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A Soluble Polymer-Supported Triflating Reagent: A High-Throughput Synthetic Approach to Aryl and Enol Triflates

Anita D. Wentworth, Paul Wentworth, Jr.,*,† U. Faruk Mansoor, and Kim D. Janda*

Department of Chemistry and Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Rd., La Jolla California 92037

kdjanda@scripps.edu

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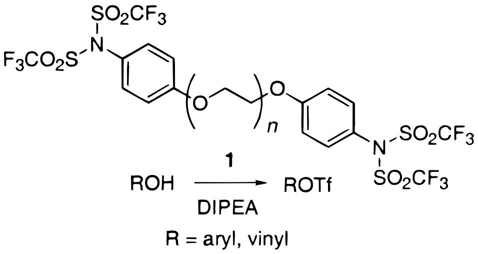
ABSTRACT



The high-yielding synthesis and application of the first example of a polymer-supported reagent for the preparation of trifluoromethanesulfonates (triflates) is described. This new reagent efficiently triflates aryl alcohols and lithium enolates in high yield (>90%). A simple precipitation and filtration to remove the excess reagent and byproduct facilitate purification of the triflate products. The PEG-supported approach is highly efficient, as the PEG-supported byproduct can be quantitatively recovered and recycled into reagent 1.

For many years functionalized polymers have been employed as stoichiometric reagents and catalysts, and also for reaction purification. However, their development and scope of employment is undergoing a rapid renaissance at present, which is undoubtedly being fueled by the special requirements of both combinatorial and "green" chemistry.[1]

Soluble polymer-supported organic chemistry, dubbed "liquid-phase" synthesis, is developing as an increasingly useful adjunct to the more classical heterogeneous resin-supported chemical methodology and combinatorial chemistry.[2] Our efforts in this area have included the development of soluble polymer-supported chemical libraries and peptidomimetics,[3] catalysts,[4] reagents,[5] linker strategies,[6] and total synthesis.[7]

Herein we describe the development of the first example of a polymer-supported triflating reagent (**1**) (Figure 1). Its utility is explored in the facile, high-yielding synthesis of aryl and vinyl triflates.

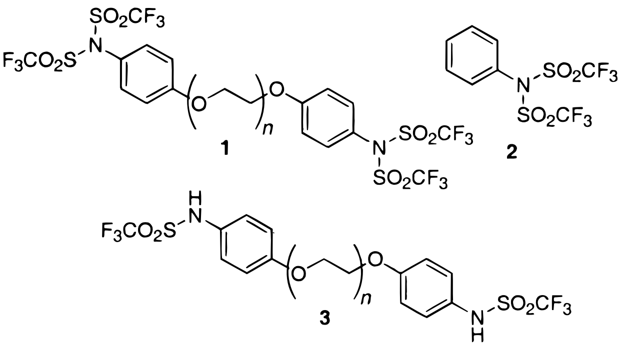


Figure 1. Components of liquid-phase and solution-phase triflation processes: PEG-supported triflimide **1**, solution-phase triflating reagent **2**, and PEG-supported triflamide **3**.

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† E-mail: paulw@scripps.edu.

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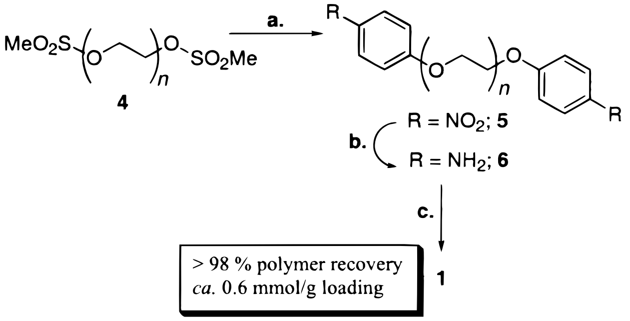
Aryl and enol triflates have tremendous synthetic utility as intermediates in palladium-, nickel, tin-, and cuprate-catalyzed cross-coupling reactions for the construction of carbon−carbon and carbon−heteroatom bonds. However, by their very nature, triflates are unstable (being prone to S_NAr routes of hydrolysis); therefore, a polymer-supported approach which removes the necessity for aqueous−organic liquid−liquid extraction and extensive column chromatography techniques may further facilitate the use of these reactive intermediates in both organic synthesis and combinatorial/high-throughput synthetic strategies.

As an entry level polymer-supported triflating agent, we substituted the soluble homopolymer, poly(ethylene glycol) (PEG), with a derivative of *N*-phenyltriflimide (**2**). The solution-phase reagent **2**,[8] originally introduced by Hendrickson[9] and McMurray,[10] is widely utilized for the generation of triflates. The chemoselectivity of **2**, when compared to trifluoromethanesulfonic anhydride (Tf_2O), results in optimal triflate yields even in the presence of amines, alcohols, or carboxylates and on relatively sensitive substrates.[11] However, the workup procedure with reagent **2** requires either an aqueous liquid−liquid extraction or silica gel chromatography to remove both the triflamide byproduct and excess starting materials. Therefore, for the reasons discussed vide supra, the application of this reagent may be facilitated considerably with a polymer-supported approach.

When designing a polymer-supported derivative, the natures of the polymer backbone and the linker have to be complementary to the chemistry being performed. We rationalized that the polyether backbone of PEG would confer both the necessary stability and homogeneous reaction conditions across the broad spectrum of reaction conditions required for aryl and enol triflate formation. Dihydroxy-PEG of average molecular weight 3400 (PEG_{3400}; equivalent to 0.6 mmol/g) was the support of choice, which couples acceptable loading levels with high polymer recoveries (>98%).[5b] The linker selected was an aryl alkyl ether, which we have shown previously to be stable under strong base and also metallating conditions.[5b]

Polymer-supported reagent **1** was synthesized in three steps starting from PEG_{3400}-dimesylate **4**,[5b] which was initially converted into the aryl alkyl ether **5** by treatment with 4-nitrophenol and cesium carbonate in warm DMF (60 °C) (Scheme 1). Catalytic reduction of the nitro group of **5** (5% Pd/C, H_2, 1 atm) furnished the polymer-supported aniline **6** which was converted into the triflimide derivative **1**, with Tf_2O and trioctylamine (TOA) at −42 °C in CH_2Cl_2. Using other tertiary amine bases, such as triethylamine or diisopropylethylamine (DIPEA), resulted in the isolation of trialkylammonium salts of trifluoromethanesulfonic acid along with the triflimide **1** during the work up of the triflation reaction. However, TOA trifluoromethanesulfonate (TOA-OTf) is soluble in diethyl ether and can be separated quantitatively from triflimide **1** during the workup. Reagent **1** was isolated, as a fine white powder, in >98% yield. The loading, determined by ^1H NMR, was quantitative (0.6 mmol/g). The ^{19}F NMR showed that the bis *N*-triflimde **1** (δ −67.1 ppm; cf. **2**, δ −67.4 ppm) was the only fluorine-containing species present, with no contamination from either triflamide **3** (δ −74 ppm) or TOA-OTf (δ −78 ppm). Stability studies, followed by ^{19}F NMR, show that the reagent is very stable; on standing in air for 2 days, **1** is <10% hydrolyzed to the polymer-supported triflamide derivative **3** (cf. with 20% hydrolysis observed with reagent **2**). This increased stability of a PEG-supported derivative, relative to its small molecule component, has been observed previously with Burgess' reagent.[12] This phenomenon may be due to a protective effect imparted by the PEG backbone, which masks the reactive terminal functionality from the environment when stored as a solid.

Scheme 1



a) *p*-nitrophenol, Cs_2CO_3, DMF (95%), b) 5% Pd/C, 1 atm H_2, (98%), c) Tf_2O, TOA, -42 °C, CH_3CN.

A range of aromatic alcohols (**7a**−**h**) was smoothly triflated by simple addition of reagent **1** to a stirred solution of the respective alcohol in CH_2Cl_2 in the presence of DIPEA (Table 1). The alcohols contain a diversity of substitution, including electron-withdrawing (**7c**) or -donating groups (**7b**), sensitive functionality (such as a ketone **7e** or aldehyde **7f**), hetreroatoms (**7g**−**h**), and hindered alcohols (**7d**). No limitations were observed with the polymer-supported triflation approach. In fact the isolated yields and reaction times with **1** were equivalent to those observed with the solution-phase reagent **2**. Product isolation involved removal of the PEG-supported triflamide byproduct **3** and by initial precipitation into diethyl ether followed by filtration. The filtrate was then

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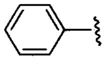
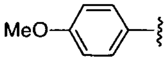
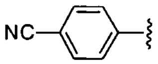
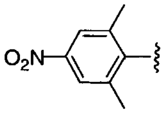
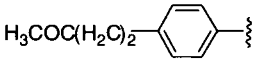
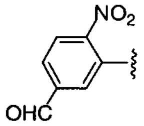
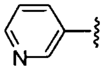
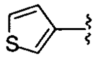
Table 1. Reaction of **1** and **2** with Aromatic Alcohols **7a−h**[a]

$$\underset{\mathbf{7}}{\text{Ar-OH}} \xrightarrow[\text{DIPEA}]{\mathbf{1}\text{ or }\mathbf{2}} \text{Ar-OTf}$$

	Ar	**LP**[b] yield[c] (purity)[f] (%)	**SP**[d] yield[c,e] (%)
7a		95 (97)	88
7b		91 (95)	87
7c		91 (92)	92
7d		88 (96)	89
7e		94 (97)	92
7f		89 (92)	95
7g		97 (92)	94
7h		93 (94)	92

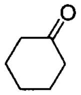
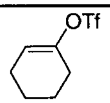
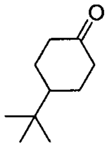
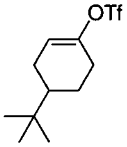
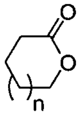
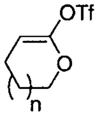
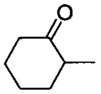
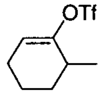
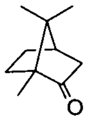
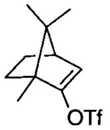
[a] Reaction conditions: The alcohol (1 eq.), triflating reagent (**1** or **2**) (2 eq.) and DIPEA were added to CH_2Cl_2 and stirred for 8 h at rt. [b] Using the liquid-phase (LP) reagent **1**. [c] Isolated yields. [d] Using the solution-phase (SP) reagent **2**. [e] Purity not determined by HPLC, because products isolated analytically pure by silica gel chromatography. [f] Purity determined by reversed-phase HPLC (VYDAC column).

concentrated and passed down a silica plug to facilitate removal of remaining traces of the PEG-supported byproduct **3** and diisopropylethylammonium trifluoromethanesulfonate (DIPEA-OTf). This gave the product triflates in excellent yields and purities. For comparison, the solution-phase reaction with reagent **2** was purified in a two-step process involving an initial aqueous extraction with a $NaHCO_3$ solution followed by silica gel chromatography.

Kinetic or thermodynamic enolate formation, through reaction of unsymmetrical ketones with properly selected strong bases, followed by treatment with **2** provides regioselective formation of vinyl triflates.[13] This is the major benefit of reagent **2** when compared to a Tf_2O/base strategy, which gives mainly the thermodynamic product with overall lower material yields.[8a] Therefore, an important evaluation of polymer-supported reagent **1** was its ability to form vinyl triflates with both high yields and regioselectivity.

For the solution-phase reaction, enolate formation is generally performed with lithium diisopropylamide (LDA) in either THF or dimethoxyethane (DME) at −78 °C.[11] PEG's known insolubility in THF below room temperature meant that all enolate generation for this study was performed in DME in which it is sparingly soluble. The reaction involved initial lithium enolate formation with the respective ketone and LDA in DME at −78 °C (1−2 h), followed by addition of **1** in DME at −78 °C. The reaction mixture was then immediately warmed to 0 °C, at which point the reaction mixture was homogeneous, and was stirred for 8 h. The results outlined in Table 2 show that polymer-supported reagent **1** is a highly efficient triflating agent of lithium enolates. The yields for all entries are similar to those obtained with the solution-phase reagent **2**. As important is that the regioselectivity of the triflation reaction is maintained, furnishing the kinetic vinyl triflate product in almost quantitative fashion (entries 4 and 5). The workup involved simple addition of the homogeneous reaction mixture into diethyl ether and removal of the byproduct **3** by filtration.

Table 2. Reaction of **1** and **2** with Lithium Enolates[a]

Entry	Substrate	Enol triflate	**LP**[b] yield[c] (%)	**SP**[d] yield (%)
1			95	88[e]
2			87	82[e]
3			n = 1, 91 n = 2, 92	75[f] 89[f]
4			95	92[e]
5			88	72[e]

[a] Reaction conditions: The ketone or lactone (1 eq.) in DME was added to a solution of LDA (1 eq.) in DME at −78 °C. The reaction was stirred for 1 h, and then the triflating reagent **1** (2 eq.) in DME was added and stirred for 8 h at 0 °C. All products gave satisfactory ^1H and ^{13}C NMR. [b] With the LP reagent **1**. [c] All yields are isolated. [d] With the SP reagent **2**. [e] Ref. 10. [f] Ref. 14.[14]

After each triflation reaction, the polymer byproduct **3** is coisolated with small amounts of DIPEA-OTf. These two components are separated by first stirring a CH_2Cl_2 solution of the mixture with Amberlite IRA-410 (strongly basic gel resin) for 1 h. Following removal of the resin by filtration, the byproduct **3** is then isolated by precipitation into diethyl ether in >98% yield. Triflation of **3** is then performed as described for amine **6**, vide supra, and polymer-supported

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triflimide **1** is isolated in >98% yield. The activity of the recycled reagent is identical to the original.

In summary, we have generated the first polymer-supported triflating reagent that is both easily synthesized and is very stable. It rapidly and efficiently triflates aryl alcohols and enolates of ketones and lactones. Furthermore, the regioselectivity observed during the triflation of unsymmetrical ketones is identical with that of a solution-phase counterpart, yielding the kinetic vinyl triflate exclusively. By comparison with the solution-phase approach, it offers the advantage of ease of purification of the triflate products by simple precipitation to remove the triflamide byproduct **3** and excess starting reagent **1**. The polymer-supported approach is also highly efficient, as the byproduct triflamide **3** can be quantitatively recovered and recycled into reagent **1**.

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Supporting Information Available: Experimental procedure for enol triflate generation. This material is available free of charge via the Internet at http://pubs.acs.org.

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