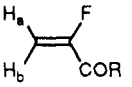
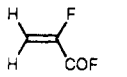
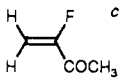
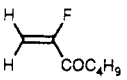
Table II. NMR Spectral Data of (1-Fluorovinyl)carbonyl Compounds 11 and 12



compounds	chemical shifts,[a] δ				coupling constants[b]			
	H_a	H_b	F	R	$^2J_{HH}$	$^3J_{FH_a}$	$^3J_{FH_b}$	J_{FR}
 11	5.6	6	−117	+14		12	46	18
 12	4.9	5.4	−116	2.3	4	17	46	3
 12′	5.1	5.65	−117	2.7 1.65 0.95	3	17	48	2

[a] Chemical shifts are expressed in ppm from TMS and $CFCl_3$ as external references. [b] Coupling constants are expressed in hertz. [c] These characteristics were in agreement with those given in the literature.[13]

(18 mL) was carefully added, and the pH was adjusted to 6 or 7. The solution was left for the night, and then the organic phase was separated, washed, and dried over magnesium sulfate. Diethyl ether was distilled off, leaving a crude oil which was flash distilled to give a clean liquid (bp 60 °C, 100 Torr; 17 g). By introduction of a known quantity of $CFCl_3$ in a sample of the distillate, one can evaluate the ratio of different fluorinated compounds obtained as in the following: 74% of **7**, 16% of **8**, and 10% of **4**. Purified alcohol **7** was obtained by a second distillation in the presence of hydroquinone (bp 98 °C, 12.5 g, yield 74%). The ^1H NMR and ^{19}F NMR data of **7** are found in Table I. Anal. Calcd for $C_3H_3F_3O$: C, 32.17; H, 2.70. Found: C, 32.34; H, 2.75.

3-Chloro-2,3-difluoroallylic Alcohol, 10. The same process applied to a solution of alcohol **9**, $CHClFCF_2CH_2OH$ (10 g, 68.4 mmol), in 10 mL of anhydrous diethyl ether, and 127 mmol of methyllithium, gave a crude distillate (bp 90–95 °C, 125 Torr; 7.8 g) from which alcohol **10** (bp 116 °C; 5.7 g) was isolated as two isomers (*E*/*Z* equal to 45/55). Their ^1H NMR and ^{19}F NMR data are found in Table I. IR (CCl_4): 3300 (OH), 1780 cm^{-1} (CF=CFCl). Anal. Calcd for $C_3H_3ClF_2O$: C, 28.04; H, 2.35. Found: C, 28.18; H, 2.48.

3-Methyl-2,3-difluoroallylic Alcohol, 8. To a solution of 10 g (76 mmol) of alcohol **4** in 30 mL of diethyl ether was added dropwise with stirring 220 mmol of methyllithium. The stirring was continued overnight at room temperature. The solution was neutralized carefully and worked up as in the preparation of **7**. A fractionation of the crude distillate gave **7** (1 g, 9 mmol) and **8** (4.6 g, 42.7 mmol, yield 56%) as a mixture of two isomers (*E*/*Z* equal to 80/20). We cannot separate these isomers by VPC through a column of SE30 heated to 130 °C. The ^1H NMR and ^{19}F NMR data of these isomers are found in Table I. IR (CCl_4): 3300, 3230 (OH), 1740, 1710 cm^{-1} (CF=CF). Anal. Calcd for $C_4H_6F_2O$: C, 44.48; H, 5.6; F, 35.18. Found: C, 44.77; H, 5.61; F, 34.12.

3-Butyl-2,3-difluoroallylic Alcohol, 8′. Similarly, a solution of 7 g (53 mmol) of alcohol **4**, 70 mL of diethyl ether, and 180 mmol of butyllithium (1.2 M solution in hexane) gave 6.8 g of crude distillate, bp 70–80 °C (15 Torr), from which 5.4 g (36 mmol) of **8′** were isolated, yield 68%. The isomers *E*, bp 176 °C, and *Z*, bp 188 °C, were separated by VPC through a column of SE 30 heated to 160 °C. The ratio *E*/*Z* was 77/23. The ^1H NMR and ^{19}F NMR data of these isomers are found in Table I. IR (CCl_4): 3300, 3230 (OH), 1732 cm^{-1} (CF=CF). Anal. Calcd for $C_7H_{12}F_2O$: C, 56.05; H, 8.06; F, 25.33. Found: (*E*) C, 56.17, H, 8.13; F, 24.62; (*Z*) C, 55.87; H, 8.93.

2-Fluoroacryloyl Fluoride, 11. Into a distillation flask containing 10 mL of concentrated sulfuric acid were added dropwise with stirring 2.5 g (22 mmol) of alcohol **7**. An exothermic reaction occurred. The volatile acryloyl fluoride **11** formed was distilled in vacuo (200 Torr) in a receiver cooled by a dry ice–acetone mixture. Obtained was 1.15 g (12.5 mmol), yield 55%. Similarly, 4.5 g (35 mmol) of alcohol **10** gave 2.78 g (29 mmol) of **11**. Yield 82%. The ^1H NMR and ^{19}F NMR data of **11** were in Table I. Treated by a solution of phenol in CH_2Cl_2 **11** gave the known phenyl 2-fluoroacrylic acid ester **2**.

Fluorovinyl Methyl Ketone, 12. A mixture of 2.4 g (18.9 mmol) of alcohol **8**, $CH_3CF{=}CF\text{-}CH_2OH$, 10 mL of tetrachloroethane, 0.5 mL of concentrated sulfuric acid, and hydroquinone was heated for half an hour on an oil bath at ca. 100 °C; it was then distilled in vacuo to give a crude distillate, bp 60–80 °C (100 Torr), 7.2 g. It contains 14.5 mmol (evaluated by ^{19}F NMR) of ketone **12**, which was separated by a second distillation in the presence of hydroquinone at room temperature under 15 Torr. Yield 1.3 g, 76%. The ^1H NMR and ^{19}F NMR spectra of **12** are in Table II. IR (CCl_4): 1730, 1710 (C=O), 1640 cm^{-1} (C=CF). These characteristics were in agreement with those given in the literature.[13]

1-Fluorovinyl *n*-Butyl Ketone, 12′. A mixture of 2.1 g (14 mmol) of alcohol **8′**, *E* and *Z* $C_4H_9CF{=}CFCH_2OH$, 5 mL of CH_2Cl_2, 0.5 mL of concentrated sulfuric acid, and hydroquinone was heated for half an hour on an oil bath at ca. 100 °C and then distilled off in vacuo to give ketone **12′**, bp 75–80 °C (160 Torr), 1.2 g (8.6 mmol), yield 61%. The ^1H NMR and ^{19}F NMR data of **12′** are in Table II. IR (CCl_4): 1710 (C=O), 1640 cm^{-1} (C=CF). Anal. Calcd for $C_7H_{11}FO$: C, 64.67; H, 8.33. Found: C, 64.00; H, 8.60.

Registry No. **4**, 76-37-9; **7**, 41578-52-3; (*E*)-**8**, 123028-47-7; (*Z*)-**8**, 123028-48-8; (*E*)-**8′**, 123028-51-3; (*Z*)-**8′**, 123028-52-4; **9**, 28885-04-3; (*E*)-**10**, 123028-49-9; (*Z*)-**10**, 123028-50-2; **11**, 60556-85-6; **12**, 2372-98-7; **12′**, 71150-92-0; CH_3Li, 917-54-4; C_4H_9Li, 109-72-8.

Trimethylsilyl Polyphosphate for Intramolecular Friedel–Crafts Cyclizations

Ellen M. Berman* and H. D. Hollis Showalter

Chemistry Department, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105

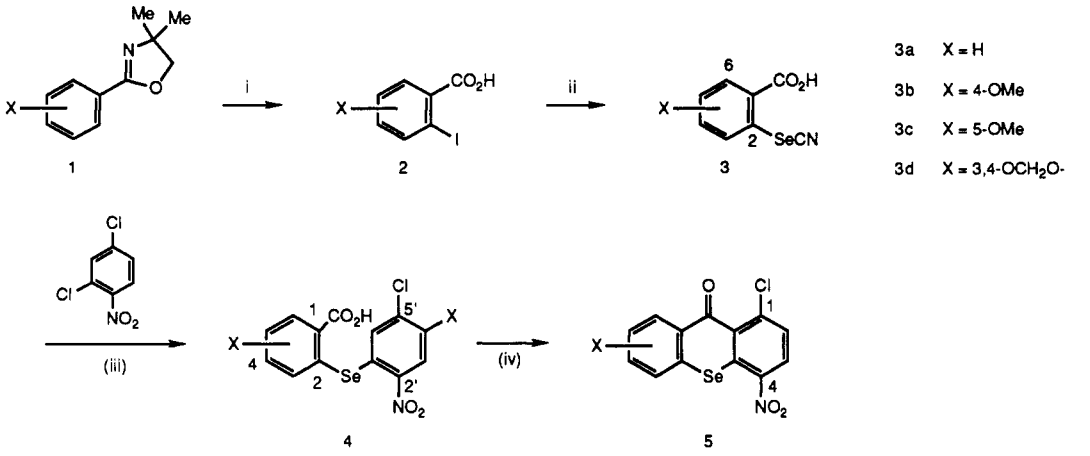
Received May 15, 1989

In connection with studies directed toward the synthesis of a novel class of DNA intercalating agents,[1] we needed to prepare a series of 9*H*-selenoxanthen-9-ones. The

(1) Presented at the 78th Annual Meeting of the American Association for Cancer Research, Atlanta, GA, May 1987; Abstract No. 1197. Berman, E.; Klohs, W.; Leopold, W. R.; Plowman, J.; Sercel, A. D.; Shillis, J.; Showalter, H. D. H.; Werbel, L. M. *Proceedings Am. Assoc. Cancer Res.* **1987**, *28*, 302.

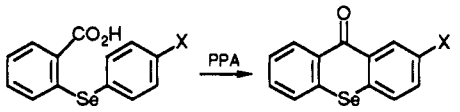
0022-3263/89/1954-5642$01.50/0

Scheme I[a]



[a] Reagents and reaction conditions: (i) *n*-BuLi/0 °C/I_2 then 6 N HCl reflux; (ii) NaSeCN/DMA/Cu/150 °C; (iii) $NaBH_4$/EtOH; (iv) PPSE/P_2O_5.

synthesis of the unsubstituted parent compound had been reported previously, and for its preparation 2-(phenylseleno)benzoic acid (X = H) was cyclized in 97% yield in PPA at 100 °C (eq 1).[2]



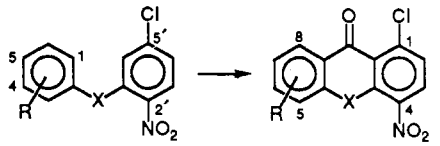
(1)

The 2-chloroselenoxanthenone (X = Cl) was similarly prepared in 80% yield when the cyclization was carried out in H_2SO_4 at 95 °C.[2]

We prepared a series of deactivated 2-(phenylseleno)-benzoic acids (4) according to Scheme I. When these 2-(phenylseleno)benzoic acids were subjected to standard methods of cyclization (polyphosphoric acid, PPA; polyphosphoric acid ester, PPE; trifluoroacetic acid, TFA/trifluoroacetic anhydride, TFAA; methanesulfonic acid, MSA/phosphorous pentoxide), only poor to moderate yields of the desired selenoxanthenones were obtained after tedious workup and purification.

In this paper we report the use of trimethylsilyl polyphosphate (PPSE) for the convenient and efficient synthesis of substituted 9*H*-selenoxanthen-9-ones and related sulfur and oxygen congeners under aprotic conditions. PPSE is suitable as an alternative to PPA and other protic reagents. Trimethylsilyl polyphosphate, prepared from P_2O_5 and hexamethyldisiloxane according to Imamoto,[3] is a stable, colorless, viscous oil that is readily soluble in organic solvents. PPSE has been reported to have broad synthetic utility, including the promotion of aldol condensations,[3] the reduction of sulfoxides,[3] Pummerer rearrangements,[4] Beckmann rearrangements,[5] and the conversion of amides to nitriles[6] and alcohols to iodides.[7] The composition and structure of the reagent has been reported.[8] Surprisingly, PPSE-promoted Friedel–Crafts cyclocondensations have, to our knowledge, never been reported.

Table I. Heteroxanthenones by PPSE-Promoted Friedel–Crafts Cyclizations (4 → 5): Comparison with Standard Methods



4 5

entry	substrate,[a] R =	product,[b] R = (mp, °C)	methods	isolated yield, %
a	1-CO_2H	unsubstituted (196–197)	PPA	43
			PPE	44
			PPSE	99
			MSA/P_2O_5	40
			TFA/TFAA	55
b	6′-CO_2H	unsubstituted (196–197)	TFA/TFAA	70
			PPSE	87
c	1-CO_2H 4-OMe	6-OMe (229–232)	PPA	18
			PPSE	94
d	1-CO_2H 5-OMe	7-OMe (222–224)	MSA/P_2O_5	–[c]
			PPE	12
			PPSE	68
e	1-CO_2H 3,4-OCH_2O	5,6-OCH_2O (241–243)	TFA/TFAA/H_3PO_4	55
			PPSE	–[c]
f	1-CO_2H (X = S)	unsubstituted (203–205)	$SOCl_2$/$AlCl_3$	77
			PPSE	67
g	1-CO_2H 5-OMe (X = S)	7-OMe (X = S) (243–247)	$SOCl_2$/$AlCl_3$	65
			PPSE	84
h	6′-CO_2H 5-OMe (X = S)	7-OMe (X = S) (243–247)	TFA/TFAA	95
			PPE	87
			PPSE	83
i	1-CO_2H 3′,5′-F (X = S)	1,3-F (X = S) (200–201)	$SOCl_2$/$AlCl_3$	51
			PPSE	96
j	1-CO_2H 5-OMe (X = O)	7-OMe (X = O) (248–251)	PPA	98
			PPSE	71
k	1-CO_2H 4-OMe (X = O)	6-OMe (X = O) (211–213)	PPA	90
			PPSE	28

[a] X = Se unless specified otherwise. All substrates except entry i are chlorinated at position C-5′. [b] All compounds had acceptable combustion analyses to within ±0.4% of the theoretical values. [c] None of the desired cyclized product was detected by the TLC analysis of the crude reaction mixture.

(2) Hori, M.; Kataoka, T.; Hsü, C.-F. *Chem. Pharm. Bull.* **1974**, *22*, 15. Sindelar, K.; Svatek, E.; Metysova, J.; Metys, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3792.
(3) Imamoto, T.; Matsumoto, T.; Yokoyama, H.; Yokoyama, M.; Yamaguchi, K.-I. *J. Org. Chem.* **1984**, *49*, 1105.
(4) Kakimoto, M.-A.; Imai, Y. *Chem. Lett.* **1984**, 1831.
(5) Gawley, R. E.; Termine, E. J. *J. Org. Chem.* **1984**, *49*, 1946. Imamoto, T.; Yokoyama, H.; Yokoyama, M. *Tetrahedron Lett.* **1981**, *22*, 1803.
(6) Yokoyama, M.; Yoshida, S.; Imamoto, T. *Synthesis* **1982**, 591.
(7) Imamoto, T.; Matsumoto, T.; Kusumoto, T.; Yokoyama, M. *Synthesis* **1983**, 460.
(8) Yamanoto, K.; Watanabe, H. *Chem. Lett.* **1982**, 1225.

According to Scheme I,[9] selenocyanates **3a–d** were prepared by treatment of the corresponding *o*-iodobenzoic acids[10] with freshly prepared NaSeCN in DMA.[11] Reductive coupling with 2,4-dichloronitrobenzene afforded the biarylselenides in excellent yield. Little, if any, of the alternate para isomer was detected. Cyclization of these 2-(phenylseleno)benzoic acids by brief treatment in neat PPSE with excess P_2O_5 at 210 °C proceeded in good yield (Table I).[12] Only in the case of the methylenedioxy compound (entry e) was cyclization with a mixture of TFA/TFAA with catalytic H_3PO_4 found to be superior.

In the sulfur series, PPSE was generally superior to $SOCl_2/AlCl_3$ (entries g–i). In the oxygen series (entries j, k), however, PPA cyclizations were higher yielding.

Since reagents for Friedel–Crafts cyclizations occasionally show substrate specificity, new alternatives are important additions to the chemist's armamentarium. We have found PPSE to be the reagent of choice for the preparation of deactivated 9*H*-selenoxanth-9-ones from their corresponding benzoic acid precursors. Given the convenience of preparation and the effectiveness of PPSE as an aprotic cyclization medium, it may prove to be the reagent of choice when other more routine methods fail.

(9) A full paper including all experimental details is in preparation for *J. Med. Chem.*

(10) The *o*-iodo acids were conveniently prepared from commercially available benzoic acids via ortholithiation and iodination of the corresponding oxazoline according to the work of A. I. Meyers; see for example: *Tetrahedron Lett.* **1980**, *21*, 3335 and references cited therein.

(11) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689.

(12) The addition of excess P_2O_5 to PPSE prepared according to ref 3 improved yields slightly. Changes if any, in the composition and structure of the resulting reagent were not investigated.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. ^1H NMR spectra were measured in $CDCl_3$ or DMSO-d_6 solutions and recorded at 100 MHz on a Bruker WP100SY instrument or at 200 MHz on a Varian XL-200 instrument. IR spectra were recorded on a Nicolet MX-1 FT-IR spectrometer system. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer.

General Procedure for Friedel–Crafts Cyclizations with PPSE. Preparation of 1-Chloro-7-methoxy-4-nitro-9*H*-selenoxanthen-9-one (5d). To a mechanically stirred mixture of 200 g of PPSE syrup[3] and 24 g of P_2O_5 at 210 °C was added 6.0 g of 2-[(5-chloro-2-nitrophenyl)seleno]-5-methoxybenzoic acid. After 20 min, the reaction was poured into an ice-cold solution of 6 N HCl. After the mixture was stirred for 3 h, the orange precipitate was collected and recrystallized from acetonitrile to give 3.58 g (68%) of the selenoxanthenone, mp 222–224 °C. Anal. Calcd for $C_{14}H_8NClSeO_4$: C, 45.62; H, 2.19; N, 3.80; Cl, 9.62. Found: C, 45.34; H, 2.31; N, 3.68; Cl, 9.32.

Registry No. **2a**, 88-67-5; **2b**, 54435-09-5; **2c**, 54413-93-3; **2d**, 123239-80-5; **3a**, 104101-90-8; **3b**, 104101-95-3; **3c**, 104101-92-0; **3d**, 123239-79-2; **4a**, 104101-87-3; **4b**, 123239-71-4; **4c**, 123239-72-5; **4d**, 123239-73-6; **4e**, 123239-74-7; **4f**, 54920-86-4; **4g**, 94636-18-7; **4h**, 94636-20-1; **4i**, 123239-75-8; **4j**, 101709-75-5; **4k**, 123239-76-9; **5a**, 104101-88-4; **5c**, 104101-94-2; **5d**, 104101-91-9; **5e**, 123239-77-0; **5f**, 41215-88-7; **5g**, 94636-19-8; **5i**, 123239-78-1; **5j**, 101709-74-4; **5k**, 101709-79-9.

Additions and Corrections

Vol. 54, 1989

Dieter Cremer,* Thomas Schmidt, Wolfram Sander,* and Peter Bischof. Electronic Structure of Carbonyl Oxides: Semiempirical Calculation of Ground-State Properties and UV–Vis Spectra.

Page 2519, right column. During the printing process Figures 3 and 4 were reversed (the captions are correct). Figure 4 (top right) is a valence spin density distribution for **13** and Figure 3 (bottom right) is a valence charge density distribution for **13**.