ORGANIC LETTERS

2001
Vol. 3, No. 17
2769−2771

A Traceless Perfluoroalkylsulfonyl (PFS) Linker for the Deoxygenation of Phenols

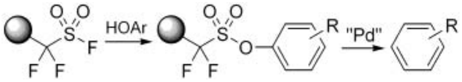
Yijun Pan and Christopher P. Holmes*

Affymax Research Institute, 4001 Miranda Avenue, Palo Alto, California 94304

chris_holmes@affymax.com

Received June 29, 2001

ABSTRACT



The synthesis of a novel perfluoroalkylsulfonyl (PFS) fluoride is described for use as a traceless linker in solid-phase organic synthesis. Attachment to the resin and subsequent coupling of a phenol affords a stable arylsulfonate that behaves as a support-bound aryl triflate. Palladium-mediated reductive cleavage of a wide variety of phenols generated the parent arenes. The resin-bound aryl triflate was shown to be stable to reductive amination conditions, and the traceless synthesis of Meclizine is reported.

The recent acceptance of combinatorial techniques into drug discovery programs has created a demand for more sophisticated linkers and polymer-supported reagents capable of generating an increasing variety of chemical classes. Traceless linkers represent an exciting aspect of solid-phase organic synthesis due to the desire to make molecules lacking any extraneous functionality. Many traceless linkers reported to date require chemical steps to be performed on the initial building block prior to attachment to the resin, as with the Group 14 metal-based linkers,[1] or are restricted to classes of starting materials with relatively few commercial members, such as arylhydrazines[2] or boronic acids.[3] As part of our interest in traceless linkers,[4] we sought a linker where the direct coupling of commercial compounds to a suitable resin was possible without prior modification, and in particular we sought to employ phenols as the initial anchoring group due to the thousands available from commercial sources. The oxygen atom of a phenol, once activated, can undergo a subsequent reduction or cross-coupling reaction and give rise to a variety of substituted aromatics at the formally "inert" oxygen position.[5,6] Aryl triflates and nonaflates have been widely used as precursors for aryl cations due to their excellent leaving group properties.[7] A solid-phase strategy of capturing phenols on resin as the triflate (or "tetraflate"), where subsequent chemistry could be performed on the immobilized molecules followed by reductive cleavage, would be a valuable combinatorial chemistry approach to diverse collections of molecules. To date there have been no reports in the literature regarding polymer-supported triflate linkers, although many sulfonyl chloride linkers have been prepared from polymer-bound sulfonic acids using $SOCl_2$, PCl_5, $POCl_3$, or related reagents.[8] Wustrow first reported the reductive cleavage of phenols from a sulfonyl chloride resin, but harsh cleavage conditions (140 °C for 12 h) and electron-deficient phenols were required due to the poor activating ability of the tosyl group.[9] We now wish to describe our efforts in developing a highly

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[1] For excellent reviews of Si- and Ge-based linkers, see: (a) Spivey, A. C.; Diaper, C. M.; Adams, H.; Rudge, A. J. *J. Org. Chem.* **2000**, *65*, 5253. (b) Lee, Y.; Silverman, R. B. *J. Am. Chem. Soc.* **1999**, *121*, 8407 and references therein.

[2] Stieber, F.; Grether, U.; Waldman, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1073.

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[4] Tumelty, D.; Cao, K.; Holmes, C. P. *Org. Lett.* **2001**, *3*, 83.

[5] (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 2271. (b) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541. (c) Kotsuki, H.; Datta, Probal, K.; Hayakawa, H.; Suenaga, H. *Synthesis* **1995**, *11*, 1348. (d) Lipshutz, B. H.; Buzard, D. J.; Vivian, R. W. *Tetrahedron Lett.* **1999**, *40*, 6871.

[6] (a) Rottlaender, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203. (b) Kamikawa, T.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 8922. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (d) Ciske, F. L.; Jones, W. D. *Synthesis* **1998**, *8*, 1195. (e) Blettner, C. G.; Koenig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885. (f) Lipshutz, B. H.; Blomgren, P. A.; Kim, S. *Tetrahedron Lett.* **1999**, *40*, 197. (g) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

[7] Ritter, K. *Synthesis* **1993**, *8*, 735.

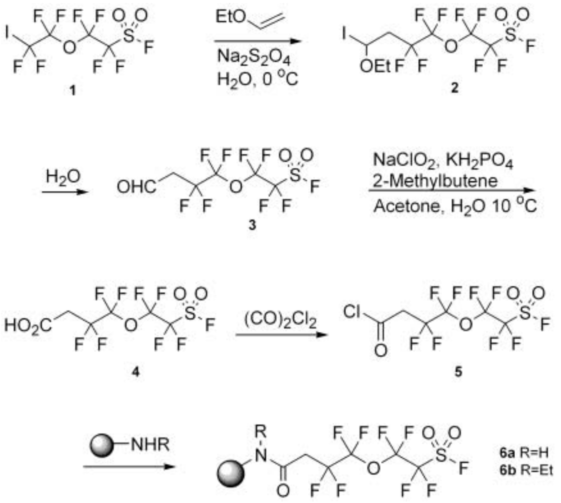
[8] (a) Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998. (b) Baxter, E. W.; Rueter, J. M.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 975. (c) Kamahori, K.; Tada, S.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2547. (d) Zhong, H. M.; Greco, M. N.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 9326. (e) ten Holte, P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 7407.

10.1021/ol0163732 CCC: $20.00 © 2001 American Chemical Society
Published on Web 08/02/2001

activated perfluoroalkylsulfonyl (PFS) linker suitable for the deoxygenation of phenols.

The synthesis of the polymer-supported perfluoroalkylsulfonyl fluoride linker **6** is shown in Scheme 1. Thus, commercial iodide **1** was allowed to react with ethyl vinyl ether through a radical mechanism to give intermediate **2**.[10] The intermediate **2** was hydrolyzed to aldehyde **3** and then oxidized with aqueous $NaClO_2$, NaH_2PO_4, and acetone at 10 °C using 2-methyl-2-butene as chlorine scavenger to afford acid **4** in 62% overall yield from **1**.[11] To minimize the hydrolysis of the SO_2F group in **3** and **4**, low temperatures (0−10 °C) and short reaction times are needed for the preparation and subsequent workup steps. Acid **4** was converted to acid chloride **5** with oxalyl chloride in CH_2Cl_2 using DMF as the catalyst. The sulfonyl fluoride resin **6** was prepared by either coupling **5** to amine resins[12] in CH_2Cl_2 or alternatively by direct coupling of acid **4** with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) as activating reagent. We initially prepared both the tertiary and secondary amide resins **6b** and **6a** due to concerns over the reactive amide present in **6a**, although we have not yet observed any differences between the two resins with the chemistries explored to date.

Scheme 1



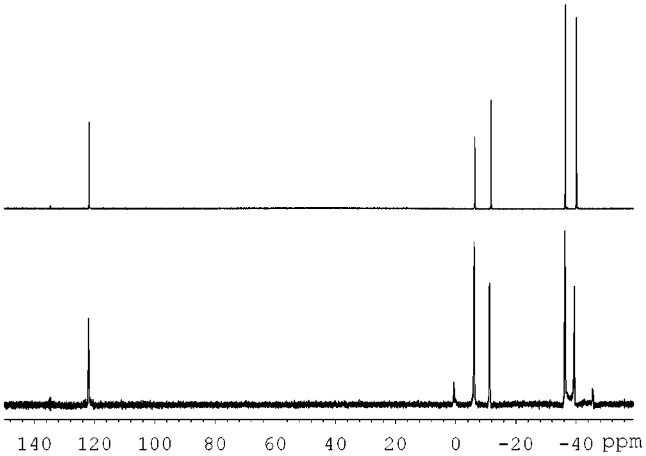
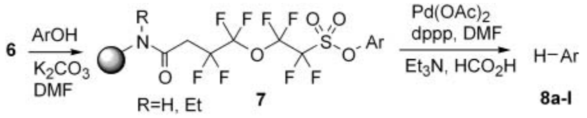


Figure 1. 282 MHz ^{19}F NMR spectra of solution-phase acid **4** in $CDCl_3$ (top trace) and gel-phase resin **6a** in $CDCl_3$ (bottom trace) using trifluoroacetic acid as reference.

The structures of the sulfonyl fluoride resins **6** were confirmed by gel-phase ^{19}F NMR analysis, and the result was compared with the solution-phase ^{19}F NMR spectra of the starting acid **4** (Figure 1). The sulfonyl fluoride signal at 121 ppm allows one to readily monitor the stability of the resin and assess the extent of loading during the next step. Several phenols with disparate steric and electronic environments were attached to resin **6** via sulfonate formation by using K_2CO_3 or Et_3N as base in DMF at room temperature. The actual loading of the phenols on resin **6** is in the range of 0.31−0.36 mmol/g resin as determined by elemental analysis. Cleavage and concomitant deoxygenation of the polymer-supported aryl perfluoroalkylsulfonate species was studied by a palladium-mediated reduction (Scheme 2).

Scheme 2



The polymer-bound aryl sulfonates were efficiently cleaved with Et_3N-HCO_2H in the presence of a catalytic amount of $Pd(OAc)_2$ and 1,3-bis(diphenylphosphino)propane (dppp) to afford high yields of reduced arenes under mild conditions (Table 1). The desired products were easily isolated by two-phase extraction, and the residual metal catalyst was removed by eluting the organic solution through a thin pad of silica gel to give products **8a−l** with purity suitable for high throughput screening (~90%). The compounds were further purified to homogeneity to obtain yield information. That a broad range of functionality is tolerated offers proof of the advantages inherent in this perfluoroalkylsulfonate strategy. The cleavage does not appear to suffer from steric nor electronic effects. The 2,6-dimethyl substitution pattern of entry 6 is noteworthy and represents the most challenging case studied. Entry 10 illustrates the chemoselectivity obtainable when one has both a phenolic and an aliphatic alcohol available for coupling. The use of symmetric bisphenols with

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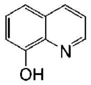
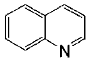
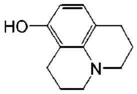
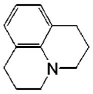
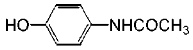
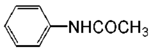
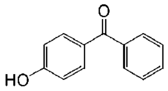
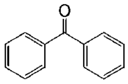
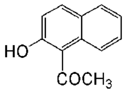
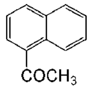
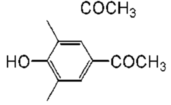
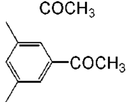
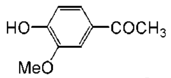
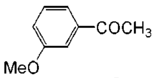
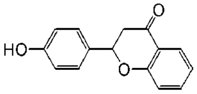
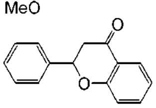
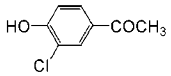
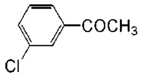
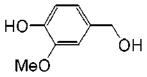
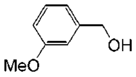
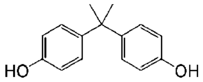
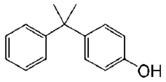
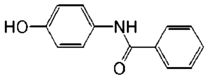
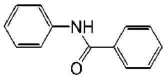
(9) Jin, S.; Holub, D. P.; Wustrow, D. J. *Tetrahedron Lett.* **1998**, *39*, 3651.

(10) Tang, X.; Hu, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, *15*, 2161.

(11) Acid **4**, clear oil. ^1H NMR ($CDCl_3$, δ): 3.18 (t, $J = 16.8$ Hz, 2 H, $CF_2CH_2CO_2H$), 8.68 (b, 1 H, CO_2H). ^{13}C NMR ($CDCl_3$, δ): 36.39 (t, $CF_2CH_2CO_2H$), 169.53 (CO_2H). ^{19}F NMR ($CDCl_3$, δ): −39.70 (CF_2), −36.14 (CF_2), −11.51 (CF_2), −6.08 (CF_2), 121.61 ($-SO_2F$), trifluoroacetic acid was used as reference. ESIMS (negative): calcd for $C_6H_3F_9O_5S$ 357.96; found *m/z* 357.0 (M − H).

(12) The secondary *N*-Et amine resin was prepared by acylation of TentaGel-NH_2 resin (RAPP Polymere, loading: 0.43 mmol/g) with acetyl chloride and subsequent reduction with $LiAlH_4$.

Table 1. Palladium-Mediated Reductive Cleavage of Polymer-Bound Aryl Perfluoroalkylsulfonates **7**[a]

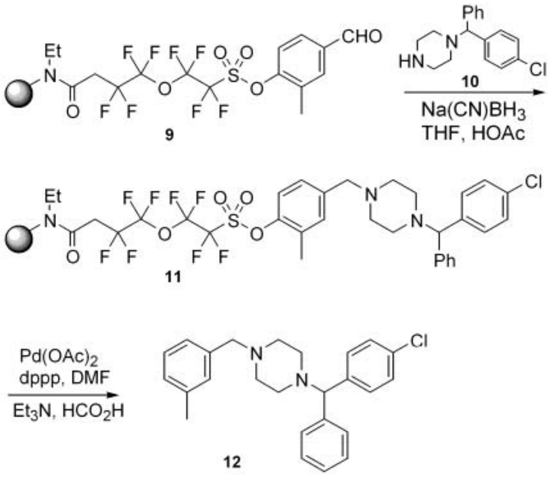
entry	starting phenol	product **8**		yield[b] (%)
1			**8a**	81
2			**8b**	74
3			**8c**	88
4			**8d**	90
5			**8e**	86
6			**8f**	85
7			**8g**	88
8			**8f**	75
9			**8i**	63
10			**8j**	86
11			**8k**	80
12			**8l**[c]	78

[a] Reductive cleavage was carried out by using resin **7** (80 mg, 0.014 mmol), $Pd(OAc)_2$ (6.0 mg), dppp (16.0 mg), HCO_2H (0.18 mL), and Et_3N (0.46 mL) in DMF (1.2 mL) at 85 °C for 120 min. [b] Isolated yields were based on the actual loading of phenols on resin **6** as determined by elemental analyses. [c] Obtained from 4-nitrophenol via reduction with $SnCl_2$ after coupling, followed by acylation with benzoyl chloride prior to reductive cleavage.

resin **6** can be used to afford monophenols after cleavage (entry 11). The linker is stable to nitro reduction conditions ($SnCl_2$ in NMP) and treatment with acid chlorides (entry 12) which represents common reaction conditions used for elaborating nitroaromatics into arylamides. In other experiments it was found that the polymer-bound aryl perfluoroalkylsulfonate functionality is stable to acidic (20% TFA in CH_2Cl_2) conditions. We are currently fine-tuning the cleavage conditions to minimize the amount of palladium catalyst required and to lower the reaction temperature.

Finally, we conducted the solid-phase synthesis of the commercial drug Meclizine **12** to further explore the stability of the aryl sulfonate linkage (Scheme 3). The polymer-supported aryl sulfonate **9** was prepared by attaching 3-methyl-4-hydroxybenzaldehyde to resin **6b**, and polymer-supported amine **11** was prepared by a reductive amination of **9** with amine **10** using $Na(CN)BH_3$ as reducing agent. Meclizine **12** was cleaved from the resin by a palladium-mediated reductive cleavage in 80% yield.[13] The synthesis of **12** illustrates the stability of the linker to basic amines and mild hydrides, while affording a high degree of activation during cleavage—note that the aryl chloride, the benzylamine, and the benzhydrylamine groups all remained intact upon cleavage. The stage is now set to further exploit this resin in the synthesis of compound libraries.

Scheme 3



In conclusion, we have developed a new polymer-supported perfluoroalkylsulfonyl (PFS) linker that allows the attachment of phenols to the solid phase and subsequent reductive cleavage to afford the parent arene. The solid-phase approach provided an operationally simple, inexpensive, and general protocol for the activation/reductive cleavage of the aryl−oxygen bond. The support-bound aryl perfluoroalkylsulfonate functionality is also amenable to cross-coupling reactions (e.g., Suzuki, Heck, and organozinc couplings) which we will report in a following communication. We are currently extending the PFS linker to the related vinyl triflate species originating from ketones for the generation of substituted olefins. We believe that the ease of preparation, excellent stability, and synthetic versatility of the polymer-supported perfluoroalkylsulfonyl fluorides **6a** and **6b** will find broad application in solid-phase synthesis and combinatorial chemistry.

Supporting Information Available: Experimental procedures for compounds **2**−**5** and resin **6a**, reductive cleavage conditions, and HPLC of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] The product **12** was characterized by ESIMS, HPLC, and ^1H NMR, and the results were compared with data for an authentic sample obtained from Sigma.