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Fluorinated Analogues of *tert*-Butyl Alcohol as Novel Protecting Groups for Use in Fluorous Synthesis

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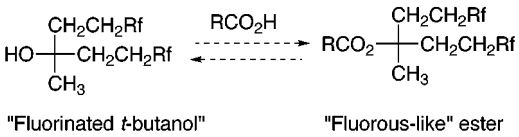
ABSTRACT



A series of fluorous derivatives of *tert*-butyl alcohol were prepared and evaluated as reagents for the protection of carboxylic acids for use in fluorous synthesis. Alcohol 3b can be employed efficiently to protect and immobilize medium-size nonpolar carboxylic acids in a fluorous phase.

Since the initial works of Horvath and Rábai,[1] fluorous-phase separation techniques are emerging as an alternative to solid-phase techniques in organic synthesis. These techniques are based on the immiscibility of perfluorinated solvents with water and most organic solvents.[2] Most organic compounds are insoluble in the fluorous phase; however, introduction of perfluorinatealkyl chains (pony tails) convert them into fluorous soluble materials that can be partitioned in the fluorous phase. This proccess can be employed for the selective extraction of fluorous components from reaction mixtures.[3]

Fluorous-phase separation techniques can be applied in several ways, depending on which is the fluorous component of the reaction mixture. In the fluorous biphasic catalysis (FBC),[4] a homogeneous catalyst is immobilized into the fluorous phase by attaching fluoro pony tails to the ligand. In fluorous synthesis, the starting substrate of the synthesis is immobilized into the fluorous phase.[5] Other applications of fluorous techniques are the utilization of fluorous reagents,[6] fluorinated scavenging agents,[7] nonmetallic catalysts,[8] etc. The Curran group also envisioned using fluorinated protecting groups in fluorous synthesis.[9]

In this context we considered the possibility of creating a new generation of fluorinated protecting groups derived from the traditional ones by attaching perfluoroalkyl chains as pony tails. Two requirements should be met by these novel compounds to be useful in fluorous synthesis: First, they should serve to protect and deprotect the substrates as

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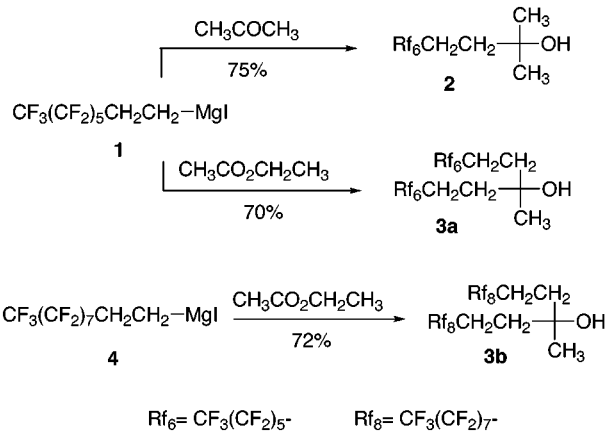
efficiently as the original protecting groups. Second, they should have the ability to immobilize the protected substrate into a fluorous phase, thus allowing its separation by simple extraction with a fluorous solvent.

In this communication we report our preliminary efforts toward the preparation of perfluorinated analogues of *tert*-butyl alcohol,[10] as reagents for the protection of carboxylic acids in fluorous synthesis.

As potential candidates for fluorous analogues of *tert*-butyl alcohol, we selected compound **2**, containing one perfluoroalkyl chain attached to the quaternary carbon through an ethylene spacer, and compounds **3a** and **3b**, having two perfluoroalkyl chains of different lengths. It is well-known that the length and number of perfluoroalkyl groups influence the solubility of perfluoroalkylated compounds in a fluorous solvent.[3,5a,11] Also the presence of several CH_2 insulating groups is necessary to minimize the effects of the perfluorinated chains in the reactivity of the modified alcohols. During the preparation of this manuscript, alcohol **3a** and very similar alcohols were prepared and were used for carbamate (BOC) rather than acyl based protecting groups.[9c] It was also shown how the fluorous solid−liquid extraction methods are much more practical and efficient than the fluorous liquid−liquid extraction methods.[9c]

Alcohols **2** and **3a** were conveniently prepared by reaction of Grignard **1** with acetone and ethyl acetate, respectively. Similarly, treatment of Grignard **4** with ethyl acetate afforded alcohol **3b** in good yield (Scheme 1). Grignards **1** and **4** were

Scheme 1. Fluorinated Analogues of *tert*-Butyl Alcohol

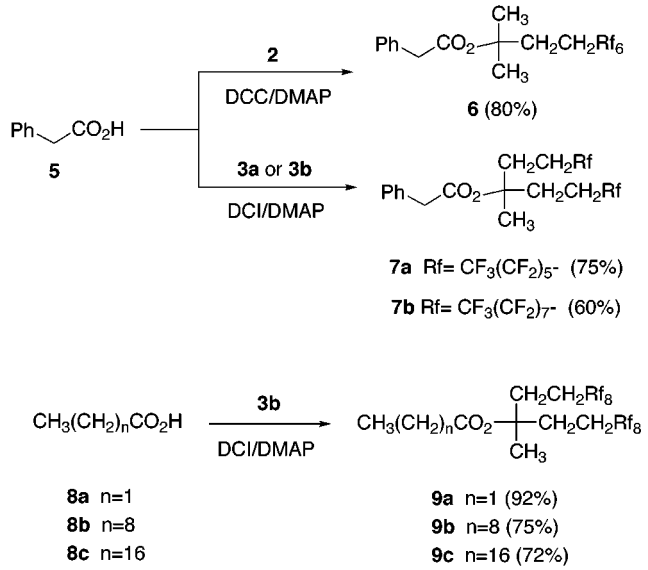


generated from the corresponding commercially available iodides.[12]

The esterification of carboxylic acids with alcohols **2** and **3** has two difficulties compared with the reaction with *tert*-butyl alcohol: First, the strong electron-withdrawing properties of the perfluoroalkyl groups must decrease the nucleophilicity of the oxygen despite the presence of the ethylene spacer.[13] Second, these alcohols have very low solubility in common organic solvents. We started our study assaying the reaction of phenylacetic acid (**5**) with **2** and **3**.

Esterification of **5** with the alcohol **2** was easily carried out under standard conditions (DCC/DMAP in dichloromethane), giving the corresponding ester **6** in 80% yield (Scheme 2). However, protection of **5** with alcohols **3a** and

Scheme 2



3b was more difficult, and poor yields of **7a** and **7b** were obtained under these conditions, a more thorough study of this reaction being necessary. Preliminary assays showed that coupling reagents such as DPC, PyBPO, HBTU, TBTU, and BOPCl were ineffective, whereas carbodiimides DCC and DIC, in combination with DMAP, gave better results, allowing the isolation of **7a** and **7b** in reasonable yields, depending on the solvent used. It is remarkable to point out that the use of common solvents such as DMF, $CHCl_3$, CH_2Cl_2, and THF for these reactions gave poor yields of product (even after raising the temperature to solubilize the reagents). Instead, the use of benzotrifluoride, a partially fluorinated solvent that is employed as substitute for CH_2Cl_2 in reactions with perfluorinated compounds,[14] allowed the isolation of **7a** and **7b** in moderate yields (75% and 60%) using DIC/DMAP as coupling reagent at 40 °C.

A preliminary evaluation of the effectiveness of alcohols **2**, **3a**, and **3b** as protecting groups for **5** showed that **3b** was

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(12) See refs 6a and 5a for the preparation of Grignard **1** and **4**.

(13) Farnhan, B. W. *Chem. Rev.* **1996**, *96*, 1633−1640.

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the most appropriate for our purposes (see below). To complete this study, a series of aliphatic acids **8a**−**c** were protected with alcohol **3b** using the optimized coupling reaction conditions described above. So, reaction of **8a**−**c** with **3b**, using DIC and DMAP as coupling reagents in benzotrifluoride, gave the corresponding esters **9a**−**c** in 92%, 75% and 72% yields, respectively (Scheme 2).

One important issue was to prove that these substrates could be readily deprotected. Treatment of esters **7a,b** and **9a**−**c** with trifluoroacetic acid for 15 h gave the original unprotected acids in quantitative yields, which could be isolated from the crude reaction mixture by means of simple washing with perfluoromethylcyclohexane. Also it was proven that these esters remained unaltered in basic media and under hydrogenation conditions (H_2/Pd−C).

Once we found the methods to protect and deprotect the acids, the next step was to study if the protected substrates were suitable to be used in fluorous synthesis. To select the most efficient protecting group, the partition coefficients (K_D)[15] of esters **6** and **7a,b** in several fluorous biphasic solvent combinations were determined.[16] As fluorous solvents, FC-72 (a mixture of perfluorohexanes) and perfluoromethylcyclohexane were used. The results of these experiments, shown in Table 1, helped us to evaluate these protecting groups with regard to their immobilization capability in a fluorous phase and also to determine the most adequate pair of solvents for the extraction.

Table 1. Partition Coefficients of Esters **7a,b** and **9a**−**c**

organic solvent	fluorous solvent	**7a**	**7b**	**9a**	**9b**	**9c**
cyclohexane	FC-72	8.26	14.62	8.10	6.72	0.91
cyclohexane	$CF_3C_6F_{11}$	5.37	13.92	9.58	12.4	2.86
toluene	FC-72	1.78	5.49	7.75	5.28	1.13
toluene	$CF_3C_6F_{11}$	2.87	9.53	6.46	17.2	3.84
CH_2Cl_2	FC-72	0.61	4.00	9.08	4.53	1.22
CH_2Cl_2	$CF_3C_6F_{11}$	1.96	6.21	15.4	13.6	4.68
chloroform	FC-72	0.69	2.55	3.06	2.63	0.53
chloroform	$CF_3C_6F_{11}$	0.86	2.70	5.93	5.74	1.64
ethyl acetate	FC-72	0.29	1.32	2.59	2.74	1.06
ethyl acetate	$CF_3C_6F_{11}$	0.58	2.04	3.25	9.86	2.08
THF	FC-72	0.37	1.30	2.70	1.70	0.50
THF	$CF_3C_6F_{11}$	0.55	3.02	5.26	4.79	1.04
acetone	FC-72	0.25	1.50	3.33	2.92	1.77
acetone	$CF_3C_6F_{11}$	0.57	2.46	6.28	5.55	2.69
acetonitrile	FC-72	3.42	9.00	6.42	11.2	14.3
acetonitrile	$CF_3C_6F_{11}$	4.81	16.2	16.9	29.9	16.4
ethanol	FC-72	3.29	7.69	4.19	5.98	8.35
ethanol	$CF_3C_6F_{11}$	4.46	10.24	16.0	11.0	11.2
methanol	FC-72	4.65	11.7	4.78	8.89	19.5
methanol	$CF_3C_6F_{11}$	11.1	20.7	10.8	27.3	33.7

Not surprisingly, ester **6** showed no affinity for the fluorous phase, demonstrating that at least two perfluorinated chains were necessary in the protecting group. Esters **7a** and **7b**, having two pony tails, showed higher affinities for the fluorous phase.

The length of the perfluorinated chain has also a great effect on the partition coefficients, and as expected, the use of labels with more fluorine atoms favors the partition into the fluorous phase.

Ester **7b** acted as a "fluorous compound" for all solvent pairs. The protected acid showed the highest partition coefficients when either lowly polar (cyclohexane, toluene) or highly polar (methanol, acetonitrile, ethanol) organic solvents were used. Also it was observed that the extraction power of perfluoromethylcyclohexane is superior to that of FC-72.

From a synthetic point of view, for the extraction to be of practical utility, the K_D values must be higher than 4, indicating that after three extractions more than 99% of the substrate draws into the fluorous phase.[17] Analysis of our results showed that with protecting group **3a** (ester **7a**) it is possible, at least, to choose a polar organic solvent and a nonpolar organic solvent to carry out the extraction in a practical way. With protecting group **3b** (ester **7b**), a greater number of organic solvents can be chosen for an efficient extraction, particularly when perfluoromethylcyclohexane is employed as fluorous solvent. Again it is possible to employ a polar or a nonpolar organic solvent but also a solvent of intermediate polarity as dichloromethane, which has a great extracting power for most organic compounds.

Once we verified that **3b** was the most efficient protecting group for our purposes, the partition coefficients of aliphatic esters **9a**−**c** were determined (Table 1). We observed that with the aliphatic series **9a**−**c** the partition coefficients are higher and so the number of pairs of solvents that can be used for a practical extraction is increased. Again perfluoromethylcyclohexane showed a greater extracting power than FC-72, and the extraction is best carried out with very polar solvents such as methanol, ethanol, and acetonitrile and with nonpolar solvents such as cyclohexane and toluene. It is also interesting to observe how the length of the hydrocarbon chain affects the K_D values. In general, for nonpolar solvents, an increase in the molecular weight of the aliphatic esters leads to a decrease in K_D, an expected result because of the decrease in fluor percentage, but also because the esters adquire a nonpolar character as a result of the longer hydrocarbon chain.

However, the situation changes for polar solvents where in general, the K_D values increase with the increase in the length of the aliphatic chain, due to the loss of polar character and therefore their affinitity in polar solvents.

This behavior suggests that we must use polar organic solvents for extractions with nonpolar esters and also that increasing the molecular weight of an aliphatic ester must

(15) $K_D = C$(fluorous phase)/C(organic phase), at 25 °C.

(16) The partition coefficients were determined by dissolving a known amount of the fluorous compound (40−70 mg) in the biphasic system (4 mL, 1:1 v/v). The resulting mixture was vigorously stirred for 15 min in a 10 mL vial, immersed in a 25 °C oil bath. After two clear layers were obtained, a 1 mL aliquot was removed from each layer with a syringe. This was evaporated to dryness, and the weight (± 0.1 mg) of each residue was determined. The partition coefficients were calculated as the ratio of the amount of residue from each layer.

(17) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's, Textbook of Practical Organic Chemistry*, 5th ed.; ELBS: London, 1989.

not be indicative of loss in fluorous affinity, despite the decrease in fluor percentage.[18] This result is significant because it demonstrates that it should be possible to extract nonpolar compounds of medium molecular weight or even larger compounds, as the trend of Table 1 shows, in an effective way without the necessity of increasing the length of the pony tails. Therefore, it could be feasible to apply these techniques to a great variety of interesting compounds such as terpenes, carotenes, etc.

(18) Polar compounds need a larger percentage of fluor than nonpolar compounds to be soluble in fluorous solvent because the fluorous solvents keep some nonpolar character (Guillevic, M. A.; Rocaboy, C.; Arif, A. M.; Horvath, I. T.; Gladysz, J. A. *Organometallics* **1998**, *17*, 707−717. Also, ref 7). For polar compounds it will be necessary to increase the length of the pony tails of the alcohol to get adequate fluorous solubility and affinity. Otherwise other nobel fluorous techniques referred to as light fluorous techniques, allow the separation of fluorous compounds readily without increasing the length of the pony tails. See ref 9c and (a) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866−8876. (b) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766−1769 and references therein.

In short, the results shown here prove that perfluorinated alcohol **3b** can be employed as reagent for carboxylic acid protection to be used in fluorous synthesis. Also we demonstrated that it is possible to use fluorous synthesis to immobilize medium-sized nonpolar substrates without using a large amount of fluor.

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Supporting Information Available: Detailed experimental procedures and ^{1}H and ^{13}C NMR data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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