J. Org. Chem. **1997,** *62,* 6714−6715

Thermal Allylations of Aldehydes with a Fluorous Allylstannane. Separation of Organic and Fluorous Products by Solid Phase Extraction with Fluorous Reverse Phase Silica Gel[†]

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Received June 12, 1997

Successful methods for combinatorial or parallel synthesis must couple efficient reaction chemistry with simple purification methods. In the ideal scenario (which is still difficult to reach for many kinds of reactions), the product of the reaction should be in a different phase from everything else remaining in the final reaction mixture.[1] When this goal is reached, the processing of a crude reaction mixture through one or more simple phase separation techniques (evaporation, extraction, filtration) provides a pure product. The traditional use of organic substrates, reactants, reagents, and catalysts is now being augmented by analogous reaction components that are water soluble[2,3] or are attached to insoluble[3,4] or soluble[5] polymers. Each of these strategic modifications is allied with a simple phase separation technique for purification (for example, acid−base extraction or filtration).

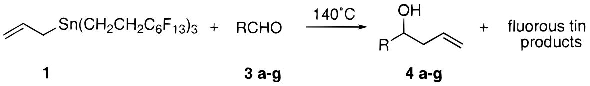
The fluorous phase[6] is emerging as a complement and supplement to the standard phases, and fluorous synthesis techniques show promise for broader applications.[1,7,8] To date, the only separation technique allied with fluorous synthesis has been organic−fluorous liquid−liquid extraction. Recently, traditional acid−base liquid−liquid extraction methods have been supplemented by solid phase extraction (SPE) techniques.[9] In these techniques, ion exchange resins are used to “extract” complementary functionalities out of the eluent and onto the column. Erstwhile chromatographies are turned into filtrations where the R_f of a given subset of molecules is (ideally) either 1 or 0 as determined by whether the molecules and the eluent bear an acid or base functionality complementary to the column or not. Similarly, size exclusion chromatography has been used to separate dendridic substrates from small organic molecules in processes that resemble filtrations more than chromatographies.[10]

Table 1. Thermal Allylations of Aldehydes with $(C_6F_{13}CH_2CH_2)_3SnCH_2CH{=}CH_2$

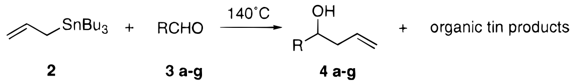
		liquid−liquid extraction		fluorous solid phase extraction		
entry	aldehyde (*R*)	crude yield, %	purity, %	crude yield, %	purity, %	isolated yield, %
a	*p*OMeC_6H_4	61	83	98	76	70
b	1-Naphthyl	92	85	95	84	70
c	$PhCH_2CH_2$	82	88	80	100	71
d	$PhCH(CH_3)$	55[a]	93	60[a]	79	40[a]
e	*c*-C_6H_{11}	62	94	100	100	80
f	*p*$NO_2C_6H_4$	90	94	98	91	85
g	*o*$NO_2C_6H_4$	98	93	94	93	88

[a] Mixture of syn/anti-isomers 1.6/1.

In this communication, we describe the synthesis of a new fluorous allylstannane, $(C_6F_{13}CH_2CH_2)_3SnCH_2CH{=}CH_2$ (**1**) and show that its thermal reactions with aldehydes are roughly comparable to the reactions with the standard reagent $Bu_3SnCH_2CH{=}CH_2$ **2** (eq 1a,b).[11] The fluorous and organic products of these reactions can be separated by fluorous−organic liquid−liquid extraction or, more conveniently, by the new technique of fluorous solid phase extraction (FSPE). This new separation technique should dramatically expand the utility and accelerate the development of fluorous synthesis methods.



(1a)



(1b)

The fluorous allylstannane **1** was readily synthesized by the reaction of allyl magnesium bromide with readily available tris[2-(perfluorohexyl)ethyl]tin bromide ($(C_6F_{13}CH_2CH_2)_3SnBr$). Preliminary attempts to conduct Lewis acid promoted reactions with **1** gave mixed results; however, we discovered that thermal allylations with **1** were roughly comparable to those with allyltributyltin.[11] All the allylation results with **1** are summarized in Table 1.

In an initial series of experiments, 3 equiv of fluorous allylstannane **1** and 1 equiv of an aldehyde were heated for 3 d at 140 °C without solvent. The crude reaction mixture was then partitioned between acetonitrile and FC-72 (fluorohexanes). The layers were separated, and after washing two more times with FC-72, the acetonitrile layer was evaporated to give the crude organic product. The crude yield of each reaction was determined by weighing, and the purity of each alcohol product **4** was determined by GC analysis against authentic samples. Most of the products were formed in reasonable yields and purities. That the impurities in these alcohols are not fluorous was clear from both weight and spectroscopic analysis. Given the high molecular weight of the fluorous piece, even relatively small amounts of fluorous impurities would quickly push the crude weight yield to exceed

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[†] Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

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S0022-3263(97)01059-1 CCC: $14.00

100%, but this was never observed. Furthermore, the protons of the ethylene group on the fluorous tin chain were not observed in the crude ^{1}H NMR spectra of the organic products. The crude fluorous product was a mixture of the starting fluorous allylstannane and what we believe to be the fluorous stannoxane: $[(C_6F_{13}CH_2CH_2)_3Sn]_2O$.[12] The reaction with phenyl propionaldehyde (entry d) provides a 1.6/1 ratio of syn- and anti-isomers; this is very similar to the ratio obtained with allyl tributyltin.[11]

Silica gel modified by highly fluorinated silyl groups ("fluorous reverse phase silica gel") has been known for some time.[13,14] And while we are not aware of any preparative separations with these types of supports, analytical experiments clearly show the trends that would be expected based on the insolubility of fluorous and organic substrates: fluorinated substrates are strongly and selectively retained on these columns when eluting with organic solvents.[13] To test the possibilities for a filtration-based separation technique, we prepared homemade fluorous reverse phase (FRP) silica gel, as shown in eq 2. Standard "flash chromatography" grade silica gel was silylated with commercially available dimethyl[2-(perfluorohexyl)ethyl]silyl chloride (**5**).[13,15] In these initial experiments, a capping procedure was not conducted, and the modified silica gel was used after a series of washings.

$$\text{Silica–OH} \xrightarrow[\textbf{5}]{ClSi(Me)_2CH_2CH_2C_6F_{13}} \underset{\text{FRP silica gel}}{\text{Silica–OSi(Me)}_2CH_2CH_2C_6F_{13}} \qquad (2)$$

The thermal allylations in Table 1 were then repeated. This time, the crude reaction product was absorbed on FRP silica and then charged to a dry packed FRP silica gel column and eluted first with acetonitrile and then with hexane to effect the solid phase extraction. Evaporation of the acetonitrile eluent provided the organic products in comparable yields and purities to the liquid–liquid extraction (see Table 1). This time, the crude organic products were all purified by standard flash chromatography over silica gel. The isolated yields of pure products were in line with expectations based on crude yield and purities. Evaporation of hexane phase provided the fractions of fluorous products which were also comparable in yield and content to the fluorous products obtained in the liquid–liquid extraction. Although hexane is satisfactory to elute the fluorous products in these experiments, early results in other systems suggest that hexane is not a powerful enough eluent to quickly remove all types of fluorous compounds from the column. In some cases, more powerfully eluting fluorinated solvents are needed. This type of purification with two stage elution by acetonitrile and hexane has also been used with success in reactions of fluorous tin hydrides and in fluorous Stille couplings.[1a,b,e] These reactions provide clean organic product in the acetonitrile phase, and the tin product from the fluorous phase is routinely recovered and reused.

We contend that the selective fluorine–fluorine interactions are an important feature of this solid phase extraction process, and we have already conducted a few control experiments to support this contention. In these experiments, the fluorous reverse phase silica gel was replaced by commercial C18 reversed phase (RP) silica gel (silicaO–Si(Me)$_2$C$_{18}$H$_{37}$).[15] We attempted to separate crude reaction mixtures of **3a** with both fluorous **1** and organic **2** allylstannanes. The crude reaction mixtures were charged onto C18 silica gel, which was then eluted with acetonitrile. While there was doubtless some separation on the C18 column, very early fractions from both experiments contained both the alcohol and tin compounds.

It is inappropriate to conclude from these simple experiments that C18 RP silica will not be useful for solid phase extractions. The FRP silica has different retentive power from normal RP silica, so comparison with identical eluting solvent is not really fair. It may be possible to find another eluent that does provide an extractive (as opposed to chromatographic[16]) type separation of the fluorous tin compounds on C18 silica. Or by using a longer alkyl side chains than a butyl on the tin atom, it may be possible to develop fully "non-fluorous" applications of this type of solid phase extraction.[17] However, we feel that increased retentive power provided by the fluorine–fluorine interactions[13] will give the FRP technique advantages in application like fluorous library synthesis where it is desirable that the mobility of the fluorous products is dictated not by the attached organic group, but by the fluorous groups that it is attached to.

The allylation chemistry reported in this paper is largely of practical value. The preliminary results suggest that the fluorous allylstannane is roughly comparable to allyltributylstannane for thermal allylations, with the advantage that the crude organic reaction products are easily freed from all fluorous tin products. However, the implications for the new separation technique of fluorous solid phase extraction are much further reaching. Unlike solid phase extractions founded on acid–base chemistry, the perfluoroalkyl groups required for fluorous techniques are highly stable and do not present liabilities in synthesis. And beyond their use for solid phase extractions to separate organic and fluorous components, we are also finding the fluorous reverse phase silica gel to be very useful in a chromatographic mode for the analysis and purification of fluorous products.

Acknowledgment. We thank the National Institutes of Health and Parke-Davis for funding of this work.

Supporting Information Available: Contains representative procedures for the radical allylation with purification by liquid–liquid and solid-phase extraction, a procedure for preparation of the FRP silica and GC-chromatograms and ^{1}H NMR spectra of all the products (37 pages).

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[12] This product is identical (proton and tin NMR) to the product obtained by hydrolysis of $(C_6F_{13}CH_2CH_2)_3SnBr$. We have not yet obtained a parent ion in a mass spectrum of this sample, but we believe it is the stannoxane and not the tin hydroxide because there is no OH stretch evident in the IR spectrum.

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