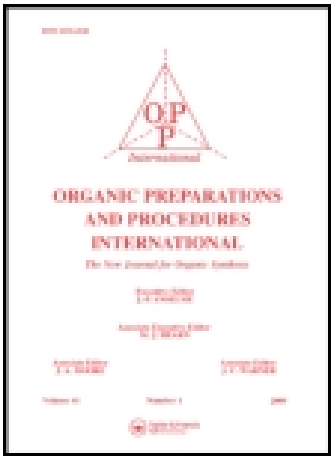

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PEG1000-Based Dicationic Acidic Ionic Liquid Catalyzed One-pot Synthesis of 1,4-Dihydropyridines via the Hantzsch Reaction

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PEG1000-Based Dicationic Acidic Ionic Liquid Catalyzed One-pot Synthesis of 1,4-Dihydropyridines *via* the Hantzsch Reaction

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Devising reactions that achieve multiple-bond formation in one operation has become one of the major challenges in the search for efficient syntheses. Multi-component reactions (MCRs) allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the creation of molecular diversity and complexity.[1–5] 1,4-Dihydropyridines display a variety of biological properties such as vasodilator, anti-tumour, broncho-dilator, anti-atherosclerotic, gero-protective and hepato-protective activity.[6] Due to their wide range of pharmacological activity and applications, a number of methods have been reported for their synthesis. The most straightforward preparation of these compounds involves multi-component considerations such as four-component condensation of aldehyde, 1,3-cyclohexanedione, active methylene compounds, and ammonium acetate;[7–11] the condensation of aromatic aldehydes, ethyl acetoacetate, and ammonium acetate[12–15] (or ethanolammonium acetate,[16] urea,[17] ammonium hydroxide solution,[18] ammonium formate,[19] *etc*.) and three-component reaction of ethyl acetoacetate, chalcones and ammonium acetate[20] *etc*. However, most of these methods require prolonged reaction times, drastic reaction conditions, tedious work-up procedures, and generate only moderate yields of the product. Therefore, it is desirable to develop improved conditions for the Hantzsch reaction.

Ionic liquids (ILs) have attracted extensive interest in recent years as environmentally benign solvents due to their favorable properties such as non-flammability, negligible vapor pressure, re-usability and high thermal stability.[21–23] Among the numerous ILs developed, poly(ethylene glycol)-linked dicationic neutral ionic liquids (PEG-DILs)[24,25] and poly(ethylene glycol)-linked dicationic acidic ionic liquids (PEG-DAILs)[26–30] have been explored as a powerful catalysts for various transformations. The PEG-DAILs (or PEG-DILs) were found to have the temperature-dependent biphasic behavior with toluene in a certain temperature (biphasic conditions at lower temperatures and monophasic at

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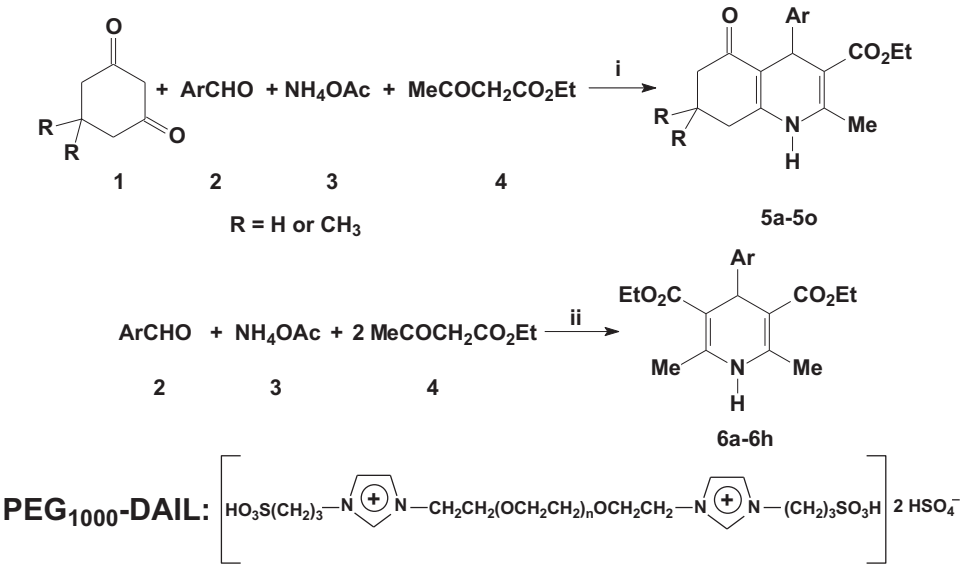

(i) PEG_{1000}-DAIL, toluene, 80°C, 15-30 min (ii) PEG_{1000}-DAIL, toluene, 80°C, 30-45 min

Scheme 1

higher temperatures).[24,26] The temperature-dependent feature of ILs provide a novel route for the separating and recycling of the catalysts.

To the best of our knowledge, there is no report on the application of PEG_{1000}-DAIL as acid catalysts for the preparation of 1,4-dihydropyridines. As part of our ongoing interest in ILs[24,25] and MCRs,[1,31–34] we now report a simple and efficient procedure for the Hantzsch reaction using PEG_{1000}-DAIL as an effective and reusable catalyst (*Scheme 1*).

Model exploratory experiments indicated that PEG_{1000}-DAIL efficiently catalyzed the reaction of benzaldehyde, 1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate to give the corresponding dihydropyridine. Although the yield rose with increasing temperatures (*Table 1*, *Entries 1–6*), the results showed the optimal temperature to be 80°C. The yields did not increase when higher temperature was employed (*Table 1*, *Entries 7 and 8*).

The performance of recycled PEG_{1000}-DAIL was investigated in the reaction of benzaldehyde, 1,3-cyclohexanedione, ethyl acetoacetate, and ammonium acetate. The data listed in *Table 1* showed that PEG_{1000}-DAIL could be re-used nine times with excellent results (*Table 1*, *Entry 6*). The bottom layer of PEG_{1000}-DAIL was recycled without any treatment and the work-up procedure of recycling is accomplished by simple phase separation.

In order to evaluate the efficiency of PEG_{1000}-DAIL as a catalyst, a range of aromatic aldehydes were similarly treated with 1,3-cyclohexanedione, ethyl acetoacetate, and ammonium acetate in the presence of PEG_{1000}-DAIL; the 1,4-dihydropyridines (**5a**–**5h**) were formed in excellent yields (*Table 2*, *Entries 1–8*). The position and/or nature of substituent on the aromatic ring had a negligible effect on the yields of the final products. Similarly,

Table 1
Optimizing the Reaction Conditions

Entry	T (°C)	t (min)	Yield (%)
1	r.t.	100	15
2	40	100	45
3	50	100	61
4	60	100	75
5	70	60	93
6[a]	80	25	93, 93, 93, 93, 91, 91, 91, 90, 90
7	90	25	93
8	100	25	93

[a]The PEG_{1000}-DAIL was run for nine consecutive cycles.

the corresponding products (**5i**–**5o**) were obtained in excellent yields when dimedone was employed under the same conditions (*Table 2*, *Entries 9–15*).

Table 2
PEG_{1000}-DAIL Catalyzed the Synthesis of 1,4-Dihydroquinolines **5a**–**5o** at 80°C

Entry	Ar	R	t (min)	Product	Yield (%)	mp. (*lit.*) (°C)
1	C_6H_5	H	25	**5a**	93	240–241 (240–241[7])
2	4-ClC_6H_4	H	20	**5b**	94	234–235 (234–235[7])
3	4-$CH_3C_6H_4$	H	30	**5c**	95	241–242 (241–242[7])
4	4-$CH_3OC_6H_4$	H	30	**5d**	92	192–194 (193–195[7])
5	4-$NO_2C_6H_4$	H	15	**5e**	94	204–205 (204–205[7])
6	3-$NO_2C_6H_4$	H	20	**5f**	93	198–200 (198–200[7])
7	2-$NO_2C_6H_4$	H	20	**5g**	91	190–192 (190–191[7])
8	4-HOC_6H_4	H	25	**5h**	93	220–222 (220–222[7])
9	C_6H_5	CH_3	25	**5i**	94	209–210 (209–210[7])
10	4-ClC_6H_4	CH_3	20	**5j**	92	229–231 (230–232[7])
11	4-HOC_6H_4	CH_3	30	**5k**	92	236–238 (237–238[7])
12	4-$CH_3C_6H_4$	CH_3	30	**5l**	94	262–264 (262–264[8])
13	4-$CH_3OC_6H_4$	CH_3	25	**5m**	95	242–244 (243–245[7])
14	4-$NO_2C_6H_4$	CH_3	20	**5n**	93	242–243 (242–244[8])
15	3-$NO_2C_6H_4$	CH_3	20	**5o**	92	175–177 (176–178[8])

This success led us to extend the Hantzsch reaction to the use of aromatic aldehydes with ethyl acetoacetate, and ammonium acetate under the same conditions. *Table 3* shows that different aromatic aldehydes reacted successfully within 45 min to give the expected products **6a**–**6h** in high yields. The nature of aldehyde has no significant effect on the reaction; both electron-rich and electron-deficient aldehydes reacted to give high yields of products.

Table 3
PEG_{1000}-DAIL Catalyzed the Synthesis of 1,4-Dihydropyridines **6a–6h** at 80°C

Entry	Ar	*t* (min)	Product	Yield (%)	mp. (mp. *lit.*) (°C)
1	C_6H_5	40	**6a**	91	156–158 (155–157[14])
2	4-ClC_6H_4	30	**6b**	93	145–147 (146–149[14])
3	4-$CH_3C_6H_4$	45	**6c**	96	136–138 (136–138[14])
4	4-$CH_3OC_6H_4$	45	**6d**	87	159–161 (160–161[14])
5	4-$NO_2C_6H_4$	30	**6e**	93	131–133 (131–134[14])
6	3-$NO_2C_6H_4$	45	**6f**	95	162–164 (161–163[14])
7	4-BrC_6H_4	30	**6g**	92	162–163 (162–163[14])
8	4-HOC_6H_4	40	**6h**	86	230–232 (230–233[14])

Comparison of the results of the condensation of benzaldehyde with ethyl acetoacetate, and ammonium acetate in *Table 4* shows that PEG_{1000}-DAIL is a more efficient catalyst with respect to times and yields than other catalysts.

Table 4
Different Catalytic Systems for the Condensation of Benzaldehyde with Ethyl Acetoacetate, and Ammonium Acetate

Entry	Catalysts	Solvents	*T* (°C)	*t* (min)	Yield (%)
1	PEG_{1000}-DAIL	toluene	80	40	91
2	PPh_3	EtOH	reflux	300	72[13]
3	MgO nanoparticles	EtOH	reflux	110	85[14]
4	$MgAl_2$-HT	CH_3CN	r.t.	390	73[35]
5	TMSCl/NaI	CH_3CN	r.t.	360	80[36]
6	Cellulose sulfuric acid	None	80	300	90[37]

In conclusion, we have developed an efficient and facile method to prepare a variety of 1,4-dihydropyridines in the presence of PEG_{1000}-DAIL. The advantages of our procedure include the elimination of the use of metals, short reaction times, operational simplicity and excellent yields of products. Simple reaction conditions, good thermo-regulated biphasic behavior of PEG_{1000}-DAIL and easy isolation of the product are additional features of this methodology, besides the excellent recyclability of the PEG_{1000}-DAIL.

Experimental Section

The PEG_{1000}-DAIL was prepared by the procedure given in the literature.[26] All the other chemicals and reagents were obtained from commercial sources and were used without further purification. ^{1}H NMR spectra were recorded on Bruker Avance DMX500. All products were known compounds and were identified by their mp and ^{1}H NMR.

General Procedure for the Synthesis of 1,4-Dihydroquinolines 5a–5o

To a solution of aromatic aldehyde (1 mmol), 1,3-cyclohexanediones (or dimedone) (1 mmol), ethyl acetoacetate (0.13g, 1 mmol) and ammonium acetate (0.077g, 1 mmol) in toluene (1.5 ml) was added PEG_{1000}-DAIL (1 ml) in tube reactor at room temperature. Then the mixture was stirred at 80°C for the specified time and monitored by TLC. After the reaction, the mixture was cooled to room temperature, the upper toluene layer was separated by decantation. The toluene was evaporated to give products **5a**–**5o** purified by recrystallization from ethanol. The bottom layer of PEG_{1000}-DAIL was reused without any treatment.

General Procedure for the Synthesis of 1,4-Dihydropyridines 6a–6h

To a solution of aromatic aldehyde (1 mmol), ethyl acetoacetate (0.26 g, 2 mmol) and ammonium acetate (0.077 g, 1 mmol) in toluene (1.5 ml) was added PEG_{1000}-DAIL (1 ml) in tube reactor at room temperature. Then the mixture was stirred at 80°C for the specified time and the reaction mixture was treated as above to afford the products **6a**–**6h**. The bottom layer of PEG_{1000}-DAIL was reused without any treatment.

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