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LETTERS

Direct condensation of carboxylic acids with polyethylene glycols catalyzed by $Sc(OTf)_3$[†]

S. Chandrasekhar,[a,]* S. Shameem Sultana,[a] Ch. Narsihmulu,[a] J. S. Yadav,[a] R. Gree[b] and J. C. Guillemin[b]

[a]*Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*ENSCR, Laboratoire de Syntheses et Activations de biomolecules, CNRS UMR 6052, Av du G Leclerc, 35700 Rennes, France*

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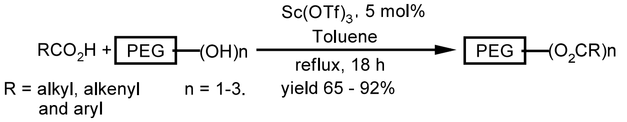
Abstract—Esterification of soluble polymers by direct condensation of equimolar amounts of carboxylic acids with polyethylene glycols is achieved using catalytic $Sc(OTf)_3$ in toluene for the first time. © 2002 Elsevier Science Ltd. All rights reserved.

Esterification is one of the most fundamental reactions in organic synthesis.[1] Conventionally, this is achieved by condensing an acid and an alcohol with one being in large excess. Also certain activators (viz, acid chlorides,[2] catalysts[3] and dehydrating agents[4]) are essential. In order to avoid environmental waste, it is highly desirable to develop new procedures for condensation where both components are taken in stoichiometric amounts. This is also essential if the substrates are scarce, highly expensive and/or are obtained after multi-step synthesis. Unfortunately, however, for loading of organic molecules onto a polymer support through an ester linkage, a large excess of the carboxylic acid moiety is essential to force the reaction to completion. This transformation is almost inevitable in solid phase organic synthesis (SPOS)[5] and combinatorial chemistry. Thus the development of new procedures wherein stoichiometric amounts of acids and alcohols are sufficient for ester formation are welcome. Some very good procedures[6] have been published recently which include (a) diphenyl ammonium triflate (DPAT)[6a] as an efficient catalyst for esterification of carboxylic acids with nearly equimolar amounts of alcohols; (b) hafnium (IV) salts;[6b] (c) $TiCl_2(ClO_4)_2$ and $TiCl(OTf)_3$[6c] reagents. All these procedures have proved to work well only in solution with the hafnium salts being an exception wherein a few polymer substrates were tested with success. This protocol requires a dehydrating agent in the form of CaH_2. The literature reported DCC mediated esterification[7] of $PEG(OH)_n$ generates stoichiometric amounts of urea which are difficult to remove from the soluble polymers and requires excess reagent and acids. We desired a clean protocol for loading carboxylic acids onto $PEG(OH)_n$ and none of the above procedures were ideal. To address this problem, we have developed a new method of loading a carboxylic acid (RCOOH) onto $PEG(OH)_n$, the reaction being catalyzed by $Sc(OTf)_3$ with simple reflux in toluene using a Dean–Stark apparatus (Scheme 1).

We first investigated the esterification[8] of benzoic acid (entry 1) with HO-(PEG)-OH (MW 2000) by dissolving both components in toluene containing 5 mol% $Sc(OTf)_3$ and refluxing for 18 h under a Dean–Stark apparatus. Toluene was evaporated, the resulting syrup was cooled to 0°C in an ice bath and was slowly added to cold ether to allow precipitation of the PEG bound benzoate. The resulting solid was washed with cold ether. The ^1H NMR confirmed that loading was achieved to an extent of 70%[9] (based on ^1H NMR integration). Other carboxylic acids, namely *m*-chlorobenzoic acid (entry 2, 75% conversion), cinnamic acid (entry 3, 73% conversion) and acrylic acid (entry 4, 85% conversion) were also loaded onto PEG-diol with varying percentages of conversion (see Table 1).



Scheme 1.

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* Corresponding author. Tel.: +091-040-7193434; fax: +091-040-7160512; e-mail: srivaric@iict.ap.nic.in

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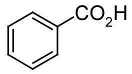
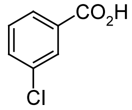
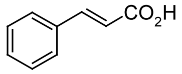
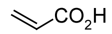
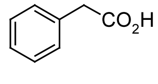
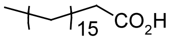
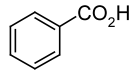
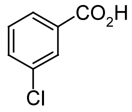
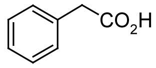
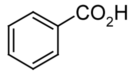
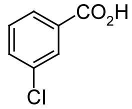
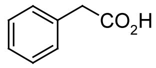
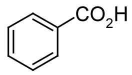
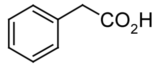
Table 1. Direct condensation of carboxylic acids with polyethylene glycols

S No	Acid	Alcohol	Conversion (%)^a
1		HO-PEG 2000-OH	70
2		" "	75
3		" "	73
4		" "	85
5		" "	87
6		" "	86
7		MeO-PEG5000-OH	70
8		" "	78
9		" "	83
10		HO-PEG 6000-OH^b	67
11		" "	73
12		" "	77
13		PEG 4400-(OH)$_3$	80
14		" "	92

^{a}Yields calculated based on ^{1}H NMR

^{b}Required a longer reaction time (36 h) and 3 eq. of carboxylic acid. Other examples required 18 h and 1.1 eq. of carboxylic acid.

Phenyl acetic acid (entry 5) was loaded to an extent of 87% with ease. The aliphatic stearic acid (entry 6) participated in esterification to an extent of 86%. Similarly PEG(OH)$_3$ having a molecular weight of 4400 was also loaded with benzoic acid (entry 13) and phenylacetic acid (entry 14) in 80% and 92% loading efficiencies. Next the more abundantly available MeO-PEG-(5000amu) was subjected to esterification (entries 7 and 8) with benzoic acid and *m*-chlorobenzoic acid to give 70% and 78% loading, respectively. The higher molecular weight (6000) PEG (OH)$_2$ was subjected to the present protocol for esterification and slightly lower percentages of loading were observed (entries 10, 11 and 12).

From the above experiments, it may be inferred that simple and unsaturated aliphatic acids (entries 3, 4, 5, 6, 9, 12 and 14) work better for loading onto PEG under the presented protocol. Also as the MW exceeds 5000 daltons, the loading is not efficient. Unusually, $PEG(OH)_3$ was more efficient than the other polymeric substrates studied.

In conclusion, a new $Sc(OTf)_3$ catalyzed esterification of carboxylic acids with (PEG) alcohols has been demonstrated which should be a useful tool for combinatorial chemistry and solid phase organic synthesis.

Acknowledgements

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8. Representative procedure: To polyethylene glycol (PEG-2000) (1 mmol), benzoic acid (1.1 mmol) and 5 mol% of $Sc(OTf)_3$ were added in toluene and the mixture refluxed for 18 h. Then the solvent was evaporated in vacuo to obtain a syrupy liquid, which was cooled and added to cold ether (20 ml) to give precipitation of acid bound PEG. The solid thus obtained was washed with cold ether (2×20 ml), and the residue was kept under high vacuum for 30 min. A sample was subjected to ^1H NMR in $CDCl_3$.
9. All compounds were characterized by ^1H NMR and mass spectroscopy.[10] Some representative data follow: **Bis(benzoyl) poly(ethylene glycol) 2000 diester (1)**: ^1H NMR ($CDCl_3$): δ 8.06 (d, 4H, $J=6.09$ Hz), 7.45 (m, 6H), 4.45 (t, 4H, $J=4$, 6.09 Hz), 4.30 (m, 4H), 3.98 (t, $J=3$, terminal-CH_2-O-of unreacted PEG), 3.6 (s, suppressed peak for PEG chain), 3.32 (unreacted -OCH_2 of PEG next to terminal -OCH_2). **Bis (cinnamoyl) poly (ethylene glycol) 2000 diester (2)**: ^1H NMR ($CDCl_3$); δ 7.68 (d, $J=16.6$ Hz, 2H), 7.53 (m, 4H), 7.38 (m, 6H), 6.47 (d, $J=16.6$ Hz), 4.35 (t, $J=4.4$ Hz, 4H), 3.98 (t, $J=3$, terminal-CH_2-O-of unreacted PEG), 3.6 (s, suppressed peak for PEG chain), 3.32 (unreacted -OCH_2 of PEG next to terminal -OCH_2).
10. A systematic study of mass fragmentation pattern, and application of this technique for characterization of small molecules will be published elsewhere.