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The Preparation of Alkenyl Fluorides from Organometallic Reagents

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Fluorination of alkenyllithium reagents can be accomplished in acceptable yield under conditions which give rise to low competitive alkene formation. These reactions are abetted by the use of the low temperature soluble, mild fluorinating agent *N*-fluoro-*N*-*tert*-butylbenzenesulfonamide; "simpler" fluorinating reagents such as F_2, XeF_2 or $FClO_3$ failed to give acceptable amounts of the fluoroolefin with these alkenyllithiums.

Introduction

Fluoroorganics are of established significance in a variety of therapeutic contexts,[1] and the physical, chemical and physiological effects of replacing hydrogen by fluorine in a variety of classes of compounds has been described from several perspectives.[1-4] Because of the importance of fluoroorganics, methodologies have been developed for specific introduction of fluorine into a variety of types of organic substrates. Many of these procedures involve highly reactive and often corrosive materials such as F_2,[5] XeF_2,[6] $FClO_3$,[7] CF_3OF,[8] CH_3COOF[9] or fluoroamine derivatives,[10] and most have focused on the preparation of fluoroalkanes or aryl fluorides. In contrast, synthetic methodology for the preparation of fluoroalkenes, especially stereospecifically, is less well developed.[11] General approaches to alkenyl fluorides involve: (1) elimination of the elements of HF from a difluorocompound;[12] (2) "reductive elimination" of fluoride and halide from an α-halo-*gem*-difluoride using a metallic reducing agent;[11d,13] (3) ring opening of *gem*-chlorofluorocyclopropanes;[11e,f,14] (4) condensation of aldehydes or ketones with fluorine-substituted nucleophiles;[11a,b,c,15] (5) photochemical ring cleavage;[16] (6) elimination of HBr from α-bromofluoro compounds;[17] or (7) fluorination of alkenylmetallics.[18] This last method for the introduction of fluorine via an organometallic is conceptually general and straightforward: the organometallic would react with a source of "positive" fluorine (robust arylmetallics have already been used in this way to prepare aryl fluorides),[19] and a variety of alkenylmetallics is readily available.

Results and Discussion

Halogen cleavage of organomercurials is a well-known method for the high yield preparation of organic halides,[20] especially those not readily obtained by direct halogenation; fluorination of alkyl- or arylmercurials occurs, but is not so efficient.[19b,c,d] Two mechanisms have been proposed for halogenation of organomercurials. In nonpolar degassed solvents, halogenation, especially with I_2, can proceed by a nonstereospecific, free radical pathway. In polar solvents (and especially in the presence of air as a radical chain terminator), halogenation of alkylmercury(II) halides can proceed through a closed, four-center transition state, with retention of configuration at carbon. "Four-centered", electrophilic cleavage of the carbon-mercury bond involves simultaneous bonding between both the attacking electrophile and a companion nucleophile. Interaction in this way may increase charge density at carbon and further activate the electrophile. (Similar processes have been proposed for other main group and d^0 transition metal organometallics.[21]) Apparently I_2, Br_2 and Cl_2 can be easily polarized by coordination to Hg(II), but such activation of F_2 is not facile.

Alkenylmercurials are easy to prepare by transmetallation[22] or by addition of nucleophiles to mercury(II)-coordinated acetylenes,[23] and a range of organic functionality is tolerated, especially in these latter procedures. In part we have focused our attention on the creation of β-alkoxy-substituted alkenylmercurials by cyclization of acetylenic alcohols.[24] Although mercury(II) catalyzed hydration of acetylenes is well-established,[25] the corresponding addition of alcohols has received little attentions. Cyclization of an ω-acetylenic alcohol could be accomplished[24] using a variety of Hg(II) species including $HgCl_2$, $Hg(OAC)_2$ and $Hg(OCOCF_3)_2$. Weak base (*ca.* 2 equiv) was necessary for the cyclization reactions; in the absence of base, only adducts between the starting acetylenic alcohol and the product enol ether were formed, and if too much base was added to the reaction mixture, no cyclized product was obtained. Cyclization of internal acetylenes is more difficult to accomplish than that of ω-acetylenic alcohols: Apparently, sterically more crowded acetylenic substrates require more strongly electrophilic metal centers to effect this transformation. However, Hg(II) salts are Lewis acids and, as such, electrophilic residues could effect double bond isomerization of product enol ethers. To create an active cyclization system which, upon cleaving the resulting organomercurial, would yield *no* by-product capable of catalyzing double bond isomerization, an *in situ* ligand modification scheme for Hg(II) was developed.[24] Cyclization was carried out at low temperature using the highly electrophilic mercuric species, $Hg(OCOCF_3)_2$. At low temperature ligand replacement was accomplished and the poor donor trifluoroacetate ligand was replaced by a better one, iodide. This both activated the organomercurial toward electrophilic cleavage (for example, protonation) and also yielded a Hg(II) species which, following cleavage, was not an isomerization catalyst.

Added base was required to prevent *in situ* protolytic cleavage of the desired alkenylmercurial intermediate. With ligand modification schemes in place, alkenyl-mercurial

compounds could be prepared and intercepted readily by an *N*-halo-succinimide. Work-up was preceded by addition of excess base to quench any residual reactivity of Hg(II) species thus formed. Simple or alkoxy-substituted alkenylmercurials could be easily converted, stereospecifically, to alkenyl iodides, bromides or chlorides using "positive halogen" reagents. *Trans*-substituted compound **1** was less reactive than its *cis* isomer, **2**, towards cyclization; the regiochemistry for cyclization was different in both cases, and the endocyclic product **3** was found to be more stable toward double bond isomerization than was the exocyclic isomer **4** (Scheme 1).

Attempts to electrophilically cleave alkenylmercurials with to "positive" fluorinating reagents failed to give the desired fluoroalkenes, and only protonated alkenes were obtained (Scheme 2).

We next explored possibilities to activate the carbon-mercury bond to make it more susceptible to electrophilic attack. The C-Hg bond in a series of compounds, C-Hg-X, varies from positively polarized at carbon (X=F) to slightly negatively polarized carbon (X=I), to substantially negatively polarized carbon (X=alkyl or aryl).[20] Corresponding efficiencies for fluorination in a series of phenylmercurials decreased rapidly for Ph_2Hg, $PhHg(OAc)$, $PhHgCl$, and $PhHg(trifluoroacetate)$.[19b] Accordingly, (alkyl)alkenylmercurial and dialkenylmercurials were prepared,[24] isolated, and treated with standard fluorinating agents (F_2, $FClO_3$); this gave fluoroalkenes, but only in low yield (<10%); *N*-fluoro-*N*-alkylsulfonamides gave only a trace of the fluoroalkene. In each case, protonated alkene was the major reaction product. (Alkyl)alkenyl-mercurials prepared *in situ* from alkenylmercuric halides and alkyllithiums also reacted with fluorinating agents to give some fluoroalkene (Scheme 3). *Equilibrium* transmetallation between diorganomercurials and organolithiums is known,[27] and it is possible, therefore, that these latter reactions might involve the *alkenyllithium* derivative prepared by such a transmetallation. Fluorination of

Scheme 1

$R = Bu^t$　　" F " $= FClO_3$, F_2, XeF_2
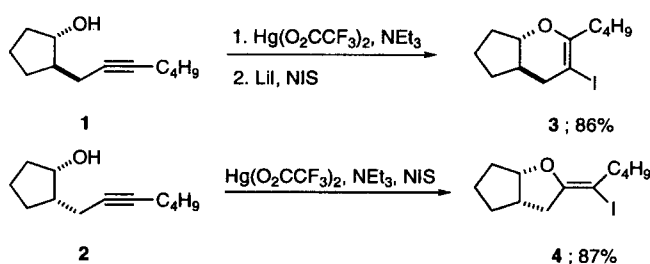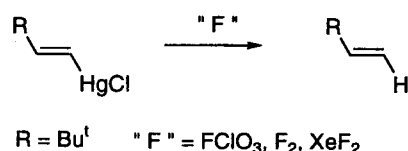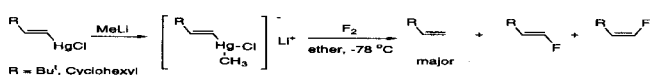
Scheme 2

Scheme 3

alkenyllithiums was therefore studied.

An alkenyllithium reagent can be prepared from an alkenyl halide and lithium metal,[28] or by transmetallation between an alkyllithium and an alkenyltin[27a,27b,29] or an alkenyl halide.[30] In this latter process, dehydrohalogenation competes with transmetallation,[31] and products obtained are derived from the corresponding acetylene. Alkenyl iodides are preferred substrates for lithiation; they are easily prepared from alkenylmetallics such as alkenylboron,[32] -aluminum,[33] -zirconium,[34] -copper[35] or -mercury compounds.[24]

As for the corresponding mercurials straightforward fluorination of organolithium reagents occasionally works well, but fails for alkenyls. Although several alkyl, aryl, heterocyclic, or enolate lithium derivatives have been converted in good yield to the corresponding fluorides with $FClO_3$,[7b,18b,18c,36] typical alkenyllithiums reacted with this reagent to give only a trace of the desired fluoroorganic. N-Fluoro-N-*tert*-butyl-*p*-toluenesulfonamide (5a) is a relatively mild agent[37] for fluorinating enolates and analogs. This material is a solid at room temperature and is not appreciably soluble in nonreacting solvents at low temperature. Terminal alkenyllithium reagents can be prepared from two equivalents of *tert*-butyllithium and an alkenyl iodide in diethyl ether at − 78 °C, but lithiation of internal alkenyl iodides must be performed below − 110 °C to prevent acetylene formation by dehydrohalogenation. To enable facile operation at low temperature, N-fluoro-N-alkyl-benzenesulfonamides were prepared.[38] These materials are liquids at room temperature and are readily soluble in nonreactive solvents even at low temperature. In fact high yield lithiation of terminal or internal alkenyl iodides could be accomplished using two equivalents of *tert*-butyllithium at − 120 °C in "Trapp" solvent (THF : ether : n-pentane=4 : 1 : 1).[28,30] Alkenyllithiums thus prepared in this way reacted with mild fluorinating agent, 5a, at − 120 °C to give the desired fluoroolefins[38,39] in good yield and the results are presented in Table 1 (Scheme 4).
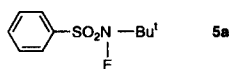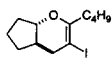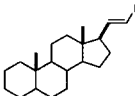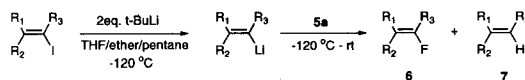

Table 1. Fluorination of Alkenyllithiums

| Entry	Alkenyl iodide	Product (yield, %)[a]	
		6	7
1	R_1=n-C_6H_{13}, R_2=R_3=H	71	15
2	R_1=Ph, R_2=R_3=H	76	10
3	R_1=R_3=n-C_3H_7, R_2=H	85	3
4	R_1=$(CH_3)_2$CH$(CH_2)_2$, R_2=H, R_3=CH_3	75	12
5	R_1=CH_3, R_2=H, R_3=$(CH_3)_2$CH$(CH_2)_2$	75	12
6	R_1=$(CH_3)_2$CHCH_2, R_2=H, R_3=C_2H_5	88	7
7	R_1=C_2H_5, R_2=H, R_3=$(CH_3)_2$CHCH_2	83	7
8		74[b]	8
9		80[b]	13

[a] All yields determined by GC except where noted. [b] Isolated yield.
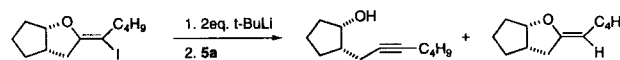
β-Alkoxy-substituted lithium reagent 8 could be successfully prepared at low temperature, without undergoing elimination of lithium alkoxide, and trapped to give fluoroalkene 9 in good yield.
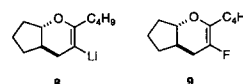
When the same procedure was attempted for the five-membered ring E-iodoenol ether 4E, lithiation occured, but only unfluorinated ring-opened products were obtained on work up (Scheme 5). (Analogous ring opening of lithium-substituted heterocycles has been reported.[40]) It has not yet been possible to enable successful fluorination for the 4E isomer: polar solvents enhance lithiation rates but destabilize the product alkenyllithium; nonpolar solvents stabilize the alkenyllithium but suppress the lithiation step.[41,42]

Experimental Section

General. All experiments were performed under an atmosphere of nitrogen or argon from which oxygen was removed by passing through a bed of BTS catalyst in reduced form (previously heated under a CO stream) and from which water was removed by passing through a column of size 4 Å molecular sieves. Liquid transfers were performed by syringe or cannula, and solid transfers were performed under a stream of inert gas or in a dry box. Ethers and hydrocarbon solvents were distilled just prior to use under nitrogen from sodium/benzophenone ketyl. Approximately 5% tetraglyme was added to solvents to ensure solubility of the ketyl. Dichloromethane was distilled under nitrogen from calcium hydride. Commercially obtained organic compounds were dried by the appropriate method and, if a liquid, distilled under nitrogen directly prior to use.

Proton and ^{13}C NMR spectra were taken on a JEOL FX 90-Q, a Bruker WM250 or GE QE300 spectrometer. Chemical shifts are reported as downfield from tetramethylsilane in units of δ with respective multiplicity and integration indicated. Fluorine NMR spectra were taken on an IBM NR80 spectrometer. Chemical shifts are reported as upfield from $CFCl_3$ in units of δ with respective multiplicity shown. Mass spectra were recorded on an A.E.I. MS-9 and gas chromatographic mass spectra on a Hewlett-Packard 5992 GC/MS. These are reported in the order: molecular ion (intensity), highest peaks (intensities). Elemental analyses were performed by Schwarzkopf Microanalytical Lab (Woodside, NY). Analytical gas chromatography was performed on a Hewlett-Packard 5840A instrument equipped with a flame ionization detector. Preparative gas chromatography was performed on a Perkin-Elmer 3920, fitted with thermal conductivity detector using a 3/8 in. × 8 ft.

column packed with 3% OV-17 on chromosorb PNAW. Analytical thin layer chromatography were performed on Analtech 250 silica gel GF plates and Macherey-Nagel Polygram SIL G/UV254 plates. Preparative LC was accomplished using silica gel (Merck grade 60, 230-400 mesh).

Preparation of N-Fluoro-N-tert-butylbenzenesulfonamide (5a). This compound was prepared by analogy with a published procedure.[37] An equivalent amount of fluorine (5% in nitrogen, 30 mL/min) was bubbled through a solution of N-tert-butylbenzenesulfonamide[43] (8.52 g, 40 mmol) in 1 : 1 mixture of CFCl₃ (400 mL) and CHCl₃ for 10 h at − 78 °C. After evaporation of the solvent, the residue was chromatographed on a silica gel column. Elution with an 1 : 1 mixture of dichloromethane and hexanes gave the product in 20% yield. Benzenesulfonyl fluoride was obtained in 25% yield, and half of the starting sulfonamide, which was recycled for fluorination reaction, was recovered. ¹H NMR (CDCl₃) δ 7.98-7.94 (m, 2H), 7.67-7.48 (m, 3H), 1.45 (d, J=1.8 Hz, 9H); ¹³C NMR (CDCl₃) δ 137.5, 133.8, 128.7, 128.6, 66.1 (d, J=12.2 Hz), 26.8 (d, J=6.1 Hz); ¹⁹F NMR (CDCl₃) δ − 62.2. HRMS calcd for C₁₀H₁₄NO₂FS 231. 0729, found 231.0717.

The following N-fluorosulfonamides were prepared from corresponding sulfonamides by the same procedure.

N-Fluoro-N-tert-butyl-p-toluenesulfonamide (5b) (15%). ¹H NMR (CDCl₃) δ 7.90-7.21 (m, 4H), 2.44 (s, 3H), 1.44 (d, J=1.8 Hz, 9H).

N-Fluoro-N-neopentyl-p-toluenesulfonamide (5c) (58%). ¹H NMR (CDCl₃) δ 7.90-7.32 (m, 4H), 2.96 (d, J =44.4 Hz, 2H), 2.47 (s, 3H), 0.97 (d, J=1.1 Hz, 9H).

N-Fluoro-N-norbornyl-p-toluenesulfonamide (5d) (70%). ¹H NMR (CDCl₃) δ 8.01-7.32 (m, 4H), 3.15-3.13 (m, 1H), 2.46 (s, 3H), 2.72-0.90 (m, 10H).

N-Fluoro-N-methyl-p-toluenesulfonamide (5e) (60%). ¹H NMR (CDCl₃) δ 7.80-7.21 (m, 4H), 3.03 (d, J= 31.6 Hz, 3H), 2.39 (s, 3H).

N-Fluoro-N-phenylbenzenesulfonamide (5f) (18%). ¹H NMR (CDCl₃) δ 7.84-7.76 (m, 2H), 7.64-7.50 (m, 2H), 7.50-7.38 (m, 2H), 7.14-7.02 (m, 2H), 7.00-6.80 (m, 2H).

Reaction of 1-Octenylmercuric Chloride with 5a. To 104 mg of the alkenyl-mercurial[44] (0.3 mmol) in 2 mL of ether was added 104 mg of fluorinating agent 5a (0.45 mmol) in 1 mL of pentane at − 78 °C. The reaction mixture was stirred overnight at room temperature. GC analysis of volatile components showed no 1-fluoro-1-octene.

Reaction of 1-Octenylmercuric Chloride Sequentially with Methyllithium and 5a. To 104 mg of the alkenylmercurial[44] (0.3 mmol) in 2 mL of ether was added 0.25 mL of methyllithium (1.2 M solution in ether, 0.3 mmol) and then 104 mg of fluorinating agent 5a (0.45 mmol) at − 78 °C. After stirring overnight at room temperature, GC/MS analysis of the volatile components indicated that the products were 1-octene and 1-fluoro-1-octene (10 : 1).

Reaction of Bis(2-ethyl-1-hexenyl)mercury with 5a. To 127 mg of the dialkenyl-mercurial[45] (0.3 mmol) in 2 mL of n-pentane was added 92 mg of fluorinating reagent 5a (0.4 mmol) in 1 mL of n-pentane at − 78 °C. After stirring for 10 min at − 78 °C, the mixture was allowed to warm to room temperature. GC analysis of volatile components indicated the only product formed was 2-ethyl-1-hexene.

Reaction of Bis(2-ethyl-1-hexenyl)mercury Sequentially with Methyllithium and 5a. To 127 mg of the dialkenylmercurial[45] (0.3 mmol) in 2 mL of n-pentane was added methyllithium (1.2 M solution in ether, 0.3 mmol) at − 78 °C. After stirring for 15 min, 92 mg of fluorinating agent 5a (0.4 mmol) in 1 mL of n-pentane was added at − 78 °C. The mixture was stirred for 10 min at − 78 °C and then allowed to warm to room temperature. GC analysis of volatile components indicated the products were 2-ethyl-1-hexene and 4-ethyl-3-octene, no fluoroolefin was formed.

Preparation of trans-1-Fluoro-1-octene. To 238 mg of trans-1-iodo-1-octene,[34] (1.0 mmol) in 9 mL of Trapp solvent mixture (THF : ether : n-pentane=4 : 1 : 1) was added 1. 18 mL of tert-butyllithium (1.7 M solution in pentane) under argon at − 120 °C. After stirring 20 min, 347 mg of fluorinating agent 5a (1.5 mmol) was added via syringe at − 120 °C. The mixture was kept at − 120 °C for 20 min and was allowed to rise slowly to room temperature. Products were separated by reduced-pressure distillation from the reaction mixture and were purified by preparative GC. Yields were determined by GC (trans-1-fluoro-1-octene, 71%, 1-octene; 15%). ¹H NMR (CDCl₃) δ 6.48 (dd, J=86.2, 11.0 Hz, 1H), 5.33 (ddt, J=19.1, 11.2, 7.8 Hz, 1H), 2.01-1.80 (m, 2H), 1.43-1.22 (m, 8H), 0.89 (t, J=7.5 Hz, 3H); ¹³C NMR (CDCl₃) δ 148.5 (d, J=253.2 Hz), 111.6 (d, J=8.1 Hz), 31.6, 29.6, 28.6, 25.0 (d, J=9.3 Hz), 22.6, 14.0; ¹⁹F NMR (CDCl₃) δ − 131.0. MS (EI) m/z 130 (13), 43 (100), 56 (53), 55 (32), 41 (31), 69 (29), 70 (19).

The following fluoroalkenes were prepared from the corresponding iodoalkenes by the same procedure (references are to preparations of the iodoalkene precursors). Characterization data are given only for fluoroolefins.

trans-4-Fluoro-4-octene[34] (85%), cis-4-Octene (3%). ¹H NMR (CDCl₃) δ 4.99 (dt, J=22.4, 7.9 Hz, 1H), 2.17 (dt, J=23.4, 7.9 Hz, 2H), 1.88 (q, J=7.5 Hz, 2H), 1.52 (sextet, J=7.3 Hz, 2H), 1.35 (sextet, J=7.3 Hz, 2H), 0.92 (t, J=7.8 Hz, 3H), 0.88 (t, J=7.8 Hz, 3H); ¹³C NMR (CDCl₃) δ 160.1 (d, J=246.2 Hz), 105.5 (d, J=22.1 Hz), 29.9 (d, J= 28.7 Hz), 27.6 (d, J=9.5 Hz), 23.3, 19.8, 13.54, 13.46; ¹⁹F NMR (CDCl₃) δ − 105.0. MS (EI) m/z 130 (45), 81 (100), 59 (96), 101 (71), 73 (54), 41 (43), 55 (37), 60 (34). HRMS calcd for C₈H₁₅F 130.1158, found 130.1151.

trans-2'-Fluorostyrene[34] (76%), Styrene (10%). ¹H NMR (benzene-d₆) δ 7.11-6.80 (m, 5H), 6.71 (dd, J= 83.2, 11.4 Hz, 1H), 6.16 (dd, J=19.4, 11.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 150.1 (d, J=259.3 Hz), 132.7 (d, J=12.5 Hz), 128.7, 127.5, 126.2, 113.9 (d, J=15.4 Hz); ¹⁹F NMR (CDCl₃) δ − 129.8. MS (EI) m/z 122 (100), 96 (26), 121 (23), 101 (16), 123 (9), 102 (7), 77 (2). HRMS calcd for C₈H₇F 122.0532, found 122.0530.

trans-4-Fluoro-6-methyl-3-heptene[34] (83%), cis-6-Methyl-3-heptene (7%). ¹H NMR (CDCl₃) δ 5.02 (dt, J=22.4, 7.9 Hz, 1H), 2.07 (dd, J=24.1, 7.0 Hz, 2H), 2.02-1.80 (m, 1H), 1.92 (quintet, J=7.6 Hz, 2H), 0.95 (t, J= 7.5 Hz, 3H), 0.92 (d, J=6.7 Hz, 6H); ¹³C NMR (CDCl₃) δ 159.1 (d, J=245.7 Hz), 108.1 (d, J=21.5 Hz), 37.1 (d, J= 27.4 Hz), 26.1, 22.2, 19.0 (d, J=9.6 Hz), 11.1; ¹⁹F NMR (CDCl₃) δ − 103.6. MS (EI) m/z 130 (9), 43 (100), 41 (39), 88 (20), 73 (17), 60 (11), 59 (10).

trans-3-Fluoro-6-methyl-3-heptene[34] (88%), cis-

6-Methyl-3-heptene (7%). ¹H NMR (CDCl₃) δ 4.94 (dt, *J*=22.5, 8.1 Hz, 1H), 2.21 (dq, *J*=22.9, 7.6 Hz, 2H), 1.79 (t, *J*=7.4 Hz, 2H). 1.60-1.50 (m, 1H), 1.06 (t, *J*=7.5 Hz, 3H), 0.87 (d, *J*=6.6 Hz, 6H); ¹³C NMR (CDCl₃) δ 161.8 (d, *J*= 246.2 Hz), 103.3 (d, *J*=22.1 Hz), 34.6 (d, *J*=9.2 Hz), 28.9, 22.1, 21.4 (d, *J*=29.1 Hz), 14.7; ¹⁹F NMR (CDCl₃) δ - 106. 2. MS (EI) *m/z* 130 (20), 87 (100), 59 (98), 41 (95), 43 (81), 56 (36), 88 (36).

trans-3-Fluoro-6-methyl-2-heptene³⁴ (75%), cis-6-Methyl-2-heptene (12%). ¹H NMR (CDCl₃) δ 5.12-4.92 (m, 1H), 2.19 (dt, *J*=23.0, 7.7 Hz, 2H), 1.61-1.43 (m, 4H), 1.39-1.37 (m, 2H), 0.89 (d, *J*=6.7 Hz, 6H); ¹³C NMR (CDCl₃) δ 160.9 (d, *J*=224.8 Hz), 99.3 (d, *J*=24.7 Hz), 35.3, 27.5, 25.6 (d, *J*=28.4 Hz), 22.4, 10.3 (d, *J*=9.7 Hz); ¹⁹F NMR (CDCl₃) δ - 104.9. MS (EI) *m/z* 130 (6), 56 (100), 41 (62), 57 (34), 73 (6), 95 (4).

trans-2-Fluoro-6-methyl-2-heptene³⁴ (75%), cis-6-Methyl-2-heptene (12%). ¹H NMR (CDCl₃) δ 5.12-4.90 (m, 1H), 1.90-1.88 (m, 2H), 1.85 (dd, *J*=17.5, 0.7 Hz, 3H), 1.65-1.45 (m, IH), 1.22-1.20 (m, 2H), 0.87 (d, *J*=6.6 Hz, 6H); ¹³C NMR (CDCl₃) δ 156.6 (d, *J*=242.4 Hz), 105.6 (d, *J*=21.0 Hz), 39.1, 27.4, 23.5 (d, *J*=9.2 Hz), 22.4, 13.8 (d, *J*=32.2 Hz); ¹⁹F NMR (CDCl₃) δ - 96.9. MS (EI) *m/z* 130 (17), 41 (100), 73 (91), 56 (43), 57 (42), 69 (38), 53 (38).

trans-2-Butyl-3-fluoro-4,4a,5,6,7,7a-hexahydro-cyclopenta[b]pyran²⁴ (7) (74%). ¹H NMR (CDCl₃) δ 3.49 (dt, *J*=7.3, 10.1 Hz, 1H), 2.53-1.10 (m, 15H), 0.88 (t, *J*=7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 143.2 (d, *J*=234.3 Hz), 141.7 (d, *J*=34.5 Hz), 81.3, 39.9 (d, *J*=9.1 Hz), 30.1 (d, *J*= 22.9 Hz), 28.9, 27.9, 27.4, 22.3, 20.6, 13.8; ¹⁹F NMR (CDCl₃) δ - 151.0. MS (EI) *m/z* 198 (21), 41 (100), 67 (91), 57 (60), 68 (50), 43 (44), 108 (43).

trans-2-Butyl-4,4a,5,6,7,7a-hexahydrocyclopenta [b]pyran (8%). ¹H NMR (benzene-d₆) δ 4.51 (dd, *J*=5.3, 1.5 Hz, 1H), 3.49 (td, *J*=9.7, 7.3 Hz, 1H), 2.22-1.20 (m, 15H), 0.88 (t, *J*=7.3 Hz, 3H). MS (EI) *m/z* 180 (14), 95 (100), 41 (85), 80 (69), 138 (64), 55 (55), 67 (55), 43 (52).

Preparation of 17-(trans-2-Iodoethenyl)-5α-androstane. To a suspension of Cp₂ZrHCl (1 g, 3 mmol, 78% pure) in benzene (5 mL) was added 0.853 g of 17-ethynyl-5-androstane (3 mmol) in 5 mL of benzene.³⁴ After stirring for 5 h at room temperature, the solvent was removed *in vacuo*. The dark solution in 5 mL of ether was cooled to 0 °C and 0.76 g of iodine (3 mmol) in 5 mL of ether was added. The mixture was allowed to warm to room temperature and was stirred for 1/2 h. The excess iodine was removed by washing the solution with aqueous sodium thiosulfate. The organic layer was separated and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on a column of silica gel. Elution with hexanes gave the product in 45% yield. ¹H NMR (CDCl₃) δ 6.45 (dd, *J*=14.3, 8.1 Hz, 1H), 5.89 (dd, *J*= 14.3, 0.9 Hz, 1H), 2.12-0.51 (m, 25H), 0.76 (s, 3H), 0.59 (s, 3H). MS (EI) *m/z* 412 (31), 41 (100), 55 (94), 67 (94), 79 (68), 397 (68), 81 (64). No attempt was made to optimize the yield of this compound.

Preparation of 17-(trans-2-Fluoroethenyl)-5α-androstane. To 4.12 g of the alkenyl iodide (10.0 mmol) in 120 mL of "Trapp" solvent mixture was added 11.8 mL of *tert*-butyllithium (1.7 M solution in pentane, 20.0 mmol) under argon at - 120 °C. The mixture was stirred for 20

min at - 120 °C and 3.47 g of fluorinating agent **5a** (15 mmol) was added *via* syringe to the reaction mixture at - 120 °C. The mixture was kept at - 120 °C for 20 min and allowed to rise slowly to room temperature. Products were separated by column chromatography. Recrystallization from hexanes gave 2.43 g of the alkenyl fluoride (80%) and 0.37 g of the alkene (13%). mp 80-81 °C; ¹H NMR (CDCl₃) δ 6.41 (dd, *J*=86.1, 11.0 Hz, 1H), 5.27 (ddd, *J*=19.8, 11.0, 8.8 Hz, 1H), 1.91-0.60 (m, 25H), 0.79 (s, 3H), 0.59 (s, 3H); ¹³C NMR (CDCl₃) δ 148.1 (d, *J*=254.4 Hz), 112.5 (d, *J*=7.9 Hz), 55.6, 55.0, 47.5, 47.4, 47.1, 43.5, 38.7, 37.4, 36.4, 35.7, 32.3, 29.0, 28.1, 26.8, 24.7, 22.2, 20.4, 12.9, 12.2; ¹⁹F NMR (CDCl₃) δ - 129.7 (dd, *J*=86.2, 20.1 Hz). MS (EI) m/z 304 (83), 289 (100), 41 (94), 67 (91), 55 (75), 72 (67), 79 (61). Anal. calcd for C₂₁H₃₃F: C, 82.84; H 10.92; F, 6.24. Found C, H, F.

17-Ethenyl-5α-androstane. ¹H NMR (CDCl₃) δ 5.80-5.70 (m, 1H), 4.96 (s, 1H), 4.93-4.90 (m, 1H), 2.01-0.60 (m, 25H), 0.79 (s, 3H), 0.59 (s, 3H). MS (EI) *m/z* 286 (83), 67 (100), 41 (96), 271 (88), 55 (86), 217 (84), 79 (70).

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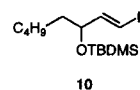
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Preconcentration of Cd by Continuous Hydroxide Precipitation-Dissolution in Atomic Emission Spectrometry

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On-line preconcentration by direct precipitation with hydroxide has been developed and applied for the analysis of Cd in Inductively Coupled Plasma Atomic Emission Spectrometry. Cadmium is continuously precipitated with hydroxide and dissolved by nitric acid in on-line mode. Currently, the enrichment factor is more than 90 times for 20.0 mL of sample and could be further increased very easily. For a large sample throughput, 1.0 mL of sample loop is used and the enrichment factor is 4.5 with the sampling speed of 15/hr. The method has been applied to the analysis of NIST reference sample and has yielded good results with the certified value.

Introduction

Cadmium has been well studied because of its high toxicity even at low concentrations.[1] Varieties of technique[2,3] to determine Cd at very low concentrations have been developed. Different species of cadmium has been separated and detected by HPLC-ICP[4,5] (High Performance Liquid Chromatography-Inductively Coupled Plasma). Also, it has often been needed to separate analytes from matrix to reduce or avoid interferences. Precipitation is a very attractive method of achieving both preconcentration and matrix separation and has been widely used in this sense.[6-8] Because of the recent development of Flow Injection Analysis (FIA), the on-line precipitation preconcentration[9-13] method has been developed and began to appear only in these days. The advantages are well discussed in other literatures.[8,13]

Most of researches[11-14] have focused on the utilization of coprecipitation because it is more efficient in collecting trace elements quantitatively. Inorganic carriers[15,16] as well as organic collectors[11,12] have been used to preconcentrate various elements. Welz et al.[11] used a "knotted" reactor instead of filter to increase sample throughput. Some of the researchers[17,18] utilized more sophisticated techniques to enhance detection limits. Nielson[18] studied the technique of on-line coprecipitation combined to hydride generation. Arsenic was first coprecipitated with hafnium. When it was dissolved in HCl, sodium tetraborate was added to generate arsenic hydride. Detection limits could be enhanced more than 30 times in Graphite Furnace Atomic Absorption Spectrometry.

Anions also could be preconcentrated and analyzed. Esmadi[19] used AgNO₃ to precipitate arsenite and cyanide

ions. After both anions were precipitated, an acid and ammonia were sent as dissolving reagents in sequence. When an acid was sent, silver arsenite was dissolved out and for ammonia, silver cyanide eluted out. The concentrations of arsenite and cyanide could be measured separately.

However, it has been a trouble to collect large amount of precipitation on a filter. Because of the back pressure at the filter region caused by the precipitates, the flow could be slowed down or even stopped. Thus, large volume of sample was difficult to be preconcentrated. Furthermore, blockage of flow frequently resulted in a poor precision. "Knotted" reactor gives less back pressure but the peak becomes broadened because of its large loop length.

Direct precipitation could be more advantageous than coprecipitation in this sense. Since no carrier is used, a large amount of sample can be preconcentrated thus increasing enrichment factor. Until now, only a few studies have been performed using direct precipitation. Valcarcel[16,18] has shown that trace amount of Pb in a rock sample can be effectively analyzed by continuous precipitation using ammonia. Our group[20,21] has recently shown that sulfide precipitation could be utilized in the analysis of tin group elements. Homogeneous precipitation of As with sulfide anion was successfully demonstrated. H₂S was generated by the hydrolysis of thioaceteamide in the reaction coil. Two most common type of precipitates, sulfide and hydroxide, are very easy to use and many cations can be precipitated.

In this research, on-line direct precipitation preconcentration by forming hydroxide precipitation is demonstrated for the analysis of Cd because it can form hydroxide precipitation very easily even at low concentration levels. Oth-