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Poly(ethylene glycol) (PEG) as an efficient and recyclable reaction medium for the synthesis of dibenz[*b*,*f*]-1,4-oxazepine

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Abstract

Poly(ethylene glycol) (PEG) has been used as a sustainable, non-volatile, and environmentally friendly reaction solvent for the synthesis of dibenz[*b*,*f*]-1,4-oxazepine (**2a**). PEG-400 as a promoter provided 89% of **2a** within 8 h. We compared the reactivity of PEG-400 with 18-crown-6, tetra-*n*-butylammonium bromide and ionic liquids as phase transfer catalysts. Further, we investigated our protocol with various PEGs, with molecular weight 200, 300, 1000, 2000, 8000, 10,000, and 20,000. The reaction provided excellent yields with low as well as high molecular weight PEGs. We also studied the effect of various organic cosolvents (polar protic/aprotic/non-polar) on the reactivity of PEG-400 for the synthesis of **2a**.

Reducing or eliminating the use of volatile organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry.[1] The demand for environmentally friendly reaction solvents to lower volatile organic compounds (VOCs) or toxic air emissions has grown, partly spurred by various government regulations.[2] The use of water as solvent is probably the most desirable approach but this is often not possible due to the hydrophobic nature of the reactants and the sensitivity of many catalysts to aqueous conditions.[3] Alternative solvents have been the subject of much research in recent years including studies of supercritical CO_2,[4] near critical water,[4] ionic liquids,[5] and fluorous based systems.[6]

Recently PEG is found to be an interesting solvent system.[7] The important difference between using PEG and other neoteric solvents is that all of the toxicological properties, the short and long-term hazards, and the biodegradability, etc., are established and known. PEG as environmentally benign protocol proved to have many applications particularly, in substitution, oxidation, and reduction reactions.

Dibenz[*b*,*f*]-1,4-oxazepine (**2a**) has been synthesized by intramolecular nucleophilic displacement of nitro or fluoro or chloro groups in high boiling polar aprotic solvents like dimethyl sulphoxide (DMSO) or dimethyl formamide (DMF) over 100 °C.[8] Further, there are few reports on the synthesis of polyfluorodibenz[*b*,*f*]-[1,4]-oxazepines by cyclization of polyfluorinated *o*-hydroxybenzylideneanilines.[9] In this Letter, we describe the use of a simple and widely available polymer, PEG and optionally its derivatives as non-toxic, inexpensive, and non-ionic liquid solvents of low volatility for the synthesis of oxazepine (**2a**) via intramolecular cyclization.

In the initial studies, the reaction was performed in traditional organic solvent (CH_3CN, Table 1, entry 1). The reaction mixture was stirred for 12 h at 100 °C to obtain 45% of oxazepine (**2a**) with 24% of imine (**2b**). The reactions in DMF (entries 3 and 4) at 50 °C and 100 °C provided 21% and 74% of **2a**, respectively, after 12 h whereas, the same reaction in the presence of PEG-400 as

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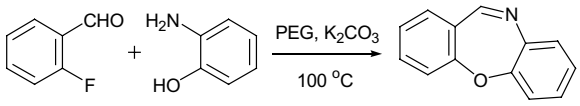
Table 1
Synthesis of dibenz[*b*,*f*]-1,4-oxazepine in poly(ethylene glycol)-400 under various reaction conditions[a]



1a **2a**, 89%

Entry	Promoter (g)	CH_3CN (mL)	Time (h)	Yield[b] (%)	
				2a	**2b**
1	—	2.0	12	45	24
2[c]	—	2.0	12	42	28
3[d]	—	—	12	21	57
4[e]	—	—	12	74	2
5	PEG-400 (0.5)	1.5	14	86	—
6	PEG-400 (1.0)	1.0	10	88	—
7	PEG-400 (2.0)	—	8	89	—
8[f]	PEG-400 (2.0)	—	1	—	90
9[g]	PEG-400 (1.0)	1.0	24	Trace	89
10[h]	PEG-400 (1.0)	1.0	24	Trace	90
11	PEG-400 (0.05)	2.0	24	60	24
12	18-Crown-6 (0.05)	2.0	24	60	23
13	TBABr (0.05)	2.0	24	64	20
14	[bmim][BF_4] (0.05)	2.0	24	58	25
15	[bmim][PF_6] (0.05)	2.0	24	57	25

[a] All reactions were carried out on a 1.0 mmol reaction scale of 2-fluoro benzaldehyde (**1a**) and 1.1 mmol of 2-amino phenol in the presence of 1.0 mmol of K_2CO_3 at 100 °C.
[b] Isolated yield.
[c] Reaction was carried out in the absence of K_2CO_3.
[d] Reaction was carried out in DMF (2.0 mL) at 50 °C.
[e] Reaction was carried out in DMF (2.0 mL) at 100 °C.
[f] Reaction was performed in sonicator at rt.
[g] Reaction was carried out at rt.
[h] Reaction was carried out at 50 °C.

environmentally friendly medium provided 89% of **2a** (entry 7).[10] PEG-400 as a reaction solvent markedly promoted the cyclization. Presumably, PEG-400 stabilizes the transition state for the reaction more than did CH_3CN and DMF resulting in an increase in the reaction rate.[11]

The series of reactions was performed to investigate the effect of concentration of solvent on the reactivity. The reaction with 0.5 g of PEG-400 provided 86% of **2a** after 14 h whereas 1.0 g of PEG-400 gave 88% of **2a** after 10 h (entries 5 and 6). We also carried out the same reaction in sonicator at room temperature but the reaction remained incomplete with 90% of imine **2b** (entry 8). Entries 9 and 10 clearly indicate the temperature effect on the synthesis of **2a**. The use of PEG-400 as a catalyst showed slow reactivity with 60% of **2a** and 24% of unreacted imine **2b** after 24 h (entry 11) whereas the very common but expensive phase transfer catalysts like 18-crown-6 and tetra-*n*-butylammonium bromide (TBABr) showed similar reactivity (entries 12 and 13). We also performed the reactions with ionic liquid as a catalyst (entries 14 and 15). Further, we conducted the reactions with 2-chloro- and 2-bromo benzaldehyde as two other substrates. In the case of chloro substrate, we observed slow reactivity with very low yield (<5%) of cyclized compound **2a** whereas, with bromo substrate, reaction did not proceed.

The search for alternative reaction media to replace volatile and often toxic solvents commonly used in organic synthetic procedures is an important objective of significant environmental consequence. So to check the eco-friendliness of PEG, we recycled PEG-400 for several times (Table 2).[10] The reaction proceeded cleanly with consistent results, although a weight loss of ~5% of PEG-400 was observed from cycle to cycle due to mechanical loss.

There are many potential advantages of replacing VOCs with PEGs. The most obvious are low cost, reduced flammability, toxicity, and environmental risk as a result of discharges of the supporting phase. We next performed the synthesis of **2a** in various PEGs with molecular weight 200, 300, 1000, 2000, 8000, 10,000, and 20,000 (Table 3, entries 1–7). Entries 1–3 completed within 12 h with excellent yields of **2a**. However, as the molecular weight of PEGs increases, viscosity increase is observed which led to highly viscous reaction mixture even after using certain amount of acetonitrile as cosolvent. Entries 4–7 provided comparatively low yield of **2a**.

In most of the methodologies, cosolvents place a dramatic effect on the reactivity, selectivity, and yield of the reaction. To check the effect of cosolvents along with PEG on the intramolecular aromatic nucleophilic displacement reaction towards the synthesis of **2a**, we performed a series of reactions in different cosolvents (polar protic/aprotic/non-polar). However, we did not observe any noticeable effect of cosolvents in the case of our methodology (Table 4).

Table 2
Synthesis of dibenz[*b*,*f*]-1,4-oxazepine in recycled poly(ethylene glycol)-400[a]

Run	1	2	3	4	5
Yield[b] (%)	89	90	90	89	88

[a] All reactions were carried out on a 1.0 mmol reaction scale of 2-fluoro benzaldehyde (**1a**), 2-amino phenol (1.1 mmol), K_2CO_3 (1.0 mmol) in recycled PEG-400 at 100 °C.
[b] Isolated yield.

Table 3
Synthesis of dibenz[*b*,*f*]-1,4-oxazepine in various poly(ethylene glycols)[a]

Entry	Promoter (g)	CH_3CN (mL)	Yield[b] (%)	
			2a	**2b**
1	PEG-200 (2.0)	—	88	—
2	PEG-300 (2.0)	—	87	—
3	PEG-1000 (2.0)	—	88	—
4	PEG-2000 (1.0)	1.0	67	18
5	PEG-8000 (0.5)	1.5	65	20
6	PEG-10000 (0.5)	1.5	68	20
7	PEG-20000 (0.5)	1.5	65	22

[a] All reactions were carried out on a 1.0 mmol reaction scale of 2-fluoro benzaldehyde (**1a**) and 1.1 mmol of 2-amino phenol in the presence of 1.0 mmol of K_2CO_3 at 100 °C for over 12 h.
[b] Isolated yield.

Table 4
Synthesis of dibenz[*b*,*f*]-1,4-oxazepine in polyethylene glycol-400 and various cosolvents[a]

Entry	Cosolvent (mL)	Yield[b] (%) **2a**
1	EtOH (1.0)	89
2	DMF (1.0)	88
3	C_6H_6 (1.0)	89
4	THF (1.0)	89
5	Ethylene glycol (1.0)	89
6	Ethylene glycol dimethylether (1.0)	88

[a] All reactions were carried out on a 1.0 mmol reaction scale of 2-fluoro benzaldehyde (**1a**), 1.1 mmol of 2-amino phenol and 1.0 mmol of K_2CO_3 in PEG-400 (1.0 g) and cosolvent (1.0 mL) at 100 °C over 10 h.
[b] Isolated yield.

In entry 2, polar aprotic solvent like DMF was used as a cosolvent which provided 88% of **2a**. When benzene and THF were used as a cosolvent we observed the same kind of behavior with 89% of **2a** (entries 3 and 4). The monomer of PEG as a cosolvent also provided high yield of **2a** (entry 5). Ethylene glycol dimethylether was also found to be a good cosolvent which provided 88% of **2a** (entry 6). In the case of entry 1 where PEG and ethanol was used as a mixture solvent system, 89% of **2a** was obtained.

In conclusion, a simple, efficient, and environmentally benign methodology towards the synthesis of oxazepine has been reported. Here PEG not only acts as a phase transfer catalyst but also as a clean solvent by significantly enhancing the intramolecular cyclization. Our protocol is a practical approach which uses PEG as a readily commercially available non-ionic liquid solvent with low cost and recyclable property. Moreover, the workup procedure is simple and convenient without any major equipment. Further studies to develop new clean methodology towards the synthesis of biologically active compounds are in progress.

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10. *Typical experimental procedure*: To the argon purged glass vial 2-amino phenol (112.3 mg, 1.1 mmol) in polyethylene glycol (400 MW, 2.0 mL) were added potassium carbonate (138.2 mg, 1.0 mmol) and 2-fluoro benzaldehyde (124.1 mg, 1.0 mmol) and stirred at 100 °C for the appropriate time (see Table 1) during which the reaction was monitored by means of Thin Layer Chromatography. The reaction mixture was extracted with ether (3 × 6 mL). The combined ether layers were washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Subsequent column chromatography over silica gel gave product **2a**. Dibenz[*b*,*f*]-1,4-oxazepine: Yellow crystalline solid; mp 72.0–72.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.13–7.28 (m, 6H), 7.36–7.49 (m, 2H), 8.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.0, 121.7, 125.4, 126.0, 127.5, 129.2, 129.5, 130.5, 133.8, 140.6, 153.0, 160.8, 160.9; MS (EI) 195 (M^+, 100). Anal. Calcd: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.75; H, 4.58; N, 7.23; Registry No. 257-07-8. *Poly(ethylene glycol) recycling procedure*: To the recovered crude PEG (≈2.0 mL) was added distilled ethanol (10 mL) and passed through a very short pad of silica gel and activated charcoal. The colorless organic layer was evaporated under reduced pressure. PEG was further dried under high vacuum over night and used for the next run.
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