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Eco-friendly polyethylene glycol promoted Michael addition reactions of α,β-unsaturated carbonyl compounds

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ABSTRACT

Intra- and inter-nucleophilic addition reactions of different α,β-unsaturated carbonyl compounds were found to be highly effective without any additives in PEG-400 as a recyclable reaction medium under neutral conditions.

There has been an increasing emphasis among researchers from both academia and industry to design synthetic strategies keeping in view the principles of 'Green Chemistry'.[1a] Adopting the principles of green chemistry means to reduce or eliminate the generation and use of hazardous substances. In recent years, replacement of hazardous solvents with environmentally benign solvents[1b,c] or development of solvent-free syntheses[2] is one of the major focus areas of Green Chemistry. The utility of alternative reaction solvents such as water,[3] ionic liquid,[4] fluorous,[5] supercritical media,[6] and polyethylene glycol (PEG)[7] is rapidly growing.

The Michael addition reaction is the one of the important methods, which is widely used in organic synthesis to make carbon–carbon and carbon–heteroatom bonds.[8] Several Lewis acid catalysts are reported to be highly effective in Michael addition of nucleophiles on α,β-unsaturated carbonyl compounds.[8]

Recently, PEG and its solutions have been introduced as interesting green solvent systems.[7] These have replaced many other 'neoteric solvents' such as ionic liquids, super-critical carbon dioxide, and micellar systems whose toxicological properties, short and long-term hazardous nature, and biodegradability have not been established completely. Low cost, reduced flammability, reduced toxicity, recyclability, completely nonhalogenated composition, easily degradable, and miscibility with wide variety of organic solvents are some of the properties that render PEG a benign alternative solvent in organic synthesis. Many organic transformations such as substitution reactions,[9] oxidation and reduction reactions,[10] Heck reaction,[11] asymmetric dihydroxylation,[12] Suzuki cross-coupling reaction,[13] Wacker reaction,[14] and partial reductions of alkynes[15] are accomplished using PEG as a solvent or co-solvent. Herein, we report catalysis-free Michael addition reactions of α,β-unsaturated carbonyl compounds in PEG-400 as a recyclable and recoverable medium.

In our efforts to study Michael addition reactions of α,β-unsaturated compounds, at first, we investigated intramolecular cyclization of 2′-hydroxychalcones **1** and 2′-aminochalcones **3**, which are reported to afford flavanones and quinolones, respectively, in low to moderate yields.[16–20] Generally, cyclization of **1** and **3** are carried out using different acids,[16] bases,[17] and other reagents[18–20] in combination with highly volatile organic solvents and under harsh reaction conditions. Flavanones and quinolones are rudimentary structures for synthesis of many biologically active potent molecules. Our initial attempts to cyclize 2′-hydroxychalcones **1** and 2′-aminochalcones **3** under conventional heating without any solvent afforded only trace amounts of products **2** and **4**, respectively, along with largely unchanged starting materials. Cyclization of **1** and **3** in polar solvents DMSO and DMF also remained incomplete under conventional heating at various temperatures.

With our recent success in the synthesis of 2-aminochromenes in aqueous PEG-400,[21] we explored cyclizations of **1** and **3** in PEG-400, and gratifyingly found that reactions were completed without any additives (Schemes 1 and 2). In order to optimize reaction temperature, a series of experiments of **1** and **3** in PEG-400 at various

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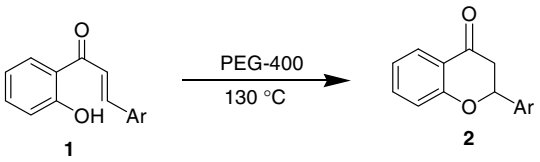
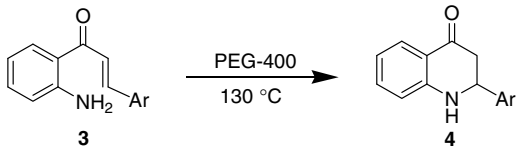


Scheme 1.



Scheme 2.

Table 1
Cyclization of 2′-hydroxychalcones **1a–g** in PEG-400

Product[a]	Ar	Time (h)	Yield[b] (%)
2a	C_6H_5	1.0	63
2b	*p*-FC_6H_4	3.0	65
2c	*p*-MeC_6H_4	2.5	62
2d	*p*-ClC_6H_4	2.5	74
2e	*p*-$MeOC_6H_4$	2.5	64
2f	2,6-$Cl_2C_6H_3$	2.5	65
2g	2-Furyl	2.5	67

[a] Products were characterized by their ^1H, ^{13}C NMR, and HRMS spectral data.
[b] Yields refer to isolated pure products.

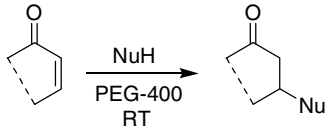
Table 2
Cyclization of 2′-aminochalcones **3a–f** in PEG-400

Product[a]	Ar	Time (h)	Yield[b] (%)
4a	C_6H_5	12.0	91
4b	*p*-MeC_6H_4	14.5	89
4c	*p*-ClC_6H_4	11.0	87
4d	*p*-$BnOC_6H_4$	11.5	88
4e	2,6-$Cl_2C_6H_3$	12.0	85
4f	2-Furyl	10.5	82

[a] Products were characterized by their ^1H, ^{13}C NMR, and HRMS spectral data.
[b] Yields refer to isolated pure products.

temperatures were performed, and it was found that 130 °C is the optimum temperature to get satisfactory results.[22] Attempts to expedite cyclizations of **1** and **3** under microwave irradiation were unsuccessful. Cyclizations of 2′-amino-chalcones **3** were convergent to completion, whereas in the case of 2′-hydroxychalcones **1** minor amounts of unreacted starting materials were recovered. The results of cyclizations of **1** and **3** are summarized in Tables 1 and 2.

Finally, intermolecular nucleophilic addition reactions of various α,β-unsaturated compounds (**5a,b**) under similar conditions were also investigated (Scheme 3). The literature reports on intermolecular Michael addition reactions of α,β-unsaturated carbonyl



Scheme 3.

Table 3
Reactions of α,β-unsaturated carbonyl compounds in PEG-400

Acceptor	Nucleophile	Product[a]	Time (h)	Yield[b] (%)
5a	$C_6H_5NH_2$	**6a**	5.0	92
5b	$C_6H_5CH_2NH_2$	**6b**	4.5	89
5b	*n*-$BuNH_2$	**6c**	5.5	84
5b		**6d**	5.5	87
5b		**6e**	6.5	89

[a] Products were characterized by their ^1H, ^{13}C NMR, and HRMS spectral data.
[b] Yields refer to isolated pure products.

compounds generally involve relatively expensive and hazardous reagents under various reaction conditions. Reactions of amines and imidazole with α,β-unsaturated carbonyl compounds (**5a,b**) in PEG-400 proceeded smoothly to afford products in good yields (Table 3, **6a–e**).[23–25] Recovered PEG-400 was recycled for the reaction of cyclohex-2-enone **5a** with aniline successively for three times without loosing product yield. Probably, weak interaction of PEG-400 via hydrogen bonding with the oxygen of enone induces electrophilic character at the β-carbon, which is attacked by the nucleophile.

In summary, we have accomplished nucleophilic addition reactions of a variety of α,β-unsaturated compounds in PEG-400, an easily recyclable and highly effective reaction medium, under neutral conditions.

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22. Synthesis of 2-(furan-2-yl)-2,3-dihydrochromen-4-one (**2g**): A mixture of **1g** (0.3 g, 1.40 mmol) and PEG-400 (0.5 mL) was stirred vigorously for 2.5 h at 130 °C. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 × 3 mL). The combined organic phase was washed with saturated brine solution, dried over anhydrous Na_2SO_4, and diethyl ether was removed by distillation. The crude product was percolated over a bed of silica gel to afford pure flavanone **2g**[26] in 67% (0.2 g) yield. Mp 74–75 °C; IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H, J = 8.0 Hz), 7.49 (m, 3H), 7.03 (dd, 1H, J = 14.0, 7.6 Hz), 6.42 (dd, 1H, J = 21.6, 3.2 Hz), 5.54 (dd, 1H, J = 11.60, 3.2 Hz), 3.2 (dd, 1H, J = 16.8, 8.0 Hz), 2.97 (dd, 1H, J = 17.20, 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.24, 160.74, 150.89, 143.43, 136.24, 126.95, 121.73, 120.93, 118.12, 110.51, 109.34, 72.27, 40.80.
Similarly, other flavanones **2a–f** and quinolones **4a–f** were synthesized and analyzed.
Compound **4f**: IR (KBr) 3325 (NH), 1690 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 1H, J = 8.0 Hz), 7.37–7.26 (m, 2H), 6.78–6.69 (m, 2H), 6.32 (d, 1H, J = 1.2 Hz), 6.25 (d, 1H, J = 1.53 Hz), 4.82 (dd, 1H, J = 9.6, 5.1 Hz), 4.77 (br s, 1H, NH), 3.07–2.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.72, 153.48, 150.61, 142.48, 135.54, 127.56, 119.34, 118.69, 117.17, 116.14, 110.21, 50.79, 42.07.
23. Representative procedure for Michael addition reaction of cyclohex-2-enone **5a**: A mixture of **5a** (0.50 g, 5.2 mmol) and aniline (0.48 g, 5.2 mmol) was placed in a round-bottomed flask containing 0.5 mL of PEG-400. The reaction mixture was allowed to stir for 5 h at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 × 3 mL). The combined organic layer was washed with saturated brine solution, dried over anhydrous Na_2SO_4, and distilled. The crude product was purified by percolation over a bed of silica gel to afford pure product **6a**[25] in 92% yield (0.90 g). Compound **6a**; IR (Neat) 3360 (NH), 1705 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19–7.13 (m, 2H), 6.77–6.58 (m, 3H), 3.8 (m, 1H), 2.82 (m, 1H), 2.40–2.25 (m, 4H), 2.04 (m, 2H), 1.73–1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.73, 146.31, 129.37, 118.64, 113.37, 52.36, 48.65, 41.23, 31.15, 22.22. Similarly, compounds **6b–e** were prepared and analyzed.
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