employed as a catalyst for the condensation of indoles with aldehydes or ketones in aqueous media to form a series of bisindolyl methanes in high yields.

Keywords Indole · Condensation · Ionic liquid · Alkylation · Prolinium triflate

Introduction

Ionic liquids (ILs) [salts with a low melting point (below 100 °C)] recently gained much attention and are mainly used as solvents in organic reactions because of some special advantages such as low vapor pressure, high thermal and chemical stability or non-flammability [1–5]. Environmentally acceptable properties of ILs motivated chemists to investigate their application in other fields such as catalysis [6]. However, there are some limitations associated with the use of ILs as catalysts. For instance, low activities urge people to use more than the stoichiometric amounts of ILs for achieving good efficiency in organic reactions. This complication is potentially the result of a lack of potential activation sites on the substrates. Also in some cases ILs are sensitive to air and moisture leading to the inactivation of the reaction if care is not taken. Therefore the design of more active ILs that can

M. Shiri (🖂)

also be employed as catalysts has been an important topic in this field of research.

One of the best type of catalysts which act efficiently in aqueous media is metal triflates. $[M_x(CF_3SO_3)_y]$ [7]. Few ionic liquids with the triflate anion ($[CF_3SO_3]^-$; OTf) are known in literature [8]. For example recently Li et al. [9–11] have investigated the catalytic activity of proline triflate.

Indoles and their derivatives are very important biological compounds that occur widely in natural products. There are also many man made indolyl derivatives which display interesting physiological activities and they have found attractive applications in medicinal chemistry [12–20]. Friedel–Crafts alkylation of indoles by employing aldehydes or ketones is one of the methods of choice for the synthesis of bisindolyl methanes (BIMs). Many advances in the strategy of BIMs synthesis were published as a result of the variation of the catalyst and due to new synthetic methods [19, 20]. Herein we present prolinium triflate as an ionic liquid which efficiently catalyze the condensation of indoles with aldehydes or ketones in aqueous media.

Experimental

Chemical materials were purchased from Merck Chemical Company in high purity. Fourier transform infrared (FT-IR) spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. The NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. High-resolution mass spectrometric data were obtained using a Bruker micro TOF-Q II instrument operating at ambient temperatures. The progress of the reaction was monitored by TLC and purification was achieved by silica gel column chromatography.

Department of Chemistry, Faculty of Science, Alzahra University, Vanak, 1993893973 Tehran, Iran e-mail: mshiri@alzahra.ac.ir

General procedure

Preparation of prolinium triflate (ProTf)

Triflic acid (Tf) (1 mL, 10 mmol) was added with a syringe to 10 mL aqueous solution of _L-proline (10 mmol) at 0 °C, while the solution was stirred. The resultant solution was stirred for a further 30 min at room temperature. Water was then removed under vacuum on a rotavap. Further removal of water was achieved using a freeze dryer to obtain gave 2.61 g, 99 % ProTf as white glassy solid. Mp: 63–65 °C, $[\alpha]_{D}^{20}$ –17.93 (*c* 8.45, MeOH).

FT-IR (KBr): 3461, 3081, 1740, 1251, 1031, 640.

¹H NMR (400 MHz, CD₃OD): $\delta = 1.94-2.04$ (m, 3H);

2.31–2.34 (m, 1H); 3.21–3.30 (m, 2H); 4.25–4.29 (m, 1H). ¹³C NMR (100 MHz, CD₃OD): δ = 24.5, 29.2, 47.19,

60.76, 121.78, 171.4.

¹⁹F NMR (377 MHz, CD₃OD): $\delta = -80.1$.

Condensation of carbonyl compounds and indoles

To a stirring mixture of indoles (2.1 mmol) and aldehydes or ketones (1 mmol) in CH₃CN (2 mL), 0.1 mmol ProTf (0.5 mL aqueous solution of ProTf (%5 w/w) was added. After 5 h the reaction was quenched by adding water (10 mL). The product was then extracted with EtOAc (2 × 10 mL), and the extract dried with anhydrous Na₂SO₄. The filtrate was evaporated and residue was purified utilizing short column chromatography (EtOAc and *n*-hexane as eluent.

Spectral data for selected compounds

3g FT-IR (KBr): 3,347 cm^{-1.1}H NMR (400 MHz, CDCl₃): $\delta = 3.67$ (s, 3H); 3.87 (s, 3H); 6.35 (s, 1H), 6.79 (m, 2H), 6. 90 (m, 2H), 6.97 (m, 1H), 7.00 (m, 2H), 7.14 (m, 2H), 7.33 (m, 2H), 7.44 (m, 2H), 7.88 (s, br, 2H).¹³C NMR (100 MHz, CDCl₃): $\delta = 55.7$, 60.8, 65.8, 110.1, 110.9, 119.1, 119.6, 120.0, 121.7, 121.8, 123.5, 123.6, 127.1, 136.6, 138.0, 146.6, 152.6. HRMS calculated for $C_{25}H_{22}N_2O_2$ [M + H]⁺ 382.1681, found 383.1896.

3I FT-IR (KBr): 3361.¹H NMR (400 MHz, CDCl₃): $\delta = 2.11$ (s, 6H), 3.71 (s, 3H), 5.91 (s, 1H), 6.81 (m, 2H), 6.86 (m, 2H), 7.11 (m, 2H), 7.38 (m, 2H), 7.71 (s, 2H).¹³C NMR (100 MHz, CDCl₃): $\delta = 12.3$, 38.4, 55.2, 109.9, 113.4, 113.7, 119.0, 119.3, 120.5, 128.9, 129.9, 131.7, 135.0, 135.8, 157.8.HRMS calculated for C₂₆H₂₄N₂O [M + H]⁺ 380.1889, found 381.1911.

Results and discussion

Due to generation of labile hydrogen in the proposed ionic liquid, proline was chosen as the nitrogen source and triflic



Scheme 1 Synthesis of Prolinium Triflate



Scheme 2 Optimisation of reaction conditions for the synthesis of BIM 3a

acid was chosen as the acid source due to its regular and efficient application in water tolerant catalytic synthesis. After addition of triflic acid to the aqueous solution of L-proline and subsequent removal of excess water an amorphous solid was observed (Scheme 1). The solid melted at 62–65 °C and showed optical rotation. FT-IR showed a broad pick in 2,400–3,200 cm⁻¹ reflected to acid and also two picks at 3,461 and 1,740 cm⁻¹ which refer to N–H and C=O respectively. The peaks in ¹H NMR and ¹³C NMR spectrometers were assigned to the corresponding hydrogen and carbon atoms respectively. However elemental analyses did not give satisfactory results due to the highly hydroscopic property of the product.

In continuation of our studies on indole chemistry [18–25], the catalytic activity of the prepared prolinium triflate (ProTf) was examined on the condensation reaction of indole with benzaldehyde (Scheme 2). BIM 3a was obtained in 75 % yield after 24 h in the presence of 10 % ProTf in CH₃CN. Surprisingly addition of some drop of water to the reaction mixture dramatically increased yield up to 92 % and reduced the reaction time to 5 h. The possibility of performing the reaction in water as solvent in the presence of ProTf was examined but the reaction was not completed and after 24 h BIM 3a was produced in only 71 % yield (Scheme 1). For comparison the effectiveness of ProTf was measured with respect to L-proline as the catalyst. When the reaction was performed with L-proline as catalyst and with either CH₃CN or in water as solvent, the reaction did not yield any product under the same conditions. Eventually the best results were gained by using a mixture of acetonitrile and solution of ProTf in water ("Experimental section").

Table 1 Condensation ofindoles and aldehydes in thepresence of $ProTf^a$

Entry	Aldehydes	Indoles	Product	Isolated	Mp (°C)	Mp (°C)[ref]
				yield (%)	(Found)	(Reported)
1	СНО			90	240-	244-246
		N H			243	[25]
					273	[23]
			HN- NH			
			3b			
2	СНО			93	182-	183-185
		N H	AYA		184	[26]
					10.	[=0]
			HN- NH			
	0110	1400	30			
3	СНО	MeO	MeO OMe	95	211-	213-216
		Ň			213	[26]
			3d			
4	СНО	Br, A		00	215	208 210
4			Br Br	00	213	208-210
	~	₩ H				[27]
			HN- KNH			
		-	36			
5	СНО			0	-	-
			$\Delta I \Delta$			
		_	O2N HN NO2			
			3f			
6	OMe MeO		OMe	93	185-	-
	U	N H	OMe		187	
			HN-" (_N /-"			
			зg			
7	CHO			85	248-	250-253
		H			250	[27]
			HNJUNH			
			3h			
8	СНО		OMe	93	187-	186-188
	MeO			20	100	100 100
					189	[25]
			HN ~ NH			
			31			
9	СНО			90	97-99	95-97
		H H				[25]
			HN_ LNH			
			зј			

Table 1 continued

Entry	Aldehydes	Indoles	Product	Isolated	Mp (°C)	Mp (°C)[ref]
				yield (%)	(Found)	(Reported)
10	СНО			92	174-	175-177
		N H	HN NH		176	[25]
11	CHO		OMe	01	101	
11	Meo			91	191-	-
		, n	HN NH		193	
12	СІ Дарана СПО			88	73-75	74-76
	() · · ·	Z H	HN Sm H			[25]
13	СНО		$\square \square$	78 ^b	72-74	71-73
		N N N N N N N N N N N N N N N N N N N	HN Sn			[25]

^a Reaction conditions: Aldehydes (1 mmol), indoles (2.1 mmol), 0.5 mL Pro $Tf_{(aq)}$ (0.1 mmol of ProTf), CH₃CN (2 mL), rt, 5 h ^b 12 h

In the next step, the general applicability of this condensation reaction was investigated (Table 1). It was observed that benzaldehyde reacted with activated indoles such as 2-methylindole, 5-methylindole and 5-methoxylindole and also the deactivated 5-bromoindole to form **3b–3e** in high yields (Table 1, entries 1–4). But the reaction of benzaldehyde with 7-nitroindole failed (Table 1, entry 5). Condensation of 2,3-dimethoxybenzaldehyde, 1-naphthaldehyde, 4-methoxybenzaldehyde, 4-methyl-benzaldehyde and also 2-chlorobenzaldehyde with indole and 2-methylindole yielded corresponding triaryl methanes **3g–3m** in 85–93 % yields (Table 1, entries 6–12). 3,3'-(Heptane-1,1-diyl)bis(1H-indole) (**3n**) has been isolated from the *n*-heptanal and indole in 78 % yield (Table 1, entry 13).

Following a similar strategy, we next focused on the synthesis of more complex BIMs. In the first synthetic variant, isatin (4a) reacted easily with indole to form 5a in 90 % yield (Scheme 3) [29]. A similar satisfactory result was obtained for the condensation of 4a with 2-methylindole. In addition BIMs 5c and 5d were isolated from the reaction of 1-methylisatin with the corresponding indoles in 94 and 91 % yields (Scheme 3) [29].

The ProTf was recovered from the aqueous layer by removal of water under reduced pressure and recycled three times with almost no loss of activity for the synthesis

Scheme 3 Reaction of indoles and isatines catalyzed with ProTf



 $R_2 = H$, Me, H

yield (%) 90, 89, 94

of **3a**. ProTf is more effective, water tolerant catalyst and even by catalytic amounts can catalyzed synthesis of BIMs as compare to the other ionic liquids (ILs) such as N,N,N,N-tetramethylguanidinium triflate (TMGTf) [30], [Hmim]Tfa and [Hmim]HSO₄ [31], [bmim]BF₄ or [bmim]PF₆ [32] which were used for this purpose.

Conclusion

In summary, prolinium triflate has been purified and characterized as an ionic liquid which catalyzes the condensation of indoles and aldehydes or ketones to form triaryl methanes in high yields. Application of water to the catalyst has improved the efficiency of the catalyst both in terms of decreased reaction times and increased yields.

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