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Ester Enolate Claisen Rearrangement Using a Polymer-Supported Silyl Triflate

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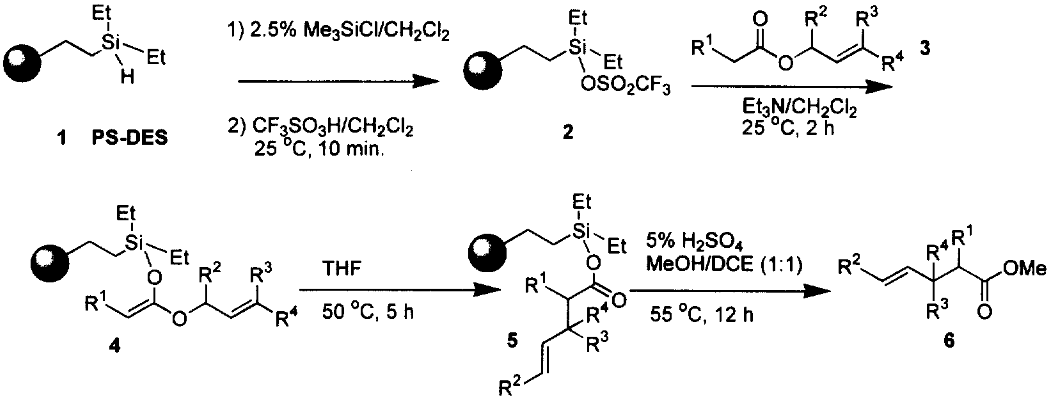
***Abstract*:** Polystyrene-diethylsilane resin (PS-DES) was treated with triflic acid to form a highly reactive polymer silyl triflate. The silyl triflate reacted with enolizable allylic esters in the presence of Et_3N to afford resin-bound silyl ketene acetals, which undergo Ireland-Claisen rearrangement at elevated temperature to provide polymer silyl esters. Transesterification of the polymeric silyl esters with 5% H_2SO_4 in 1:1 $MeOH/ClCH_2CH_2Cl$ (DCE) afforded methyl ester products. © 1999 Elsevier Science Ltd. All rights reserved.

While solid-phase organic synthesis has continued to play an important role in parallel synthesis of small organic molecules,[1] polymer-supported reagents and scavengers[2] have also found increasing utility. We have developed a novel trialkylsilane resin as a linker in solid phase organic synthesis, which allows attachment of alcohols, aromatics, and acetylenes through a silyl chloride intermediate[3] and direct attachment of alcohols and carbonyl compounds *via* dehydrogenation or reduction.[4] During the course of our studies, it was of interest to convert the silane moiety to a reactive silyl triflate for use as a polymer reagent. In solution, silyl triflates are commonly employed and react with α-methylene ketones, aldehydes, and carboxylic esters to form silyl enol ethers.[5] Silyl ketene acetals have also been extensively utilized in ester enolate Claisen rearrangements.[6,7] In this article, we present a procedure for the activation of PS-DES resin[8] to give a polymer silyl triflate, and its use in the formation and Ireland-Claisen rearrangement of resin-bound silyl ketene acetals (**Scheme 1**).

Scheme 1. Ester Enolate Claisen Rearrangement



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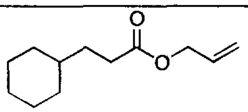
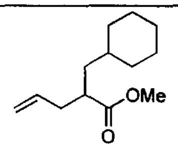
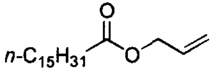
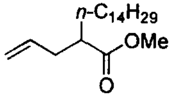
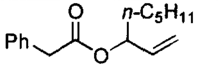
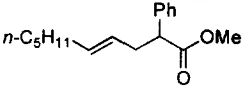
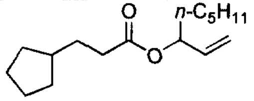
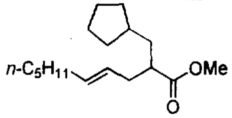
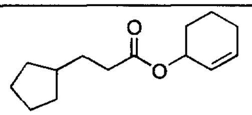
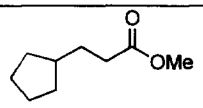
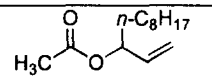
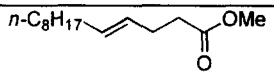
PS-DES resin (**1**) was pre-dried with 2.5% trimethylsilyl chloride in CH_2Cl_2 to remove traces of moisture prior to silyl triflate formation. After further washing (2 x CH_2Cl_2), the resin was treated with triflic acid (6 equiv) in CH_2Cl_2 to afford PS-DES triflate (**2**).[9,10] Triflation was monitored using FT-IR by examination of the Si-H stretch for PS-DES resin (2095 cm^{-1}) which disappeared after treatment with triflic acid for 10 min. The silyl triflate resin was further characterized by gel-phase ^{19}F NMR.[11] A signal was found at –79.7 ppm for the silyl triflate resin using $CDCl_3$ as solvent with trifluorotoluene as internal standard (CF_3Ph: –63.2 ppm).[12] Although gel-phase NMR experiments were performed on carefully handled, dried resin, the polymer silyl triflate is moisture sensitive and should be used *in situ* and *immediately after preparation* for optimum results.

The viability of PS-DES triflate as a polymer reagent was initially tested by attachment of alcohols (silyl ether formation) and enolizable ketones (silyl enol ether formation). 4-(4-Methoxyphenyl)-1-butanol and *p*-bromoacetophenone (3 equiv) were reacted with PS-DES triflate (1 equiv) in the presence of Et_3N (8 equiv, 2 h) to afford a resin-bound silyl ether and silyl enol ether, respectively. Cleavage using AcOH/THF/H_2O (6:6:1, 60 °C, 2 h)[4] recovered 4-(4-Methoxyphenyl)-1-butanol (65%) and *p*-bromoacetophenone (71%) as determined by GC (internal standard).

Table 1. Results of Ester Enolate Claisen Rearrangement Using the Silyl Triflate Resin

Entry	Allyl Ester (3)	Product (6)	Yield (%)	GC Purity (%)
1			58	92
2			53	86
3			56	95
4			52	97
5			60	100
6			0	NA

To further demonstrate the utility of the silyl triflate **2** as a polymer reagent, allylic esters (**3**)[13] were reacted with PS-DES silyl triflate followed by Ireland-Claisen rearrangement to produce silyl esters (**5**) which were then cleaved from the support by transesterification (**Scheme 1**).[14] Results for representative reactions are provided in **Table 1**. A variety of allyl esters were used to form methyl ester products (**6**, **Scheme 1**). The chemistry sequence could be monitored qualitatively using FT-IR. FT-IR analysis of bound silyl ketene acetals (**4**) showed a weak carbonyl absorption, which suggested that some Claisen rearrangement had occurred at room temperature during ketene acetal formation. After heating, the PS-DES silyl esters **5** showed a strong IR stretch (C=O: 1710-1720 cm^{-1}). FT-IR was also used to monitor the completion of transesterification to form methyl esters (disappearance of C=O stretch). In the single case examined (entry 5), an allylic ester derived from a cyclic allylic alcohol ionized at the allylic position and trapped the resulting ester moiety to form methyl 3-cyclopentyl propionate after cleavage from the resin. For entry 6, no methyl ester product was produced after transesterification with 5% H_2SO_4 in MeOH:DCE (1:1).[15] However, FT-IR analysis of the resin products from acetic acid ester cases showed a strong C=O stretch (1715 cm^{-1}). In solution, reaction of esters with silyl triflates/Et_3N yields a mixture of O- and C-silylated products and acetic acid esters generally form C-silylated products exclusively under these conditions.[16] The prolongation of the alkyl chain in the acyl group favors O-silylation.[5] It is therefore likely that in cases where acetic acid esters were utilized, C-silylation occurred and the resin-bound α-silyl esters were stable to the transesterification conditions.

In summary, a method for generation of a reactive polymer silyl triflate has been developed. The polymer silyl triflate reacted with allylic esters to form silyl ketene acetals, which undergo Ireland-Claisen rearrangement to form resin-bound silyl esters. Transesterification of polymer silyl esters cleanly produced methyl ester products. Further functionalization reactions of silyl ester intermediates and alternate cleavage protocols are possible. Additional applications of polymer-supported silyl triflates are ongoing, as described in the accompanying manuscript.[17]

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Reference and Notes

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[1] (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. For a recent review, see (b) Thompson, M. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

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[7] (a) Ireland, R. E.; Wipf, P.; Xiang, J. *J. Org. Chem.* **1991**, *56*, 3572. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650.

[8] PS-DES resin is commercially available from Argonaut Technologies, San Carlos, CA.

[9] For preparation of silyl triflates in solution, see: (a) Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1985**, *26*, 6113. (b) Hudrlik, P. F.; Kulkarni, A. K. *Tetrahedron Lett.* **1985**, *26*, 1389. (c) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1961**, *22*, 3455.

[10] PS-DES resin (200 mg, 0.74 mmol/g, 0.15 mmol) was loaded into a 5 mL Teflon reaction vessels on the Quest 210 Organic Synthesizer (Argonaut Technologies). Reaction vessels were then purged with nitrogen for 2 minutes. To the resin was added 4 mL 2.5% trimethylsilyl chloride in CH_2Cl_2 and the mixture agitated for 30 min. The resin was then washed with dry CH_2Cl_2 (2 x 4 mL), followed by addition of freshly prepared 2% CF_3SO_3H solution in CH_2Cl_2 (4 mL, 0.90 mmol, 6 equiv) Immediate gas evolution was observed. The amber-colored mixture was agitated for 10 min, the reaction vessels emptied, and the triflate resin washed with CH_2Cl_2 (2 x 4 mL). The PS-DES silyl triflate resin was used *immediately after generation.*

[11] Bruce C. Hamper and Thomas J. Owen, Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, MO, unpublished results.

[12] For examples of gel-phase ^{19}F NMR, see: (a) Shapiro, M.J.; Kumaravel, G.; Petter, R.C.; Beveridge, R. *Tetrahedron Lett.* **1996**, *37*, 4671. (b) Svensson, A.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1996**, *37*, 7649. (c) Stones, D.; Miller, D.J.; Beaton, M.W.; Rutherford, T.J.; Gani, D. *Tetrahedron Lett.* **1998**, *39*, 4875. (d) Svensson, A.; Bergquist, K-E.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1998**, *39*, 7193.

[13] *Representative procedure for the preparation allyl esters* (**Entry 3, Table 1**): To a 25 mL round-bottom flask was added 1.32 g of PS-DIEA resin (Argonaut Technologies, 4.85 mmol, 3.68 mmol/g, 1.5 equiv). The flask was purged with argon and 3 mL CH_2Cl_2 was added followed by 500 µL of 1-octene-3-ol (3.24 mmol, 1 equiv). After stirring for 5 min, phenylacetyl chloride (640 µL, 4.85 mmol, 1.5 equiv) was added and the reaction mixture stirred at room temperature for 2 h. Then 1.34 g PS-Trisamine resin (Argonaut Technologies, 4.85 mmol, 3.62 mmol/g, 1.5 equiv relative to 1-octene-3-ol) was added followed by 10 mL CH_2Cl_2. The reaction mixture was stirred for 3 h. The combined filtrate and two CH_2Cl_2 washes were concentrated to afford the allyl ester product. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24 (m, 5 H, Ph-H), 5.72 (m, 1 H, =CH-), 5.14 (m, 3 H), 3.54 (s, 2 H, $-CH_2-$), 1.57-0.83 (m, 11 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.50, 136.35, 133.91, 129.07, 128.34, 126.84, 116.32, 74.96, 41.42, 33.76, 31.14, 24.22, 22.12, 13.56. Yield: 90%, GC purity: 94%.

[14] *Representative procedure for Ireland-Claisen rearrangement-transesterification* (**Entry 1, Table 1**): PS-DES silyl triflate resin was prepared according to ref. 10. Allyl cyclohexane propionate (**3**, 0.45 mmol, 3 equiv)/Et_3N (165 µL, 1.2 mmol, 8 equiv) / CH_2Cl_2 (4 mL) mixture was added under nitrogen. The mixture was agitated for 2 h at 25 °C. The resin was then washed with 10% Et_3N/CH_2Cl_2 (2 x 4 mL), CH_2Cl_2 (2 x 4 mL), THF (3 x 4 mL). Then 4 mL THF was added and the mixture heated to 50 °C for 4 h to generate silyl ester **5**. The vessels were emptied and the resin was then washed with THF (2 x 4 mL) and DCE (2 x 4 mL). Then 5% (v/v) H_2SO_4 in MeOH/ DCE (1:1) was added and the mixture heated to 55 °C for 12 h. The cleavage solution and two DCE washes were neutralized using aqueous $NaHCO_3$ and dried over $MgSO_4$. The solution was then filtered and the filtrate concentrated to provide methyl (3-cyclohexyl-2-allyl) propionate in 58 % yield (GC purity: 92 %) ^1H NMR ($CDCl_3$, 300 MHz): δ 5.77 (m, 1 H, =CH-), 4.99 (m, 2 H, $=CH_2$), 3.60 (s, 3 H, $-CH_3$), 2.47-2.11 (m, 2 H), 2.64-0.65 (m, 14 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.37, 135.43, 116.40, 51.02, 39.29, 36.73, 35.30, 33.25, 32.59, 26.18, 25.85 ppm.

[15] Other acetic acid esters (*e.g.* geranyl acetate, linalyl acetate) were also used yielding similar results.

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