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A simple and green procedure for the conjugate addition of thiols to conjugated alkenes employing polyethylene glycol (PEG) as an efficient recyclable medium

Ahmed Kamal,* D. Rajasekhar Reddy and Rajendar

Division of Organic Chemistry, Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India

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Abstract—Polyethylene glycol (PEG) is found to be an inexpensive, nontoxic, environmentally friendly reaction medium for the conjugate addition of thiols to conjugated alkenes to afford the corresponding adducts in excellent yields under mild and neutral conditions. Products of undesirable side reactions resulting from polymerization are not observed. The use of PEG avoids the use of either acid or base catalysts for this conversion and moreover PEG can be recovered and reused.

Green chemistry is becoming a central issue in both academic and industrial research in the 21st century,[1] and the development of environmentally benign and clean synthetic procedures has become the goal of present day organic synthesis. Organic reactions without the use of harmful organic solvents are now of great interest in organic synthesis.[2] Attempts have been made to develop solvent-free chemistry, which to some extent have been successful in a few transformations.[3] More recently, attention has been drawn to the development of environmentally benign solvents such as ionic liquids,[4] water,[5] and polyethylene glycol.[6] It is customary to measure the efficiency of a catalyst by the number of cycles for which it can be reused. Similarly, the value of a new solvent medium primarily depends on its environmental impact, the ease with which it can be recycled, low vapor pressure, nonflammability and high polarity for solubilization. However, in performing the majority of organic transformations, solvents play an important role in mixing the ingredients to make the system homogeneous and allow molecular interactions to be more efficient.

The Michael reaction since its discovery in 1889 is one of the most important reactions in organic chemistry.[7] The conjugate addition of thiols to electron-deficient olefins to form a carbon–sulfur bond constitutes a key reaction in biosynthesis as well as in organic synthesis.[8] Organosulfur compounds are also useful in the synthesis of biologically active compounds such as the calcium antagonist diltiazem.[9] Consequently, a large number of reagents have been reported in the literature for the addition of mercaptans to conjugated alkenes.[10] In order to avoid side-reactions, several inorganic salts have been introduced in the presence of strong acid or base.[11] A number of procedures, either based on activation of thiol by a base or activation of the acceptor olefins with Lewis acids have been used.[12] More recently, tetrabutylammonium halide has been used as phase-transfer catalyst.[13] There is also a recent report of carrying out these reactions in ionic liquids and a mixture of ionic liquids and water (2:1).[14] Ionic liquids have been shown to have serious drawbacks, especially imidazolium systems with PF_6 and BF_4 anions are as toxic as benzene to certain aquatic ecosystems, and also liberate hazardous HF during recycling. Apart from this, the high cost[15] and disposability of these solvents also limit their utility. The use of strong acids (polymerization of vinyl ketones) and bases in the medium, toxic catalysts, harsh conditions, far from satisfactory yields and selectivities due to the occurrence of side-reactions restrict practical applications in industry.

Keywords: Conjugate addition; Thiols; Conjugated alkenes; Polyethylene glycol.

* Corresponding author. Tel.: +91 40 27193157; fax: +91 40 27193189; e-mail addresses: ahmedkamal@iict.res.in; ahmedkamal@iictnet.org

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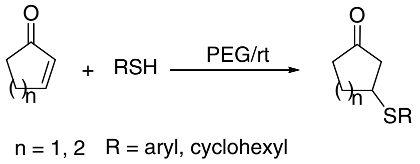
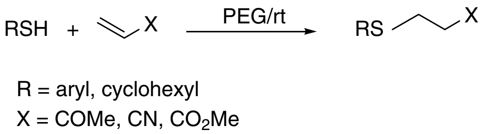
PEG and its monomethyl ethers are inexpensive, thermally stable, recoverable, and nontoxic media for phase-transfer catalysts.[16] PEG, a biologically acceptable polymer used extensively in drug delivery and in bioconjugates as tool for diagnostics, has hitherto not been widely used as a solvent medium but has been used as a support for various transformations.[6,17] Herein, we report PEG 400 as a recyclable reaction medium for conjugate addition of various thiols to conjugated alkenes at room temperature without the use of any acid or base catalyst (Schemes 1 and 2). Such reactions do not generate any toxic waste products.

Our efforts began with thiophenol and 2-cyclohexen-1-one in the presence of PEG 400 (Table 1, entry 1) at room temperature for 30 min, the corresponding adduct was obtained in 92% yield. Other thiols were reacted with a variety of conjugated alkenes in polyethylene glycol (Table 1). The reaction proceeds efficiently at room temperature without the need for any further acid or base catalyst and goes to completion in a short time (20–45 min).[18] This methodology is compatible with various α,β-unsaturated ketones, nitriles, and esters and different substituted aromatic thiols or cyclohexanethiol under mild reaction conditions. No by-product formation was observed. Moreover, these reactions are clean with excellent yields compared to conventional methods, have shorter reaction times, higher selectivities and a recyclable reaction medium.

The catalytic activity of polyethylene glycol for these conjugate additions was established by the fact that there was no reaction in the absence of PEG. We suggest that the mechanism of addition of thiols to conjugated alkenes employing polyethylene glycol as the reaction medium involves the formation of a hydrogen bond between the thiol and the polyethylene glycol hydroxyl group, which makes the S–H bond weaker, enhancing the nucleophilicity of sulfur for addition to electron-deficient alkenes.

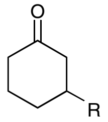
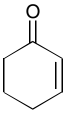
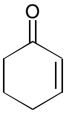
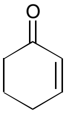
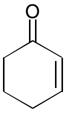
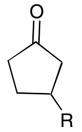
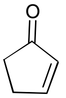
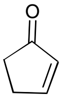
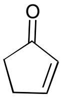
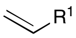
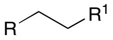


Scheme 1.



Scheme 2.

Table 1. Conjugate addition of thiols to conjugated alkenes using PEG

Entry	Conjugated alkene	Product	Time (min)	Yield[a,b] (%)
				
1		R = C_6H_5S	30	92
2		R = p-ClC_6H_4S	25	92
3		R = o-MeC_6H_4S	30	90
4		R = $C_6H_{11}S$	40	88
				
5		R = C_6H_5S	40	90
6		R = p-ClC_6H_4S	35	88
7		R = p-$OMeC_6H_4S$	45	86
				
8	R^1 = COMe	R = C_6H_5S	20	94[c]
9	R^1 = COMe	R = p-ClC_6H_4S	20	92
10	R^1 = COMe	R = o-MeC_6H_4S	20	88
11	R^1 = COMe	R = p-C_6H_4S	20	90
12	R^1 = COMe	R = $C_6H_{11}S$	30	84
13	R^1 = CN	R = C_6H_5S	20	92
14	R^1 = CN	R = p-ClC_6H_4S	25	90
15	R^1 = CN	R = o-MeC_6H_4S	25	88
16	R^1 = CN	R = p-$OMeC_6H_4S$	30	92
17	R^1 = CN	R = $C_6H_{11}S$	40	86
18	R^1 = CO_2Me	R = C_6H_5S	25	90
19	R^1 = CO_2Me	R = p-ClC_6H_4S	30	90
20	R^1 = CO_2Me	R = o-MeC_6H_4S	30	86

[a] All the products were characterized by mass, ^1H NMR, and IR spectroscopy and by comparison with literature data.

[b] Isolated yields.

[c] PEG was recovered and reused for five consecutive runs in this reaction without any change in the yield or purity.

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18. *General procedure*: A mixture of thiol (1 mmol), alkene (1.2 mmol) and PEG 400 (2 g) was placed in a 10 mL round-bottomed flask. The mixture was left stirring at room temperature until the reaction was complete (Table 1). The reaction mixture was extracted with dry ether, the extract dried and concentrated under reduced pressure and the resulting crude product was purified by silica column chromatography using EtOAc and hexane (1:9) as an eluent to obtain the adduct in excellent yield. The recovered PEG can be reused for a number of cycles without significant loss of activity. Spectral data for 3-phenylthiocyclohexan-1-one (**1**) (Table 1, entry 1): ^{1}H NMR 200 MHz ($CDCl_3$): δ 1.75 (m, 2H), 2.10 (m, 2H), 2.35 (m, 2H), 2.40 (d, $J = 10.9$, 1H), 2.70 (dd, $J = 10.9$, 4.41, 1H), 3.45 (m, 1H), 7.25 (m, 3H), 7.45 (m, 2H); IR: 1712, 749, 693 cm^{-1}. Spectral data for 3-phenylthiocyclopentan-1-one (**5**) (Table 1, entry 5): ^{1}H NMR 200 MHz ($CDCl_3$): δ 1.95–2.05 (m, 1H), 2.34–2.65 (m, 5H), 3.90 (q, $J = 6.3$ Hz, 1H), 7.29–7.35 (m, 3H), 7.40–7.43 (m, 2H); IR: 1743, 742 cm^{-1}.