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DIMETHYLALUMINUM METHANESELENOLATE—A USEFUL REAGENT FOR THE PREPARATION OF SELENOESTERS. A NEW FRIEDEL–CRAFTS ACYLATION PROCEDURE PROMOTED BY Cu(I)

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Abstract—The preparation of a new aluminum reagent, dimethylaluminum methaneselenolate ($Me_2AlSeMe$) is described. The reactivity of this aluminum reagent toward a variety of organic substrates has been studied. $Me_2AlSeMe$ will convert O-alkyl esters to selenoesters in high yield. These selenoesters function as extremely reactive acyl transfer agents and are converted to acids, esters, and amides on reaction with water, alcohols or amines in the presence of a selenophilic metal cation. The selenoesters will, moreover, acylate reactive arenes and heterocyclic compounds when cuprous triflate is employed as the selenophilic metal cation. This latter transformation constitutes a new transition metal promoted variant of the Friedel–Crafts acylation reaction.

INTRODUCTION

A host of organoaluminum reagents of the general formula R_2AlX have been developed and used to effect important functional group transformations in organic chemistry.[1] While aluminum hydrides have long enjoyed widespread success as mild, selective reducing agents,[2] most other important members of this genre consist of aluminum bonded to a Group IV, V, or VI element.

In the Group IV series, diethylaluminum cyanide stands out as a mild reagent for effecting both the 1,2- and 1,4-addition of HCN to saturated and unsaturated carbonyl compounds, respectively.[3–5] Epoxides can also be opened by diethylaluminum cyanide to afford β-hydroxy nitriles.[6]

In the Group V series, dimethylaluminum amide has been used to convert carboxylic esters to amides and nitriles, the later transformation requiring that two equivalents of the aluminum reagent be employed.[7,8] Dimethylaluminum (trimethylsilyl)methylamide readily reacts with ketones, esters and amides to yield a product in which the carbonyl oxygen has been replaced by nitrogen.[9] Diethylaluminum 2,2,6,6-tetramethylpiperidide has, on the other hand, been found to induce the regiospecific isomerization of epoxides to allylic alcohols under mild conditions.[10]

While dialkylaluminum azides,[11,12] hydrazides,[13] phosphides and arsides[14] have been prepared and characterized, no synthetic uses for these reagents have been reported to date.

Diethylaluminum ethoxide, an easily prepared reagent of the Group VI series, has been used to effect the conversion of lactones to ω-hydroxy esters.[15,16] Additionally, alkoxyaluminum intermediates are involved in the Oppenauer oxidation of alcohols and the related Meerwein–Ponndorf–Verley reduction of ketones.[17] Diorganoaluminum peroxides have also been prepared and characterized.[18]

Among the Group VI elements, the aluminum–sulfur reagents have found the most extensive utilization in organic synthesis. Hirabayashi *et al.* first utilized diethylaluminum ethanethiolate in lactone bond fission and insertion reactions.[19] More recently, Hatch and Weinreb prepared dimethylaluminum 2-methyl-2-propanethiolate from trimethylaluminum and t-butyl mercaptan and showed that it can be used to convert methyl and ethyl esters to their corresponding t-butyl thioesters,[20] useful reagents for macrolactone synthesis.[21]

Corey and Beames have also shown that dimethylaluminum benzylthiolate and dimethylaluminum benzenethiolate readily convert methyl phenylacetate into the corresponding thioesters.[22] Additionally, Corey found that the bis(dimethylaluminum) reagents generated from 1,2-ethanedithiol and 1,3-propanedithiol react with lactones to form 1,3-dithiolane and 1,3-dithiane ortho ester derivatives. These reagents will convert esters which contain an α-hydrogen into a very useful class of intermediates, the ketene thioacetals.[23]

While not strictly a member of the R_2AlX class, it is nonetheless important to mention that a related reagent, tris(phenylthio)aluminum, will convert esters into phenyl thioesters and ketene thioacetals in good yield.[24]

From the foregoing synopsis, it can be seen that aluminum–sulfur reagents have found genuinely important utility in synthesis. It would thus appear that the corresponding aluminum–selenium reagents (and aluminum–tellurium compounds as well) might also possess substantial synthetic utility, especially in view of the immense scope of organic chemistry which has been detailed for selenium.

The driving force in all of the reactions described above is, of course, the exchange of a relatively weak Al—X bond for the stronger Al—O bond. The "hard" aluminum ion forms a strong, tight bond with the "hard" oxygen atom more readily than a "soft", polarizable atom, such as sulfur or selenium. From the standpoint of Pearson's principle of hard and soft acids and bases,[25] one would predict then that aluminum–selenium reagents of the R_2AlSeR' type should exhibit favorable reactivity towards esters.

In the following sections, the preparation of dimethylaluminum methaneselenolate ($Me_2AlSeMe$) and the transformation of O-alkyl esters to their

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corresponding methyl selenoesters with this reagent are described. In addition, several applications of these versatile compounds, the selenoesters, are described wherein soft, selenophilic metal cations are used to trigger their reactions with electron rich species.[26]

RESULTS AND DISCUSSION

Preparation of dimethylaluminum methaneselenolate and reactions with O-alkyl esters

Zakharkin and Gavrilenko had shown previously that the heating of elemental selenium with neat triethylaluminum or triisopropylaluminum leads to insertion of selenium into the carbon–aluminum bond with the formation of $Et_2AlSeEt$ or $(i\text{-}Pr)_2AlSei\text{-}Pr$.[27] These workers did not explore the chemistry of these compounds beyond the analysis of their hydrolysis products and their ability to add one or two additional selenium atoms at higher temperatures.

We thus sought initially to generate an appropriate aluminum–selenium reagent in a form more easily handled than provided by the method of Zakharkin and Gavrilenko. The commercial availability of trialkylaluminum reagents in various organic solvents did, of course, make it possible to avoid the difficulties associated with handling the neat trialkylaluminums. We thus chose to examine the preparation of the selenium reagent from trimethylaluminum in toluene.

This choice was predicated on the basis of the following considerations: (a) any seleno-compounds which might be generated from the aluminum–selenium reagent would give an easily identifiable methyl singlet in their ^{1}H-NMR spectra. The interpretation of the mass spectra of these products would likewise be simplified; (b) the use of toluene would provide a solvent of sufficiently high boiling point to effect insertion of selenium into the carbon–aluminum bond.

Powdered selenium (1.04 equiv, ROC/RIC) was thus dried *in vacuo* with heating for several hours. After cooling to room temperature, 1.00 equiv of trimethylaluminum (17 wt % in toluene, Texas Alkyls) was added via syringe, and the black–gray mixture was heated to reflux under a blanket of argon. Within 2 hr, the reaction mixture had lost its gray color, and had taken on a translucent yellow appearance. The solution was cooled, and the unreacted selenium allowed to precipitate. The clear, yellow solution of dimethylaluminum methaneselenolate was transferred to a dry, septum-capped argon-filled Erlenmeyer flask by a double-tipped stainless steel cannula.[28] The reagent was found to retain its activity for approximately one month when stored in this manner at room temperature. When the solution was kept in the freezer or stored for prolonged periods at room temperature, an uncharacterized white precipitate formed, and the apparent titre decreased.

$$(CH_3)_3Al + Se(s) \xrightarrow[\text{toluene}]{\Delta} (CH_3)_2AlSeCH_3$$
1

To test this new reagent, freshly distilled methyl heptanoate was dissolved in dry, argon degassed dichloromethane. The solution was cooled to 0°, and 1.1 equiv of **1** was added in one portion by syringe. After stirring for 30 min at 0°, the ice bath was removed and the yellow solution warmed to room temperature over 30 min. TLC analysis of the reaction solution showed complete disappearance of starting material. The reaction was quenched with a portion of moist sodium sulfate, the crude product was extracted with ethyl ether, and the extracts were dried with anhydrous magnesium sulfate. The ethereal extract was concentrated by rotary evaporation to afford Se-methyl heptaneselenolate (**2**) in quantitative yield. The dark yellow oil was purified by bulb-to-bulb distillation to furnish pure **2** in 95% yield. A number of other exemplary selenoesters prepared from **1** are depicted in Table 1.

$$CH_3(CH_2)_5CO_2CH_3 \xrightarrow[CH_2Cl_2]{1} CH_3(CH_2)_5COSeCH_3$$
2

Both methyl and ethyl esters were found to react with equal facility. The t-butyl ester of octanoic acid, however, proved resistant to the standard conditions. It was converted to its selenoester only in low yield after refluxing in dichloromethane with 2 equiv of **1**. While δ-valerolactone was converted cleanly to the hydroxyselenoester (**12**) in 78% yield, γ-butyrolactone was recovered unchanged, even after refluxing the reaction mixture for prolonged periods. In contrast, *trans*-2-hydroxycyclohexaneacetic acid γ-lactone provided hydroxyselenoester **13** in 80% yield. Compound **13** was observed to undergo reclosure to lactone at the temperature required for bulb-to-bulb distillation at aspirator pressure (118°, 23 mm Hg).[29] The ethylene ketal protected derivative of methyl levulinate provided selenoester **14** in 94% yield without concomitant opening of the ketal.

When several non-ester substrates were treated with dimethylaluminum methaneselenolate, some very interesting observations were made. Cyclohexene oxide underwent epoxide opening to afford selenide **17** in 96% yield. In fact, epoxide opening occurs in preference to selenoester formation (see **15** and **16**), as was demonstrated with ethyl 2,3-epoxybutyrate.

While both the amide group and the isolated double bond of N-methyl-3-cyclohexenyl carboxamide were unreactive towards **1**, 2-cyclohexenone underwent 1,4-conjugate addition to furnish **18** in 87% yield. Ethyl 2-butenoate afforded an inseparable mixture of 1,2-, 1,4- and other uncharacterized addition products when treated with **1**. These results thus set some limits on the use of dimethylaluminum methaneselenolate in reactions with polyfunctional molecules.

Other methods of selenoester preparation

Prior to the development of the above methodology, selenoesters were produced almost solely by the reaction of selenols or metal selenolates (Na, Mg, Pb, Cd, etc.) with acid chlorides.[30,31] The reaction of selenocarboxylates with alkyl or aralkyl halides was reported in 1972 and this represents a second general method for their formation.[30,32]

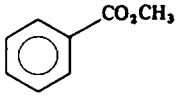
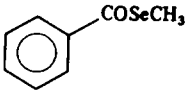
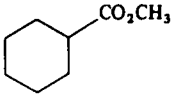
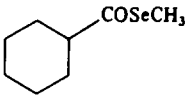
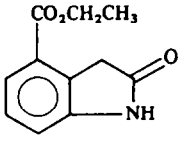
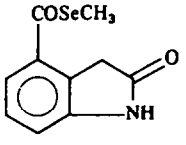
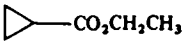
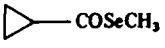
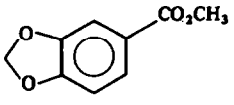
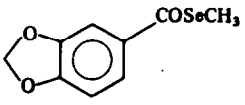
$$RCOCl + R'SeX \xrightarrow{\text{pyridine}} RCOSeR' + XCl$$

$X = H$ or M^{+n}

$$RCOSe^{\ominus} + R'X \rightarrow RCOSeR'$$

Due to the usefulness of selenoesters as active acyl transfer agents in, for example, macrolactone synthesis,

Table 1.

Starting material	Product and spectral data IR (C=O)[b] cm^{-1} NMR δ MS: m/e[d]	Isolated yield (%)[a]	Kugelrohr oven temperature (pressure) R_f = (solvent)[c]
		99	112° (33 Torr)
	3		
IR (film) 1666 cm^{-1} NMR (CCl_4, 60 MHz) δ 2.34 (s, 3H), 7.14–8.08 (m, 5H) MS m/e 202, 200, 198, 197, 196 (M^+), 105 (base peak)			R_f = 0.39 (A)
		93	90–92° (29 Torr)
	4		
IR (film) 1692 cm^{-1} NMR (CCl_4, 60 MHz) δ 0.92–2.85 (br m, 11H), 2.15 (s, 3H) MS m/e 208, 206, 204, 203, 202 (M^+), 160 (base peak)			R_f = 0.53 (A)
		80	—[e]
	5		
IR (KBr) 1694, 1653 cm^{-1} NMR ($CDCl_3$, 60 MHz) δ 2.36 (s, 2H), 2.73 (s, 3H), 3.66 (br s, 1H), 6.93–7.80 (br m, 3H) MS m/e 257, 255, 253, 252, 251 (M^+), 160 (base peak)			R_f = 0.59 (D)
		96	53° (27 Torr)
	6		
IR (film) 1686 cm^{-1} NMR (CCl_4, 60 MHz) δ 0.68–1.43 (m, 4H), 1.87–2.33 (m, 1H), 2.20 (s, 3H) MS m/e 166, 164, 162, 161, 160 (M^+), 69 (base peak)			R_f = 0.43 (A)
$CH_3CH_2O_2C(CH_2)_5CO_2CH_2CH_3$	$CH_3SeCO(CH_2)_5COSeCH_3$	95	105° (1.75 Torr)
	7		
IR (film) 1724, 1704 cm^{-1} NMR (CCl_4, 60 MHz) δ 1.12–1.97 (br m, 6H), 2.18 (s, 6H), 2.58 (t, J = 7 Hz, 4H) MS m/e 223, 221, 219, 218, 217, 125 ($M^+ - SeCH_3$), 69 (base peak)			R_f = 0.51 (B)
		quant	150° (27 Torr)
	8		
IR (CCl_4) 1681 cm^{-1} NMR (CCl_4, 60 MHz) δ 2.28 (s, 3H), 5.96 (s, 2H), 6.72 (d, J = 8 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 7.39 (dd, J = 8, 2 Hz, 1H) MS m/e 246, 244, 242, 241, 240 (M^+), 148 (base peak)			R_f = 0.48 (C)

(*continued*)

Table 1—*continued*

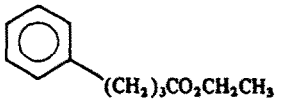
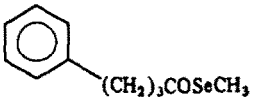
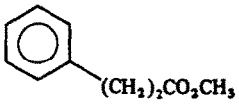
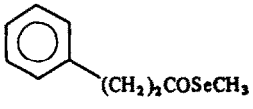
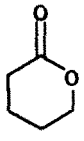
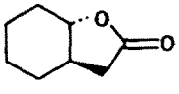
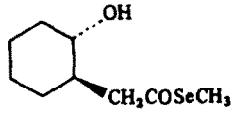
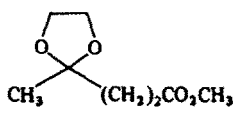
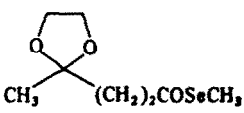
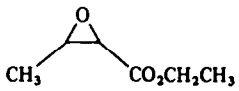
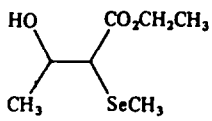
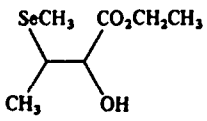
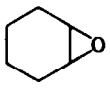
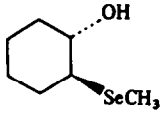
Starting material	Product and spectral data IR (C=O)[b] cm^{-1} NMR δ MS: m/e[d]	Isolated yield (%)[a]	Kugelrohr oven temperature (pressure) R_f = (solvent)[c]
		70	—[t]
	9		
IR (film) 1709 cm^{-1} NMR (CCl_4, 60 MHz) δ 1.62–2.28 (m, 2H), 2.17 (s, 3H), 2.36–2.95 (m, 4H), 7.11 (s, 5H) MS m/e 147 ($M^+ - SeCH_3$), 91 (base peak)			R_f = 0.40 (A)
		62	115° (34 Torr)
	10		
IR (film) 1703 cm^{-1} NMR (CCl_4, 60 MHz) δ 2.18 (t, J = 6 Hz, 2H), 2.20 (s, 3H), 2.78 (t, J = 6 Hz, 2H), 7.00–7.33 (m, 5H) MS m/e 230, 228, 226, 225, 224 (M^+), 133 (base peak)			R_f = 0.54 (C)
$CH_2{=}CH(CH_2)_2CO_2CH_3$	$CH_2{=}CH(CH_2)_2COSeCH_3$	84	86° (29 Torr)
	11		
IR (film) 1704 cm^{-1} NMR (CCl_4, 60 MHz) δ 2.02–2.90 (m, 4H), 2.19 (s, 3H), 4.77–5.27 (m, 2H), 5.43–6.17 (m, 1H) MS m/e 166, 164, 162, 161, 160 (M^+), 54 (base peak)			
	$HO(CH_2)_4COSeCH_3$	78	113° (25 Torr)
	12		
IR (film) 1727 cm^{-1} NMR (CCl_4, 60 MHz) δ 1.03–2.90 (m, 4H), 2.20 (s, 3H), 3.53 (t, J = 6 Hz, 2H), 3.92 (br s, 1H), 4.22 (t, J = 6 Hz, 2H) MS m/e 101 ($M^+ - SeCH_3$), 100, 70, 56, 55, 42 (base peak), 41, 29, 28, 27			R_f = 0.35 (D)
		80	67° (0.20 Torr)
	13		
IR (CCl_4) 1705 NMR (CCl_4, 250 MHz) δ 1.19–2.25 (br m, 11H), 2.18 (s, 3H), 3.02–3.12 (m, 1H), 3.67 (dt, J = 10.42, 3.62 Hz, 1H) MS m/e 142, 141 ($M^+ - SeCH_3$), 140 ($M^+ - HSeCH_3$), 68 (base peak)			R_f = 0.50 (D)
		94	95° (32 Torr)
	14		
IR (CCl_4) 1710 cm^{-1} NMR (CCl_4, 60 MHz) δ 1.25 (s, 3H), 1.92 (t, J = 7 Hz, 2H), 2.15 (s, 3H), 2.63 (t, J = 7 Hz, 2H) MS m/e 225, 223, 221, 220, 219 (M^+), 82 (base peak)			R_f = 0.58 (C)

Table 1—*continued*

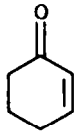
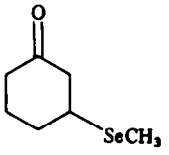
Starting material	Product and spectral data IR (C=O)[b] cm^{-1} NMR δ MS: *m/e*[d]	Isolated yield (%)[a]	Kugelrohr oven temperature (pressure) R_f = (solvent)[c]
	 **15**	92[a] **15:16** = 3:1	63° (25 Torr)
	 **16**		R_f = 0.18 (C) **15** R_f = 0.27 (C) **16**

15: IR (CCl_4) 3650–3350, 2995, 2945, 2920, 1720, 1450, 1378, 1305, 1185, 1140 cm^{-1}
NMR (CCl_4, 60 MHz) δ 1.28 (t, J = 7 Hz, 3H), 1.38 (d, J = 6 Hz, 3H), 2.03 (s, 3H), 3.07 (d, J = 9 Hz, 1H), 3.08 (br s, 1H), 3.62–4.30 (br m, 1H), 4.16 (q, J = 7 Hz, 2H)
MS *m/e* 228, 226, 224, 223, 222 (M^+), 69 (base peak)

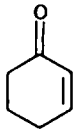
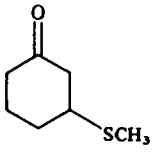
16: IR (CCl_4) 3550, 2995, 2945, 2880, 1740, 1452, 1385, 1260, 1230, 1135 cm^{-1}
NMR (CCl_4, 60 MHz) δ 1.33 (t, J = 7 Hz, 3H), 1.38 (d, J = 6 Hz, 3H), 2.03 (s, 3H), 2.82 (d, J = 6 Hz, 1H), 2.90–3.33 (m, 1H), 4.20 (s, 1H), 4.22 (q, J = 7 Hz, 2H)
MS *m/e* 228, 226, 224, 223, 222 (M^+) 69, 52 (base peak)

	 **17**	96	102° (25 Torr)

IR (film) 3463–3240, 2864, 2800, 1447, 1274, 1075, 1019, 955 cm^{-1} R_f = 0.20 (B)
NMR (CCl_4, 250 MHz) δ 1.12–2.28 (m, 8H), 1.94 (s, 3H), 2.49 (dt, J = 10.27, 3.89 Hz, 1H), 2.68 (br s, 1H), 3.20–3.32 (m, 1H)
MS *m/e* 216, 214, 212, 211, 210 (M^+), 82 (base peak)

	 **18**	87	104° (25 Torr)

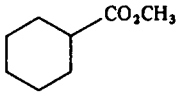
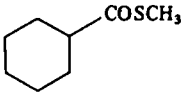
IR (film) 2895, 2837, 1705, 1439, 1027, 967 cm^{-1} R_f = 0.64 (D)
NMR (CCl_4, 250 MHz) δ 1.60–1.88 (m, 2H), 1.99 (s, 3H), 2.04–2.32 (m, 4H), 2.41 (dd, J = 13.12, 10.62 Hz, 1H), 2.67 (dd, J = 13.12, 3.75 Hz, 1H), 3.10 (m, 1H)
MS *m/e* 194, 192, 190, 189, 188 (M^+), 97 (base peak)

	 **19**	72[h]	90° (24 Torr)

IR (film) 2940, 2925, 2900, 2875, 1710, 1450, 1425, 1345, 1315, 1290, 1225 cm^{-1}
NMR (CCl_4, 60 MHz) δ 1.20–3.20 (m, 9H), 2.10 (s, 3H)
MS *m/e* 144 (M^+), 97, 96, 69, 55, 41 (base peak)

(*continued*)

Table 1—*continued*

Starting material	Product and spectral data IR (C=O)[b] cm^{-1} NMR δ MS: m/e[d]	Isolated yield (%)[a]	Kugelrohr oven temperature (pressure) R_f = (solvent)[c]
	 **20**	92[h]	84° (20 Torr)
	IR (film) 1685 cm^{-1} NMR (CCl_4, 60 MHz) δ 0.87–2.70 (m, 11H), 2.23 (s, 3H) MS m/e 158 (M^+), 143, 111, 83 (base peak), 55		R_f = 0.45 (A)

[a] All products were purified by bulb-to-bulb distillation except compounds **5** and **13**.
[b] Only the frequency of the seleno- or thioester carbonyl is given, except in cases of epoxide opening or 1,4-conjugate addition.
[c] The TLC solvent systems used consisted of the following mixtures of hexane and ethyl acetate: A, 9:1; B, 4:1; C, 3:1; D, 1:1.
[d] All mass spectra were taken at 70 eV. For selenium containing compounds, the M^+ is given for the five most abundant isotopes, ^{82}Se, ^{80}Se, ^{78}Se, ^{77}Se, ^{76}Se.
[e] The product is a crystalline solid, m.p. 203–205° (methanol).
[f] The product was isolated by chromatography on 150 g of Florisil, 19:1 hexane–ethyl acetate as eluent.
[g] The combined yield of the two isomers, with relative ratios as determined by NMR integration and chromatography.
[h] Product prepared with the analogous sulfur reagent $(CH_3)_2AlSCH_3$, produced and used in the same manner as **1**.

other workers have also devoted some effort toward the development of new and mild methods for their preparation. Gais has reported that carboxylic imidazolides and 1,2,4-triazolides react with selenols at or below room temperature to afford selenoesters under almost neutral conditions.[33] Additionally, the enol esters which are formed by treatment of a carboxylic acid with 4-dimethylamino-3-butyn-2-one react with the Li, Na or K salt of phenylselenol to afford the corresponding selenoester in good yield.[34]

Lastly, Back *et al.* reported that diverse selenolesters can be prepared in high yield by the oxidation of N-acylhydrazides with benzeneseleninic acid in the presence of triphenylphosphine.[36]

$$RCONHNH_2 + PhSeO_2H \xrightarrow{Ph_3P} RCOSePh$$

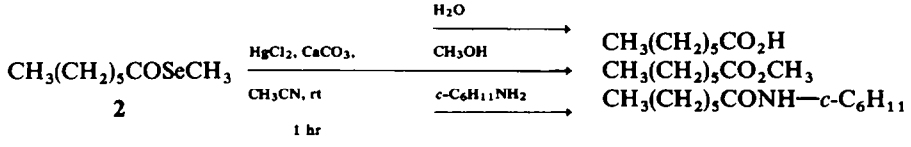
Activity of methylselenoesters as acyl transfer agents

Acyl–heteroatom bond formation. The ability of selenoesters to perform as active acyl transfer agents

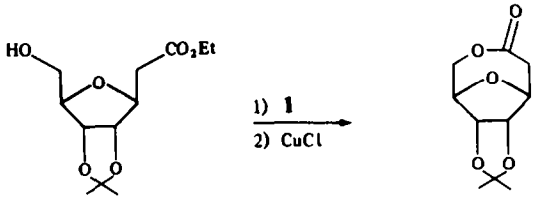
Grieco *et al.* found that a carboxylic acid will react with an aryl selenocyanate in the presence of tributylphosphine to yield a selenoester in fair to good yield.[35]

$$RCO_2H + ArSeCN \xrightarrow{n\text{-}Bu_3P} RCOSeAr$$

was readily demonstrated by the facile hydrolysis, methanolysis and aminolysis of **2**. Simply stirring selenoester **2** with water, methanol or cyclohexylamine in a mixture of mercuric chloride–calcium carbonate–acetonitrile afforded the corresponding acid, ester or amide in high yield.

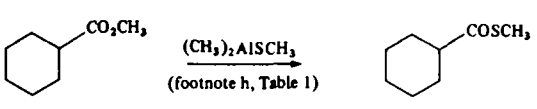


This facile acyl–selenium bond cleavage was found to be promoted by Cu(I) and Cu(II) salts as well. The isopropylidine derivative of ribofuranosylacetate **21** was converted to its selenol ester in good yield using an excess of **1**. On treating this compound with either cuprous or mercuric chloride, the (Gensler) lactone **22** was formed, a product of some use for the synthesis of various C-nucleoside antibiotics.[37–39]



21 **22**

It was anticipated that selenoesters would be more reactive than thioesters as a consequence of the weak carbon–selenium bond. To compare the reactivity of selenoesters to that of thioesters, the methyl seleno-ester of cyclohexanecarboxylic acid was prepared. Methanolysis of **4** under the same conditions as used for **2** (*vide supra*) was complete within 15 min at room temperature. In contrast, Masamune *et al.* reported that methanolysis of the S-t-butyl thioester of cyclohexanecarboxylic acid required refluxing in acetonitrile for 3 hr in the presence of $HgCl_2$–$CdCO_3$–CH_3OH. To determine what effect the alkyl substituent bonded to the Group VIA atom had on the rate of the methanolysis, the methyl thioester **23** was prepared from methyl cyclohexanecarboxylate and dimethyl-aluminum methanethiolate. Treatment of **23** under identical conditions as employed for **4** furnished only 20% of the O-methyl ester after 24 hr at room temperature as ascertained from NMR integrations.



23

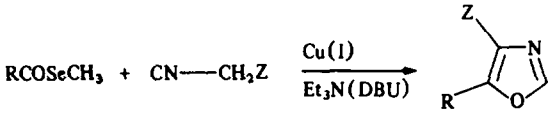
This observation is in complete accord with the results of an aminolysis rate study reported by Mautner *et al.*[40] It was found that N,Se-dibenzoylselenocysteamine reacted with n-butylamine more than 100 times faster than the corresponding thioacyl analog. Mautner *et al.* postulated that the large differences in reactivity and entropies of activation of seleno- and thioacyl compounds were related to the greater propensity of selenium to serve as a leaving group from the tetrahedral transition state intermediate.

Carbon–carbon bond forming reactions. Thioesters of coenzyme A are important in biological systems as intermediates in carboxylic acid metabolism. They act as active acyl transfer agents keying, for example, the important carbon–carbon bond forming reaction found in the synthesis of acetoacetyl CoA.[41]

$$CH_3COSCoA + HO_2CCH_2COSCoA \rightarrow CH_3COCH_2COSCoA + CoA$$

In view of the important biological functions of thioesters, and the readily demonstrated reactivity of selenoesters, it was thus reasoned that the latter compounds might also prove useful in carbon–carbon bond forming processes.

This study was originally initiated in order to achieve a new synthesis of 2-unsubstituted oxazoles. It was anticipated that selenoesters, in the presence of a soft, selenophilic metal cation, could replace acid chlorides in reactions with activated isonitriles to form these heterocycles.[42] The metal cation would promote displacement of the methylselenyl group by the weakly nucleophilic anion of the activated isonitrile **24** to afford a β-ketoisonitrile which would then cyclize to the 4,5-disubstituted oxazole **25**. The process might thus serve as a useful variant of the standard Schöllkopf oxazole synthesis.



24a; Z = $CO_2CH_2CH_3$ **25a**; R = n-$(CH_2)_5CH_3$; Z = $CO_2CH_2CH_3$
24b; Z = Tos **25b**; R = n-$(CH_2)_5CH_3$; Z = Tos

This prediction was borne out, as was demonstrated with Se-methyl heptaneselenoate (**2**). Selenoester **2** was added to a mixture of 1.5 equiv each of dry triethylamine (or 1,5-diazabicyclo[5.4.0]undec-7-ene), cuprous oxide, and ethyl isocyanoacetate (**24a**) in dry tetrahydrofuran. After stirring for 12 hr at room temperature, 4-carboethoxy-5-n-hexyloxazole (**25a**) was isolated in 85% yield after chromatography. Other oxazoles prepared in this manner as well as their physical and spectral properties are listed in Table 2.

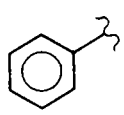
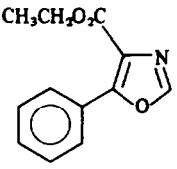
The results of the foregoing experiments demonstrated that selenoesters could indeed behave like acid chlorides. With these facts in mind, an intriguing idea emerged. Could selenoesters serve as latent oxocarbenium ions, their formation being triggered by the use of a soft, selenophilic metal cation? This notion suggested that selenoesters might participate in other processes, such as the Friedel–Crafts acylation of aromatic compounds. It was envisioned that a system could be devised in which acylation would proceed under relatively mild to neutral conditions by the use of metal salts not possessing the high Lewis acidity characteristic of the main group elements.

$$RCOSe—CH_3 \xrightarrow{M^{+n}} [R—C{\equiv}O]^+ + CH_3SeM^{+(n-1)}$$

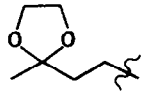
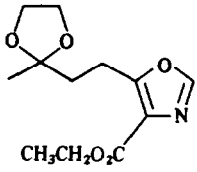
While the earlier studies had shown that Hg(II) and Cu(I and II) salts were effective in the hydrolysis, alcoholysis, and aminolysis of selenoesters, these salts failed to promote acylation of the electron rich aromatic anisole with selenoester **2** in either benzene or tetrahydrofuran as solvent.

Attempts to use partially organic-solvent-soluble salts, such as mercuric and cuprous trifluoracetates, were also unsuccessful. No traces of the desired acylation products could be detected; only the corresponding acid from partial hydrolysis of the selenoester was observed. Similar negative results were obtained when heterogeneous reaction mixtures of

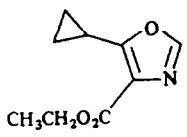
Table 2.

Selenol ester (R)	Isocyanide (Z)	Base	Reaction time (hr)	Product and spectral data IR: cm^{-1} NMR: δ MS: *m/e* High resolution MS	% Yield[a] R_f (solvent system)[b]
 **3**	$CO_2CH_2CH_3$ **24a**	$(CH_3CH_2)_3N$	14	 **26**	60

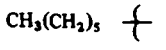
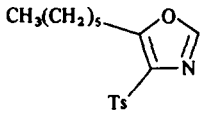
IR (film) 3112, 2997, 1727, 1617, 1589, 1527, 1497, 1380, 1232, 1097, 702, 654 cm^{-1} $R_f = 0.26$ (A)
NMR (CCl_4, 60 MHz) δ 1.40 (t, J = 7 Hz, 3H), 4.48 (q, J = 7 Hz, 2H), 7.33–8.33 (*m*, 5H), 7.90 (*s*, 1H)
MS *m/e* 217 (M^+), 216 (base peak), 172, 145, 144, 105, 77, 43, 41, 29
m/e calc for $C_{12}H_{11}NO_3$: 217.0739 (parent); found: 217.0740

 **14**	$CO_2CH_2CH_3$ **24a**	$(CH_3CH_2)_3N$	11	 **27**	92

IR (film) 3137, 3000, 2910, 1724, 1609, 1529, 1454, 1384, 1270, 1190, 1064 cm^{-1} $R_f = 0.26$ (B)
NMR (CCl_4, 60 MHz) δ 1.37 (s, 3H), 1.40 (t, J = 7 Hz, 3H), 2.07 (m, 2H), 3.16 (m, 2H), 3.97 (s, 4H), 4.38 (q, J = 7 Hz, 2H), 7.76 (s, 1H)
MS *m/e* 255 (M^+), 240, 194, 143, 122, 88 (base peak), 43
m/e calc for $C_{12}H_{15}NO_5$: 255.1107 (parent); found: 255.1103

 **6**	$CO_2CH_2CH_3$ **24a**	$(CH_3CH_2)_3N$	6	 **28**	61

IR (film) 3125, 2960, 2930, 2900, 2870, 1709, 1530, 1410, 1385, 1295, 1260, 1150, 1085 1045 cm^{-1} $R_f = 0.25$ (A)
NMR (CCl_4, 60 MHz) δ 0.67–1.67 (m, 4H), 1.40 (t, J = 7 Hz, 3H), 2.37–3.02 (m, 1H), 4.38 (q, J = 7.0 Hz, 2H), 7.60 (s, 1H)
MS *m/e* 181 (M^+), 135 (base peak), 107, 80, 79, 69, 54, 43, 40, 30, 28
m/e calc for $C_9H_{11}NO_3$: 181.0739 (parent); found: 181.0734

 **2**	Ts **24b**	DBU	20	 **25b**	40

IR (film) 3130, 2960, 2930, 2858, 1590, 1587, 1518, 1467, 1458, 1328, 1302, 1292, 1242, 1141, 1120, 1082, 812, 712 cm^{-1} $R_f = 0.25$ (A)
NMR (CCl_4, 90 MHz) δ 0.70–2.00 (m, 11H), 2.37 (s, 3H), 3.01 (t, J = 7 Hz, 2H), 7.52 (ABq, J = 8 Hz, $\Delta\nu$ = 50 Hz, 4H), 7.57 (s, 1H)
MS *m/e* 307 (M^+), 250, 237 (base peak), 152, 151, 139, 107, 100, 98, 92, 83, 68, 66, 54, 52, 29, 28
m/e calc for $C_{16}H_{21}NO_3S$: 307.1242 (parent); found: 307.1242

[a] Isolated yield of products, chromatographed on Florisil.
[b] TLC solvent systems used: A, 3:1 hexane–ethyl acetate; B, 4:1 hexane–ethyl acetate.
[c] All mass spectra taken at 70 eV.

mercuric chloride, silver nitrate, cuprous chloride and cuprous oxide were examined.

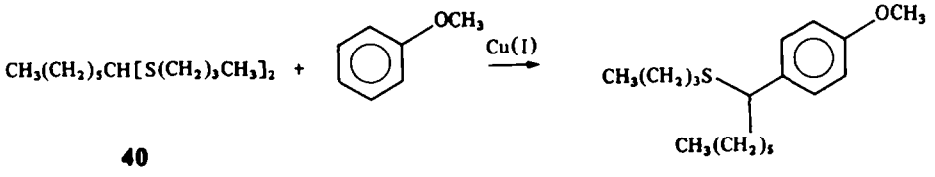
In contrast, the highly reactive, crystalline copper(I) triflate–benzene complex ($[(CF_3SO_3Cu)_2PhH]$, **29**), was found to readily promote the desired transformation. This oxygen and moisture sensitive complex, first described by Saloman and Kochi, is easily prepared from anhydrous cuprous oxide and trifluoromethanesulfonic acid anhydride in refluxing benzene.[43] The reaction of anisole and **2** in the presence of 1.2 equiv of **29** was complete within minutes at room temperature in benzene as solvent. The pure product **30** was isolated by bulb-to-bulb distillation at reduced pressure in 81% yield, and was found to consist of only the *para* isomer within the limits of ^{1}H-NMR detection. Table 3 displays the results of a number of other acylation experiments carried out in the same manner.

Toluene apparently represents the lower limit of arene reactivity, for it was acylated in only low yield by this method. Arenes possessing electron withdrawing groups (e.g. methyl benzoate, chlorobenzene, etc.) and benzene itself failed to give any detectable amounts of acylation products.

An intramolecular version of this process is exemplified by selenoester **9**, which cyclized to furnish 1-tetralone in good yield. An attempt to prepare 1-indanone in an analogous fashion proved fruitless. A variety of heterocyclic compounds such as furan, thiophene, pyrrole, and N-methylindole underwent acylation in good to excellent yield under the standard conditions.

A by-product of this acylation process is trifluoromethanesulfonic acid, a substance which could conceivably have deleterious effects upon acid labile substrates. Therefore, a means of removing this very strong acid from the reaction medium was sought. Although a number of amine bases were examined (proton sponge, diisopropylethylamine,[44] 2,6-lutidine,[45] 1,1,3,3-tetramethylurea,[46] and 2,6-di-t-butyl-4-methylpyridine[47]), all were found to block the activity of the copper reagent, presumably through preferential σ- or π-complexation to the copper reagent. Only with calcium carbonate present was acylation of anisole still found to occur. The presence of triflic acid does not appear, however, to be a major drawback, for the acid-labile substrate furan was acylated in nearly quantitative yield, as noted previously.

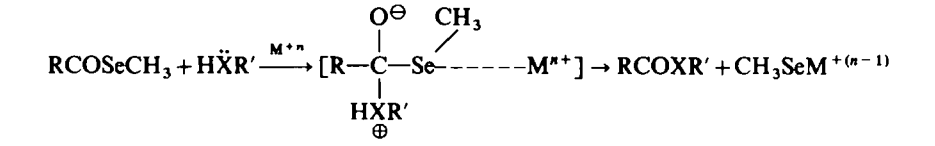
One might also anticipate from the aforementioned experiments, and the results of Mukaiyama *et al.*'s studies on bivalent sulfur compounds, that sulfur stabilized carbenium ions could participate in the analogous Friedel–Crafts alkylation of aromatics.[45,48] Cuprous triflate had been shown earlier by Cohen to be a highly effective reagent for the generation of sulfur-stabilized carbenium ions from thioacetals and thioketals. This idea was tested in only one instance with the bis(n-butylthio)acetal of n-heptanal (**40**). A mixture of anisole and cuprous triflate was treated with **40** under conditions similar to those described for the acylation reaction. The alkylation product **41** was isolated in 80% yield.



40 **41**

Mechanistic considerations of the reactions of selenoesters

In the initial experiments described for selenoesters with mercury and copper salts, no determined effort was made to discover any intermediates in the hydrolysis, methanolysis, or aminolysis reactions. It was conjectured that the reaction may proceed through a normal tetrahedral-type intermediate, with the metal ion coordinating to the departing selenolate. Alternatively, the formation of the aforementioned oxocarbenium ion could also be postulated. The possibility of a ketene-type intermediate was considered; however, the observation that methanolysis of the methyl selenoester of benzoic acid took place rapidly under the standard conditions weakened this idea.

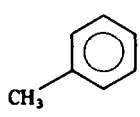
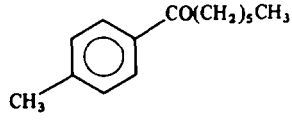


Cuprous oxide may play a double role in the synthesis of 2-unsubstituted oxazoles from selenoesters and activated isocyanides. Besides functioning as an efficient scavenger for the selenium moiety in this reaction, Cu(I) and Cu(II) salts readily form reactive complexes with isocyanides.[49] Saegusa *et al.* have utilized the catalytic activity of copper–isocyanide complexes in such versatile reactions as the dimerization of α,β-unsaturated carbonyl and nitrile compounds,[50] and in Michael addition reactions.[49] They also reported that isocyanides possessing an acidic α-hydrogen undergo novel and useful cycloadditions with α,β-unsaturated nitriles and carbonyl compounds to furnish Δ^1-pyrrolines and Δ^2-oxazolines, respectively. The intermediacy of a copper–isocyanide complex in these reactions was supported by the observation that optically active α-phenylethyl isocyanide was readily racemized at room temperature in the presence of cuprous oxide.[49]

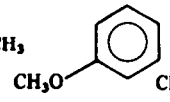
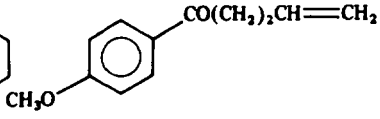
When Se-methyl heptaneselenoate was reacted with isocyanide **24a** in the absence of cuprous oxide, nearly three days were required for complete disappearance of the starting selenoester. The presence of oxazole **25a** was detected by TLC analysis and by the ^{1}H-NMR spectrum of the crude product. An attempt to isolate this oxazole and the other more polar by-products was, however, unsuccessful.

With regard to the Friedel–Crafts chemistry, two possible reaction mechanisms were considered: (a) formation of an oxocarbenium type species **43** via Cu(I) promoted departure of the selenium group, and (b) the

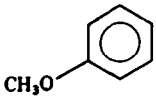
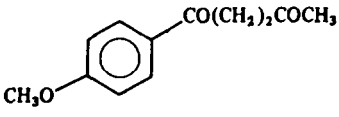
Table 3.

Selenoester	Aromatic compound	Product and spectral data IR: [b] cm^{-1} NMR: δ MS: [d] m/e High resolution MS	Reaction time (min) Kugelrohr oven temperature (pressure)	Isolated yield (%) R_f = (solvent)[c]
$CH_3(CH_2)_5COSeCH_3$		 **31**	150 90° (0.30 Torr)	23[e] 83:17 *para–ortho*

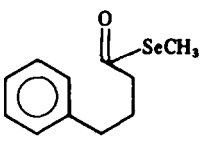
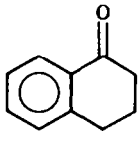
IR (film) 1680, 1685 cm^{-1} R_f = 0.35 (A)
NMR (CCl_4, 60 MHz) δ 0.60–2.00 (m, 11H), 2.39 (s, 3H), 2.83 (t, J = 7 Hz, 2H), 7.45 (ABq, J = 7 Hz, $\Delta\nu$ = 36 Hz, 4H)
MS *m/e* 204 (M^+), 189, 134, 119 (base peak), 113, 91, 65, 44, 42, 29
m/e calc for $C_{14}H_{20}O$: 204.1514 (parent); found: 204.1517

$CH_2{=}CH(CH_2)_2COSeCH_3$		 **32**	30 90° (0.30 Torr)	63

IR (film) 1676 cm^{-1} R_f = 0.18 (A)
NMR (CCl_4, 90 MHz) δ 2.20–2.53 (m, 2H), 2.81 (d, J = 7.5 Hz, 1H), 2.88 (dd, J = 8.5, 1.5 Hz, 1H), 3.78 (s, 3H), 4.27–5.29 (m, 2H), 5.53–6.00 (m, 1H), 7.25 (ABq, J = 8.5 Hz, $\Delta\nu$ = 100.6 Hz, 4H)
MS *m/e* 190 (M^+), 135 (base peak), 107, 100, 92, 84, 78, 56, 42, 40, 29, 27
m/e calc for $C_{12}H_{14}O_2$: 190.0994 (parent); found: 190.0993

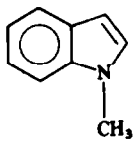
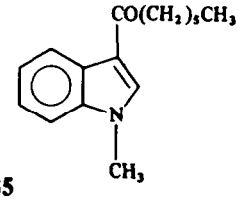
$CH_3CO(CH_2)_2COSeCH_3$		 **33**	3 102° (0.80 Torr)	60[g] 2:1 *para–ortho*

IR (film) 1770, 1730, 1714 cm^{-1} R_f = 0.18 (B)
NMR (CCl_4, 60 MHz) δ 1.67 and 1.72 (two s's, 3H), 2.32–2.67 (m, 4H), 3.78 and 3.87 (two s's, 3H), 6.99 and 6.67–7.55 (Abq, J = 9 Hz, $\Delta\nu$ = 25.5 Hz, and m, 4H)
MS *m/e* 206 (M^+), 191 (base peak), 163, 151, 135, 99, 92, 78, 33
m/e calc for $C_{12}H_{14}O_3$: 206.0934 (parent); found: 206.0939

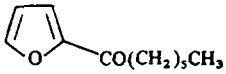
		 **34**	5 68° (0.15 Torr)	70

IR (film) 1680 cm^{-1}
NMR (CCl_4, 60 MHz)[g] 1.77–3.10 (m, 6H), 6.93–8.00 (m, 5H) R_f = 0.43 (B)

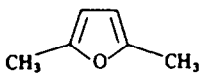
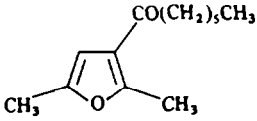
Table 3—*continued*

Selenoester	Aromatic compound	Product and spectral data IR: [b] cm^{-1} NMR: δ MS: [d] *m/e* High resolution MS	Reaction time (min) Kugelrohr oven temperature (pressure)	Isolated yield (%) R_f = (solvent)[c]
$CH_3(CH_2)_5COSeCH_3$		 **35**	25 125° (0.40 Torr)	85

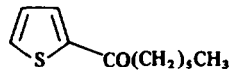
IR (CCl_4) 1650 cm^{-1} R_f = 0.28 (B)
NMR (CCl_4, 60 MHz) δ 0.53–2.00 (br m, 11H), 2.63 (t, J = 7 Hz, 2H), 3.71 (s, 3H), 7.00–7.37 (m, 3H), 7.44 (s, 1H), 8.17–8.47 (m, 1H)
MS *m/e* 243 (M^+), 131 (base peak), 87, 73, 71, 70, 60
m/e calc for $C_{16}H_{21}NO$: 243.1623 (parent); found: 243.1625

$CH_3(CH_2)_5COSeCH_3$		 **36**	15 113° (28 Torr)	quant

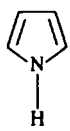
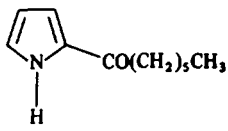
IR (film) 1680 cm^{-1} R_f = 0.26 (A)
NMR (CCl_4, 60 MHz) δ 0.30–2.00 (m, 11H), 2.77 (t, J = 7 Hz, 2H), 6.52 (dd, J = 4, 2 Hz, 1H), 7.13 (d, J = 4 Hz, 1H), 7.55 (d, J = 2 Hz, 1H)
MS *m/e* 180 (M^+), 123, 110 (base peak), 95, 43, 41, 39, 29, 27
m/e calc for $C_{11}H_{16}O_2$: 180.1150 (parent); found: 180.1162

$CH_3(CH_2)_5COSeCH_3$		 **37**	10 85° (27 Torr)	91

IR (film) 1677 cm^{-1} R_f = 0.35 (A)
NMR (CCl_4, 60 MHz) δ 0.63–1.87 (br m, 11H), 2.23 (s, 3H), 2.50 (s, 3H), 2.53 (t, J = 7 Hz, 2H), 6.07 (s, 1H)
MS *m/e* 208 (M^+), 151, 138, 123, 109, 95, 81, 67, 43 (base peak), 29, 27
m/e calc for $C_{13}H_{20}O_2$: 208.1463 (parent); found: 208.1455

$CH_3(CH_2)_2COSeCH_3$		 **38**	20 80° (0.10 Torr)	81

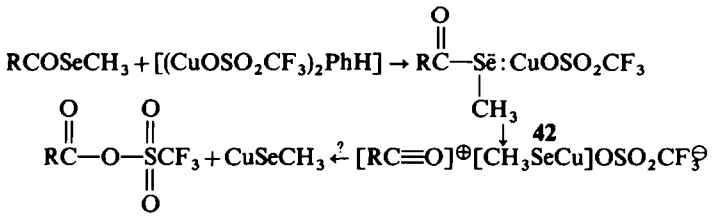
IR (film) 1678 cm^{-1} R_f = 0.35 (A)
NMR (CCl_4, 60 MHz) δ 0.67–2.00 (br m, 11H), 2.80 (t, J = 7 Hz, 2H), 7.00 (dd, J = 9, 4 Hz, 1H), 7.51 (ABq, J = 1 Hz, $\Delta\nu$ = 9 Hz, 1H), 7.53 (br s, 1H)
MS *m/e* 196 (M^+), 139, 126 (base peak), 111, 74, 60, 43, 41, 39, 29, 27
m/e calc for $C_{11}H_{16}OS$: 196.0922 (parent); found: 196.0929

$CH_3(CH_2)_5COSeCH_3$		 **39**	15 77° (0.17 Torr)	64

IR (film) 1648 cm^{-1} R_f = 0.14 (A)
NMR (CCl_4, 60 MHz) δ 0.67–2.00 (br m, 11H), 2.73 (t, J = 7 Hz, 2H), 6.07–6.27 (m, 1H), 6.70–6.27 (m, 2H), 10.67 (br s, 1H)
MS *m/e* 179 (M^+), 122, 109 (base peak), 94, 88, 74, 66, 61, 44, 42, 40, 29, 27
m/e calc for $C_{11}H_{17}NO$: 179.1310 (parent); found: 179.1310

[a] Purification was accomplished by bulb-to-bulb distillation in all cases.
[b] Only the frequency of the ketone carbonyl absorption is given.
[c] The TLC solvent systems used are: A, 9:1 hexane–ethyl acetate; B, 3:1 hexane–ethyl acetate.
[d] All mass spectra were taken at 70 eV.
[e] The *ortho/para* ratio was determined by comparing the areas of their gas–liquid chromatography (GLC) traces. GLC was performed on a 10 ft 3% OV-17 analytical column, at 40 psi of helium carrier gas pressure, temperature programmed from 110–280° at 8° min^{-1}, then held at 280° for 32 min.
[f] This selenoester was prepared by A. Vasilakis.
[g] The *ortho/para* ratio was determined by comparing the integration values of the singlet at δ 3.78 and 3.87.

intermediacy of a mixed carboxylic-trifluoromethanesulfonic anhydride (**44**).



44 **43**

The former case is a variation of the classical Friedel–Crafts acylation intermediate, represented as the equilibrium between the donor–acceptor form **42**[51] and the ionic form **43**. The existence of these forms in solution has been firmly established by a variety of spectral methods in normal Friedel–Crafts reactions with acyl halides. Both may serve as the acylating agent, the donor–acceptor complex **42** by a substitution mechanism and the oxocarbenium form **43** via an ionic mechanism.

It is important to emphasize that these copper-promoted acylation procedures differ mechanistically from the classical Friedel–Crafts process in that the former depends upon the complexation of a soft, selenophilic Cu(I) species to the departing anionic group. The latter furnishes a similar intermediate but through a sequence involving initial complexation of a hard metal catalyst (e.g. $AlCl_3$, BF_3, etc.) to the hard carbonyl oxygen.[51]

Mixed carboxylic-trifluoromethanesulfonic acid anhydrides are well precedented acylating agents.[52] Intermediate **44**, which could conceivably arise from attack of the triflate anion on either **42** or **43**, might thus be responsible for the observed reactions. Such a possibility was tested in part by generating a mixed anhydride *in situ* from silver trifluoromethanesulfonate and acetyl chloride in benzene, and then reacting this with anisole for approximately 18 hr at room temperature. A complex potpourri of products was generated from which a mixture of the *ortho* and *para* acetylated anisoles could be distilled in low yield.

Finally, the copper-promoted acylation reaction was shown not to a simple acid-catalyzed process. No reaction between anisole and Se-methyl heptaneselenoate was observed when these components were stirred with triflic acid in the absence of cuprous triflate under the standard conditions.

Other potential applications of selenoesters

One important area of synthesis in which selenoesters may find considerable use is in macrolide construction.[21] The successful preparation of Gensler's lactone with Cu(I) and the reclosure of selenoester **13** to its corresponding lactone upon heating suggest that both "soft" metal-promoted and thermal processes for lactone construction should be synthetically useful.

The similarity in chemical behavior between the selenoesters and the acid chlorides does further suggest that the latter should react with organocuprates to form ketones.[53] Indeed, on exposing **2** to 1.0 equiv of lithium dimethylcuprate, 2-octanone was obtained in 91% isolated yield. Additionally, Back and Kerr recently found that copper or cuprous iodide will catalyze the insertion of diazomethane into the acyl–selenium linkage of selenoesters to yield selenomethyl ketones in good yield.[54]

Other uses for the selenoesters are certainly likely to emerge as chemists begin to better understand and appreciate their properties and their novel reactivities.[55]

EXPERIMENTAL

Dimethylaluminum methaneselenolate (**1**). Approximately 4.10 g (52.0 mmol) of selenium powder (ROC/RIC, 200 mesh) was dried by heating *in vacuo* for several hours. After cooling to room temperature, 25.2 ml (50.0 mmol) of trimethylaluminum (17 wt% in toluene, Texas Alkyls) was added rapidly by syringe. This grayish-black mixture was heated to reflux with stirring for 2 hr, cooled to room temperature, and the unreacted selenium powder was allowed to precipitate. The yellow-colored solution was transferred into a dry, argon-filled, septum-fitted Erlenmeyer flask via a double-tipped stainless steel cannula. This solution could be stored at room temperature under a positive pressure of argon for periods of up to one month. An uncharacterized white solid was found to form over longer periods of time, or if the solution was stored in the refrigerator, with an accompanying loss in reagent efficacy. Aliquots were withdrawn as needed with dry, argon-purged syringes. The concentration of the dimethylaluminum methaneselenolate was assumed to be approximately the same as the initial trimethylaluminum–toluene solution.

Se-*Methyl heptaneselenoate* (**2**). To a solution of 288 mg (2.00 mmol) of distilled methyl heptanoate in 5 ml of argon-degassed dichloromethane at 0° was added 1.10 ml (2.20 mmol) of dimethylaluminum methaneselenolate (**1**) (1.98 M in toluene) by syringe. After 30 min at 0°, the yellow solution was warmed to room temperature over 30 min, then quenched with moist sodium sulfate. The reaction mixture was extracted with ether, dried with anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to yield a noxious yellow oil. Purification by bulb-to-bulb distillation (95°, 30 Torr) gave 393 mg (95%) of **2** as a clear yellow oil: R_f = 0.68 (9 : 1 hexane–ethyl acetate); IR (film) 2985, 2830, 1729, 1459, 1371, 734 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.63–2.00 (br m, 11H), 2.16 (s, 3H), 2.54 (br t, J = 7 Hz, 2H); MS (70 eV) *m/e* 204, 205, 206, 208, 210 (M^+, ^{82}Se, ^{80}Se, ^{78}Se, ^{77}Se, ^{76}Se), 113 (base peak).

Methyl heptanoate. To a mixture of 293 mg (1.08 mmol) of sublimed mercuric chloride and 214 mg (2.14 mmol) of anhydrous calcium carbonate in 2.8 ml of dry acetonitrile was added 109 mg (0.53 mmol) of Se-methyl heptaneselenoate (**2**). Then 32 mg (0.99 mmol) of absolute methanol was added by syringe, and the mixture was stirred at room temperature for 1 hr, at which time TLC analysis indicated the absence of selenoester. The reaction mixture was diluted with 8 ml of pentane, filtered through a pad of Celite, and the filtrate concentrated by rotary evaporation. The crude product was purified by bulb-to-bulb distillation (75°, 30 Torr) to yield 67 mg (88%) of a clear, colorless oil, which had NMR and IR spectra identical with an authentic sample of methyl heptanoate. In the same fashion, treatment of separate

mixtures of $HgCl_2$–$CaCO_3$–2–CH_3CN with 1 equiv of water and N-cyclohexylamine furnished n-heptanoic acid and N-cyclohexylheptanamide in 97 and 88% yields, respectively. Both compounds exhibited IR and NMR spectra consistent with these assignments.

4-Carboethoxy-5-n-hexyloxazole (**25a**). To a mixture of 108 mg (0.75 mmol) of dry cuprous oxide, 76 mg (0.75 mmol) of dry triethylamine, and 79 mg (0.70 mmol) of ethyl isocyanoacetate[69] in 5 ml of dry THF was added 102 mg (0.49 mmol) of Se-methyl heptaneselenoate (**2**). This maroon-colored mixture was stirred at room temperature for 11.5 hr, at which time TLC showed no remaining selenoester. The reaction mixture was filtered through a plug of celite, and the filter cake washed with ether. Concentration of the combined filtrates by rotary evaporation followed by chromatography on 15 g of Florisil with 3:1 hexane–ethyl acetate as eluent (R_f = 0.21) furnished 82 mg (85%) of pure oxazole **25a** as a clear yellow oil: IR (CCl_4) 2960, 2934, 2875, 1720, 1612, 1528, 1470, 1380, 1324, 1188, 1122 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.51–2.01 (m, 11H), 1.40 (t, J = 7 Hz, 3H), 3.02 (t, J = 7 Hz, 2H), 4.29 (q, J = 7 Hz, 2H), 7.76 (s, 1H); MS (70 eV) *m/e* 225 (M^+), 180, 179, 168, 155 (base peak), 123, 122, 109, 43, 29. *m/e* calc for $C_{12}H_{19}NO_3$: 225.1372; found: 225.1376.

bis(Copper(I) trifluoromethanesulfonate)–benzene complex (**29**). To a mixture of 5.72 g (40.0 mmol) of dry cuprous oxide in 180 ml of dry benzene was added 15.10 g (53.5 mmol) of distilled trifluoromethanesulfonic acid anhydride. The mixture was heated at reflux with stirring for approximately 3 hr. During this time, the mixture lost its opaque, maroon color and assumed a turbid, light-brown appearance. The hot solution was filtered through a coarse-fitted Büchner funnel in a dry nitrogen atmosphere to remove insoluble impurities. The green-colored filtrate was allowed to cool in a nitrogen-filled glove bag. After a short time, a large amount of fine white crystals precipitated from the solution. These were collected by filtration and washed with 40 ml of dry benzene. The Büchner funnel containing the white crystals was transferred to a vacuum desiccator, where drying was allowed to occur overnight. The desiccator was filled with argon, then transferred to a nitrogen-filled glovebag, where it was opened. Approximately 15.10 g (75.0%) of cuprous triflate thus obtained was transferred into dry glass ampules, which were sealed with a natural gas–oxygen torch. Stored in this manner, the cuprous triflate remained stable for several months.

1-(4-Methoxyphenyl)-1-heptanone (**30**). To a mixture of 54 mg (0.54 mmol) of anhydrous calcium carbonate and 235 mg (0.47 mmol) of cuprous triflate [$(CuOSO_2CF_3)_2Ph$] (**29**) in 7 ml of dry benzene was added 60 mg (0.55 mmol) of distilled anisole. To this off-white-colored mixture was added 104 mg (0.50 mmol) of Se-methyl heptaneselenoate (**2**) with stirring at room temperature. The mixture became a clear amber solution within minutes, and slowly darkened to a deep brown, heterogeneous mixture. TLC after 40 min indicated no unreacted selenoester. The reaction mixture was filtered through a sintered glass funnel to remove solids, and the filter cake was washed with additional benzene. The combined washings and filtrate were then washed with 4 × 5 ml portions of 6 M ammonium hydroxide and once with brine. The combined aqueous washes were reextracted once with a 10 ml portion of benzene, which was combined with the first extract, and dried with anhydrous magnesium sulfate. Filtration and concentration by rotary evaporation of this extract yielded 122 mg of a viscous white oil. Bulb-to-bulb distillation of 89 mg of this oil (84°, 0.18–0.20 Torr) afforded 62 mg (81%) of white plates: R_f = 0.22 (9:1 hexane–ethyl acetate); m.p. 38.6–39.8°; IR (CCl_4) 2960, 2930, 1672, 1600, 1515, 1465, 1364, 1265, 1210, 1120, 850 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.48–2.02 (m, 11H), 2.80 (t, J = 7.0 Hz, 2H), 3.88 (s, 3H), 7.28 (ABq, J = 9.0 Hz, $\Delta\nu$ = 62.6 Hz, 4H); MS (70 eV) *m/e* 220 (M^+), 150, 135, 134 (base peak), 107, 77. *m/e* calc for $C_{14}H_{20}O_2$: 220.1463 (parent); found: 220.1463.

n-Butyl-1-(2-methoxyphenyl)- and n-butyl-1-(4-methoxyphenyl)-n-heptylsulfide (**41**). To a mixture of 225 mg (0.45 mmol) of cuprous triflate–benzene complex **29** and 5 ml of dry benzene was added 44 mg (0.41 mmol) of anisole. To this off-white-colored mixture was added 112 mg (0.40 mmol) of 1,1-bis(n-butylthio)heptane (**40**).[70] The reaction was stirred at room temperature for 29 min, at which time TLC indicated that the reaction was complete. The mixture was diluted with an additional 20 ml of benzene, then washed with 2 × 5 ml of 6 M ammonium hydroxide. The combined aqueous washes were reextracted with 10 ml of benzene, and the total organic solution was dried with anhydrous magnesium sulfate. The drying agent was removed by suction filtration, and the filtrate was concentrated at reduced pressure by rotary evaporation. The crude product was purified by bulb-to-bulb distillation (82°, 0.26 Torr) to afford 91 mg (80.1%) of pure thioether **41**. The purified product was analyzed by GLC on a 10 ft × 1/4 in 15% SE-30 column at a temperature of 235° with a flow rate of 60 ml min^{-1} of helium at 40 psi. Two products were detected, the major one with t_r (10.2 min), and the minor one with t_r (11.3 min). The relative ratio of these two peaks ~92:8, respectively, was obtained by comparing the individual peak areas with the combined peak areas: R_f = 0.22 (9:1 hexane–ethyl acetate); IR (film) 2950, 2920, 2900, 1608, 1510, 1464, 1378, 1300, 1248, 1172, 1036, 822 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.67–2.80 (br m, 23H), 3.67 and 3.70 (two s's, 3H), 6.80 (ABq, J = 9.0 Hz, $\Delta\nu$ = 17.9 Hz, 4H); MS (15 eV) *m/e* 275, 209, 186, 177, 121, 56 (base peak).

2-Octanone via lithium dimethylcuprate. To a mixture of 106 mg (0.56 mmol) of purified cuprous iodide (extracted with ethyl ether in a Soxhlet extractor, dried under vacuum, and protected from light) and 3 ml of dry ether was added 0.70 ml (1.00 mmol) of methyllithium (1.43 M in ether) dropwise with stirring at 0°. After approximately 40 min at 0°, the yellow color of the initial mixture had discharged, and the mixture assumed a tan or buff appearance. This mixture was cooled to −78°, and 104 mg (0.55 mmol) of Se-methyl heptaneselenoate (**2**) was added by syringe in 3 ml of diethyl ether in one portion with stirring. After 1 hr at −78°, no selenoester **2** was detected by TLC. The reaction was quenched by the dropwise addition of 1 ml of saturated ammonium chloride at −78°, followed by warming to room temperature. The crude product was isolated by washing the ethereal portion with 2 × 5 ml portions of saturated ammonium chloride and reextracting the combined aqueous washings with an equivalent volume of ether. The ethereal layers were combined and dried with anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation, to yield a yellow oil. A portion (30 mg) of the crude product was purified by bulb-to-bulb distillation (70°, 37 Torr) to afford 24 mg (91%) of a colorless oil which gave an NMR spectrum identical with authentic 2-octanone.

Acknowledgements—We are indebted to the National Institutes of Health for their support of these investigations.

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