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Synthesis and applications of a highly fluorous alkoxy ethyl ether protective group

Peter Wipf * and Jonathan T. Reeves

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

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Abstract

A readily recyclable, fluorous alkoxy ethyl ether protecting group has been developed that allows for simple purification of small to medium-sized organic molecules by liquid–liquid extraction with FC-72/organic/aqueous solvents. The precursor vinyl ether **3** can be prepared in large quantity in a straightforward two step reaction sequence. Primary, secondary, and tertiary alcohols are protected in good to excellent yields, and the fluorous label is removed by mild acid treatment. The *N*-protection of 2-fluoroaniline demonstrates the feasibility of using **3** with amines. © 1999 Elsevier Science Ltd. All rights reserved.

For the further development of fluorous phase chemistry[1] into a practical strategy for combinatorial and parallel synthesis, a variety of fluorous phase labels must be made available. Ideally, these labels would be easily prepared in large quantity, installed and removed from a substrate using mild reaction conditions, and would be recyclable after cleavage. In addition, these phase labels should be tolerant, as a group, to all possible reaction conditions, such that an appropriate label could be chosen which would be amenable to any given sequence of reactions. We reported previously on the synthesis and applications of a fluorous THP protecting group (FTHP).[2] This recyclable label compliments the previously used fluorinated silyl ether[3,5] due to its much improved stability to basic, nucleophilic, and even mildly acidic reaction conditions. In this paper we report on an alternative recyclable fluorous acetal protecting group **3** with higher fluorous content which is installed and removed under mildly acidic conditions.

The synthesis of vinyl ether **3** begins with commercially available iodide **1** (Scheme 1). Formation of the Grignard reagent from **1** is effectively accomplished with sonication for the reaction initiation. Thus, treatment of an ether suspension of excess magnesium powder with 0.1 equivalents of **1**, sonication for 20 minutes, and subsequent addition of an additional 2.4 equivalents of **1** in Et_2O provided the Grignard reagent after a two hour reflux period. Dropwise addition of one equivalent of ethyl formate to the reaction mixture and further refluxing for five hours gave the crude fluorous alcohol **2** after standard workup. This compound was conveniently purified by washing the crude solid with dichloromethane to give a 93%

* Corresponding author.

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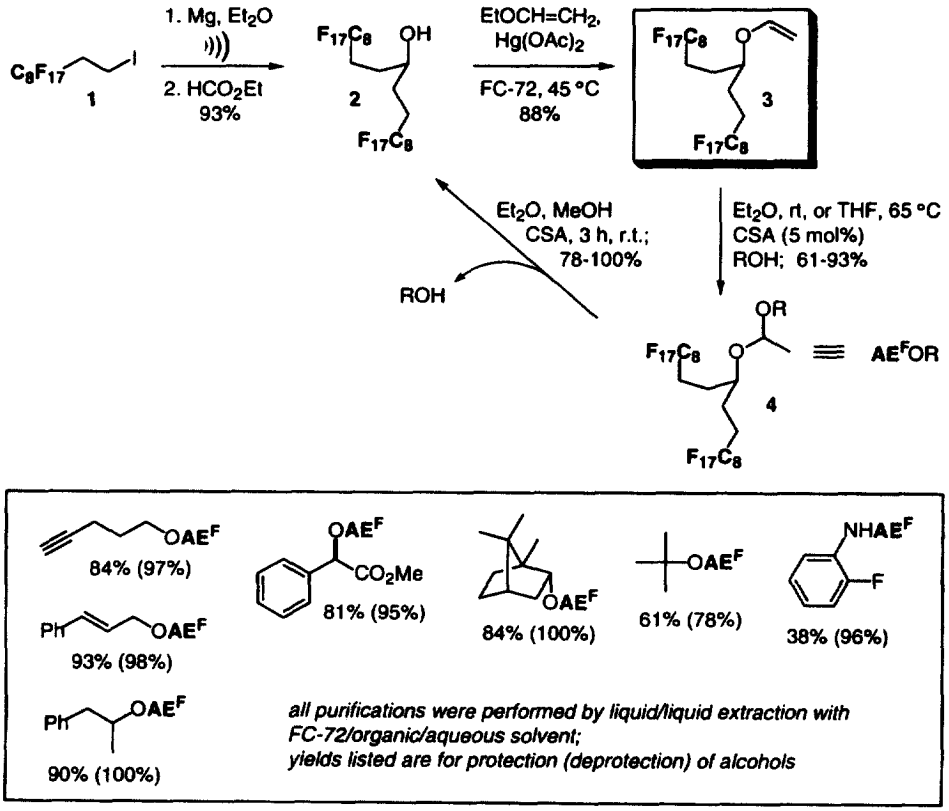
yield of **2**. Vinylation[4] of **2** with 0.5 equivalents of mercuric acetate in a 1:1 mixture of ethyl vinyl ether and FC-72 at 45°C for 40 hours gave vinyl ether **3** in 51% yield, with 42% recovered alcohol **2** (88% yield based on recovered starting material). The extremely apolar **3** could be isolated by filtration of the crude product mixture through a short pad of SiO_2 with hexanes, since the RF value of **3** is 0.9 in hexane, while **2** has an RF close to zero in hexane. The unreacted **2** can then be resubjected to the vinylation reaction, allowing for ~70% conversion to **3** after two runs. Accordingly, vinyl ether **3** is readily prepared in multigram quantities.



Scheme 1.

Protection of alcohols with **3** proceeds under mildly acidic conditions. Treatment of an Et_2O solution of 1 equivalent of a primary alcohol and 3 equivalents of **3** with 5 mol% of camphorsulfonic acid for three hours at room temperature provided the desired protected alcohols **4** ($ROAE^F$) in 84–93% yields, with the majority of the excess of vinyl ether recoverable. Secondary and even tertiary alcohols are similarly protected in good yields using THF as solvent at 65°C for 30–45 min. The moderate yield obtained for protection of *tert*-butyl alcohol compares nonetheless well to the protection of this sterically hindered and volatile substrate with the fluorous THP^F label.[2] The alkoxy ethyl (AE^F) fluorous label could also be installed on the nitrogen atom of an aniline, although the yield still requires further optimization (Scheme 1).[5] All protected and fluorous-tagged substrates were purified from excess **3** by column chromatography on SiO_2. Separation was generally very straightforward due to the considerable R_f-differences between **3** and **4**, and the pre-purification of the reaction mixture from organic impurities by extraction with FC-72.[6]

Deprotection of fluorous acetals **4** proceeded under mild conditions as well. Treatment of the protected substrates in a 1:1 solution of Et_2O and MeOH with 5 mol% of CSA gave, after one hour, excellent yields of deprotected substrates as well as a quantitative recovery of fluorous alcohol **2** (see Scheme 1). After completion of the reaction, the products were isolated in pure form by simple 3-phase extraction (reaction mixture/saturated aqueous $NaHCO_3$/FC-72). Alcohol **2** can be resubjected to vinylation to give **3** and thus is efficiently recycled.

In conclusion, we have developed a recyclable highly fluorous acetal protecting group that is likely to find broad applications in fluorous synthesis as well as in fluorous/solid phase combinations and other parallel synthesis strategies. The precursor vinyl ether **3** can be prepared in large quantities in a straightforward two step reaction sequence. Primary, secondary, and tertiary alcohols can be protected in good to excellent yields. The *N*-protection of 2-fluoroaniline demonstrates the feasibility of using **3** with amines, even though the protection yield under the standard conditions used for alcohols still requires further improvement. After protection with the $\mathbf{AE^F}$-group, a substrate is capable of undergoing a series of reactions in which purification of products can be accomplished by simple liquid–liquid extraction with FC-72 or filtration through fluorous reverse-phase SiO_2.[7] Deprotection occurs under mild acidic conditions, and the fluorous label is easily isolated and effectively recycled.

Compared to our $\mathbf{THP^F}$-function,[2] the $\mathbf{AE^F}$-group is more readily cleaved and recycled and has a higher affinity toward the fluorous environment. There is a direct correlation between the number of fluorine atoms in a molecule and its selective solubility in perfluorinated solvents.[1a] With the exception of small organic molecules, most compounds protected with the $\mathbf{THP^F}$-function[2] were insufficiently fluorous for efficient liquid–liquid extraction and rapid purification required fluorous reverse-phase SiO_2 (FRP). In particular in preparative scale synthesis, the broad use of FRP chromatography is currently limited by the high costs of the stationary phase. Due to the higher level of fluorination of the $\mathbf{AE^F}$-group, all substrates shown in Scheme 1 could be purified by simple liquid–liquid extraction. This phase label is therefore ideally suited for the protection of larger quantities or higher molecular weight organic molecules under basic and/or nucleophilic reaction sequences. We are currently applying the $\mathbf{AE^F}$-label to a combinatorial synthesis of analogs of the antimitotic natural product curacin A.[8]

Acknowledgements

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6. Preparation of **2**: a suspension of 4.2 g (0.173 mmol) of Mg powder and 2.5 g (4.36 mmol) of iodide **1** in 20 mL of Et_2O was sonicated for 20 min. To this black mixture was added dropwise a solution of 22.5 g (39.2 mmol) of iodide **1** in 150 mL of Et_2O. The reaction mixture was heated at reflux for 2 h, and the solution was cannulated away from the excess Mg into a new flask. After dropwise addition of 1.40 mL (17.4 mmol) of ethyl formate, the black solution was heated at reflux

for 5 h. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride solution and extracted with Et_2O. The organic extracts were dried (Na_2SO_4) and concentrated. The crude product was washed with CH_2Cl_2 and dried in vacuo to give 14.92 g (16.15 mmol, 93%) of **2** as a white solid: mp 98–101°C; IR (KBr) 3461, 1204, 1146 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.20 (d, 1H, *J*=6.0 Hz), 3.80–3.73 (m, 1H), 2.60–2.15 (m, 4H), 1.95–1.65 (m, 4H); ^{13}C NMR (TFA) δ 125.0–105.0 (m, 16 C), 79.4, 28.4, 25.9; MS (EI) *m/z* (rel. intensity) 907 ([M–OH]$^+$, 2), 887 (6), 477 (100). Preparation of **3**: a mixture of 14.92 g (16.15 mmol) of **2**, 2.6 g (8.1 mmol) of $Hg(OAc)_2$, 100 mL of ethyl vinyl ether, and 100 mL of FC-72 (commercially available from 3 M) was heated at reflux for 40 h. After cooling to room temperature, the reaction mixture was transferred to a separatory funnel, and the layers were separated. The organic layer was extracted with FC-72 (three times), and the combined FC-72 extracts were dried (Na_2SO_4), and concentrated. The crude product was loaded onto a short (1.5 in.) pad of SiO_2 and washed with hexanes until no more **3** was shown to be eluting via TLC. The hexane washings were concentrated to give 7.85 g (8.2 mmol, 51%) of **3** as a white solid, mp 36–38°C. Flushing the SiO_2 pad with EtOAc, followed by concentration of the filtrate gave 6.29 g (6.8 mmol, 42%) of **2**. Spectroscopic data for **3**: IR (KBr) 3131, 1646, 1617, 1209, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (q, 1H, *J*=6.6 Hz), 4.35 (d, 1H, *J*=14.2 Hz), 4.10 (d, 1H, *J*=6.5 Hz), 3.91 (p, 1H, *J*=5.5 Hz), 2.35 to 2.00 (m, 4H), 1.95–1.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 150.0, 125.0–105.0 (m, 16 C), 89.8, 76.4, 26.7 (t, *J*=22.1 Hz), 24.8; MS (EI) *m/z* (rel. intensity) 950 (M$^+$, 7), 887 (20), 391 (100). Protection of cinnamyl alcohol: to a solution of 10.5 mg (0.08 mmol) of cinnamyl alcohol and 223 mg (0.24 mmol) of **3** in 3 mL of Et_2O was added 1 mg (5 mol%) of 10-camphorsulfonic acid (CSA). The solution was stirred at rt for 3 h. Saturated $NaHCO_3$ solution was added, and the reaction mixture was extracted with FC-72 (three times). The combined FC-72 extracts were dried (Na_2SO_4), and concentrated. Column chromatography on SiO_2 (hexanes:Et_2O, 95:5) gave 101 mg (0.11 mmol, 64%) of **3** and 79 mg (0.073 mmol, 93%) of the desired **AE^F**-protected cinnamyl alcohol as a colorless oil: IR (neat) 3032, 2981, 1491, 1204, 1148, 907 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.21 (m, 5H), 6.60 (d, 1H, *J*=15.9 Hz), 6.25 (dt, 1H, *J*=5.9, 15.9 Hz), 4.81 (q, 1H, *J*=5.3 Hz), 4.26–4.13 (m, 2H), 3.80 (p, 1H, *J*=5.5 Hz), 2.40–2.00 (m, 4H), 1.90–1.75 (m, 4H), 1.37 (d, 3H, *J*=5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 136.6, 132.4, 128.7, 127.9, 126.5, 125.4, 125.0–105.0 (m, 16 C), 99.0, 73.4, 65.8, 26.4, 20.4; MS (EI) *m/z* (rel. intensity) 951 ([M–$OCH_2CHCHPh$]$^+$, 9), 887 (9), 577 (8), 477 (50), 118 (100). Deprotection of **AE^F**-protected cinnamyl alcohol: a solution of 71 mg (0.065 mmol) of **AE^F**-OCH_2CH=CH-Ph and 1 mg (5 mol%) of CSA in 1 mL of MeOH and 1 mL of Et_2O was stirred at rt for 1 h. The reaction mixture was then transferred to a separatory funnel, and saturated $NaHCO_3$ solution and FC-72 were added. The organic and aqueous layers were washed with FC-72 (three times). The combined FC-72 extracts were dried (Na_2SO_4), and concentrated to give 60 mg (100%) of **2**. The organic layer was dried (Na_2SO_4), and concentrated to give 8.6 mg (98%) of cinnamyl alcohol.

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