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SELENOESTERS IN ORGANIC SYNTHESIS.

1. CONVERSION OF MIXED CARBOXYLIC ACID ESTERS TO SELENOESTERS

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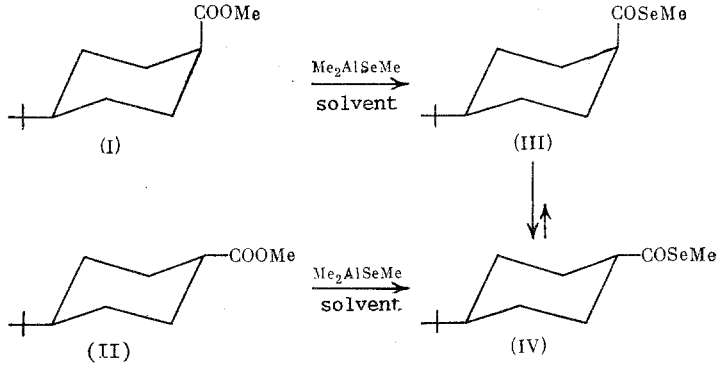
A recurrent problem in organic synthesis involves conversion of mixed esters to ketones of varying structures. One of the better methods of ketone synthesis is based on the reaction of organometallic compounds with carboxylic acid derivatives [1]. The use of mixed esters for this purpose is complicated by difficulties in hydrolyzing the esters and converting the free carboxylic acids to active acylating agents. Although a significant number of methods have been developed recently to deblock or deprotect carboalkoxy groups [2], in many cases (particularly in the synthesis of natural products) this approach is unsuitable due to the lability of the rest of the molecule or to the loss of stereochemistry at a chiral center α to the carboalkoxy group as a result of enolization during the hydrolysis step.

A method was recently reported for the rapid and efficient conversion of mixed esters to selenoesters upon treatment with dimethylaluminum methyl selenide; it was also shown that the latter derivatives easily underwent hydrolysis, alcoholysis, and ammonlysis reactions in the presence of mercury salts [3, 4]. Selenoesters were also found to be more active than their closely related analogs, thioesters. The limits of this reaction, and, more importantly, the effect of steric factors, solvent properties, and other reaction conditions on the course of the reaction, have not been studied.

In order to develop the practical potential of this method in complex organic synthesis, we have investigated the influence of the structure of the starting material, i.e., of the mixed ester, and also the effect of solvent properties on the selectivity of the mixed ester to selenoester conversion reaction. We have also investigated various pathways for the conversion of selenoesters to ketones, particularly α,β-unsaturated ketones, with special attention directed toward the synthesis of complex organic molecules [5, 6].

The esters of cis- (I) and trans-4-tert-butylcyclohexanecarboxylic acid (II) [7] were selected as model compounds in order to assess the behavior of configurationally unstable centers α to the carboalkoxy group under the conditions of selenoester synthesis.



The reaction was conducted in several different solvents (Figs. 1 and 2) in order to determine optimum reaction conditions which would provide a maximum conversion rate and a minimum amount of isomerization of the axial isomer (III) to the equatorial isomer (IV). It

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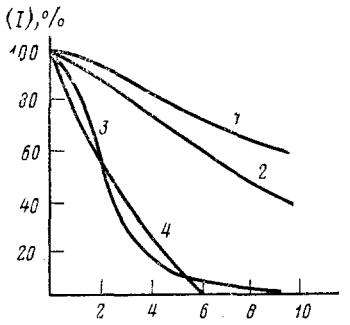


Fig. 1

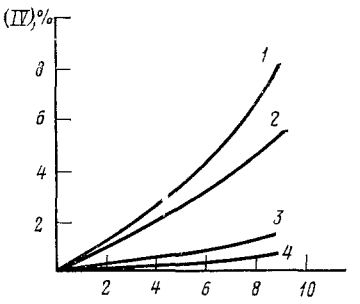


Fig. 2

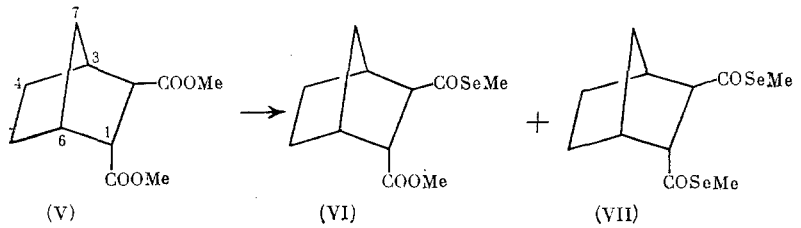
Fig. 1. Conversion of (I) upon treatment with Me_2Al·SeMe in various solvents: 1) THF; 2) CH_2Cl_2; 3) Ph·CH_3; 4) Et_2O.

Fig. 2. Formation of (IV) during the reaction of (I) with $Me_2AlSeMe$ in various solvents: 1) $PhCH_3$; 2) CH_2·Cl_2; 3) Et_2O; 4) THF.

was found that the nature of the solvent exerts a profound influence on both the rate of selenoester formation as well as the amount of isomerization of (III) to (IV). Diethyl ether proved to be the best solvent, both in terms of the rate of reaction and the stereochemical purity. For the solvent series Et_2O:$PhCH_3$:CH_2Cl_2, the relative rates of reaction of (I), calculated at 20% conversion, were ca. 10:5:1. More basic solvents (dioxane, THF) suppress the isomerization reaction, but this is accomplished at the expense of significant reduction in the rate of the main reaction. The use of noncoordinating solvents ($PhCH_3$, CH_2Cl_2) is accompanied by the formation of the isomeric selenoester (IV). Dimethylaluminumalkoxides, which are formed during the course of the reaction, or other Lewis acids, which may be introduced along with the reagents or appear as a result of side reactions, are probably responsible for the isomerization reaction.

The selenoesters (III) and (IV) were isolated chromatographically, and their purities were determined by capillary GLC; their structures were verified on the basis of their PM spectral data. Replacement of the methoxy group by a selenomethyl group is accompanied by the appearance of a three proton signal at 2.19 ppm (for III) or 2.17 ppm (for IV) in place of the signal at 3.68 (I) or 3.66 ppm (II), respectively. The PMR spectrum of the selenoester (III) contains a signal for the α-proton at 2.77 ppm as a triplet of triplets with a spin-spin coupling constant of 5 and 2.5 Hz, respectively, consistent with its equatorial orientation; in the selenoester (IV), the α-proton gives rise to a PMR signal at 2.45 ppm as a triplet of triplets with a spin-spin coupling constant of 11.5 and 3 Hz, respectively, consistent with its axial orientation.

Further research on this reaction has shown that treatment of mixed esters with Me_2AlSe·Me is very sensitive to steric factors; it is therefore possible to carry out the selective conversion of one ester group in the presence of a second ester group in the same mixture. Complete conversion of the equatorial isomer (II) to the ketone (IV) is complete in 1 h in CH_2Cl_2, whereas the axial isomer (I) is completely reacted only after 30 h. This reaction can be used to effect kinetic separation of isomeric 4-tert-butylcyclohexanecarboxylic acid esters. Treatment of a mixture of esters (I) and (II) with $Me_2AlSeMe$ (molar ratio 1:1:1.2) over a 2 h period, followed by hydrolysis of the resulting selenoesters with $HgCl_2$—HgO, gave the pure axial isomer (I) in 90% yield.



Marked selectivity for the equatorial carbomethoxy group was also obtained for the reaction of the weakly differentiated bicycloheptane derivative (V). Treatment of the diester (V) with 0.5 equivalents of $Me_2AlSeMe$ in ether under standard reaction conditions gave 67.5% of the monoselenoester (VI) and only 15.8% of the diselenoester (VII). The structures of these materials were confirmed by comparison of their ^{13}C-NMR and PMR spectra. For instance, in the PMR spectrum of (V), the signal for H^1 appears as a doublet of doublets of doublets at 3.22 ppm ($J_{1,2}$ = 5.5; $J_{1,6}$ = 4.2; $J_{1,7}$ = 2 Hz), the H^2 signal is a doublet of doublets at 2.83 ppm ($J_{2,3}$ = 1.7 Hz), and the CH_3 groups are represented by singlets at 3.68 and 3.71 ppm. In the transition to the monoselenoester (VI), the H^2 proton signal is shifted downfield to 3.13 ppm, whereas the H^1 proton signal position is almost unchanged (3.23 ppm). The CH_3 group attached to the selenium atom appears as a singlet at 2.21 ppm, and the methoxy group signal remains constant at 3.72 ppm. In compound (VII), both the H^1 and H^2 proton signals are shifted to weaker field, the 3.52 and 3.18 ppm, respectively. The signals for the newly introduced selenomethyl groups appear as singlets at 2.26 and 2.21 ppm, respectively.

Similar trends are observed in the ^{13}C-NMR spectra of compounds (V)-(VII). Thus, in the parent diester (V), the following signal assignments have been made: 51.7 (C^1), 51.9 (C^2), 48.8 (COOMe attached to C^1), and 49.55 (COOMe attached to C^2) in the spectrum of (VI), the signal due to C^1 and COOMe attached to C^1 remain in place, the C^2 signal is shifted to 61.4 ppm, and a new selenomethyl signal appears at 4.8 ppm. The transition to the diselenoester (VII) is accompanied by displacement of all of the original signals (C^1 60.25, C^2 61.6, COSeMe 4.85 and 4.97 ppm).

The structures of both the acyl and alkoxy fragments in the carboxylic acid esters exert a significant influence on the rate of the ester → selenoester conversion reaction. The use of capillary GLC to monitor the reaction course revealed that the n-butyl ester of butyric acid was more than 100 times more reactive than the corresponding sec-butyl ester. It was also found that tert-butyl and trimethylsilyl esters of the same acid were totally inert under these reaction conditions; these results are consistent with those obtained by other authors [3].

The dependence of the reactivity of a mixed ester on the structure of its acyl fragment is not quite so strong, but is also noteworthy. For instance, competitive reactions involving the methyl esters of cyclohexanecarboxylic acid (X), cyclohexaneacetic acid (VIII), and 1-methylcyclohexanecarboxylic acid (XII) in various solvents ($PhCH_3$, Et_2O, THF, and CH_2Cl_2) yielded the following relative rate data, 10:5:1, respectively. The structures of the cyclohexaneacetic (IX), cyclohexanecarboxylic (XI), and 1-methylcyclohexanecarboxylic (XIII) acid selenomethyl esters were established on the basis of their mass spectra and also by chromatography. The retention times of the selenoesters (on capillary GLC) are significantly longer than those of their ester precursors. The mass spectra of the selenoesters, on the other hand, are very similar, and the fragmentation patterns do not differ greatly from those of the precursor mixed esters. The main fragmentation pathways appear to involve cleavage between the cyclohexyl residue (m/e 83) and the side chain, and also between the selenium atom and the carbonyl group (m/e 125 for (IX) and (XIII), m/e 111 for (XI)). The mass spectra of the selenoesters (IX) and (XIII) contain very low intensity peaks for the molecular ions at m/e 218 and 220; the intensity ratio of these peaks corresponds exactly to that expected on the basis of the isotopic composition of the selenium atom. A combination of GLC and mass spectral data was thus necessary to establish the structure of the selenoester products.

Our results have clearly demonstrated that the reaction of mixed esters with $Me_2AlSeMe$ is very sensitive to the nature of the solvent used as well as to the structure of the precursor ester. By taking advantage of configurational differences as well as structural differences involving the alcohol and acyl components of an ester, it is possible to work selectively with one functional group in a complex molecule containing at least two carboalkoxy functional groups.

EXPERIMENTAL

PMR and ^{13}C-NMR spectra were recorded on a Bruker WM-250 spectrometer (in $CDCl_3$ versus TMS as internal standard, δ). Thin layer chromatography was carried out on Silufol UV-254 plates, and GLC analyses were carried out on a Biokhrom-21 chromatograph (using glass capillary columns with XE-60, 50 m). Mass spectra were obtained on a Varian MAT-111 (Gnom) spectrophotometer. Column chromatography was conducted using Silpearl (25-40 μm) silica gel and a continuous linear solvent gradient at a pressure of 0.5-1.2 atm.

Methyl Esters of 4-Tert-Butylcyclohexanecarboxylic Acids (I) and (II). A solution of 3.1 g (17.3 mmole) of cis-4-tert-butylcyclohexanecarboxylic acid in 30 ml of CH_2Cl_2 and containing 0.126 g (1.73 mmole) of DMF was treated with 22.8 ml of a 1.14 N solution of $(COCl)_2$ (25.9 mmole) in CH_2Cl_2. The mixture was stirred at 20°C for 1 h, and then concentrated at 2 mm Hg pressure. The residue was taken up in 20 ml of CH_2Cl_2, cooled to 0°C, and then treated with 5.1 ml (63 mmole) of pyridine and 2.5 ml (63 mmole) MeOH in 20 ml of CH_2Cl_2. The mixture was stirred 1.5 h at 20°C, 30 ml of water was added, and the mixture was extracted with $CHCl_3$. The extract was washed with 1 N HCl, a solution of $KHCO_3$, NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed by evaporation, and the residue was distilled under vacuum. Yield 3.16 g (92.5%), bp 65-67°C (0.2 mm), purity > 99% (capillary GLC). PMR spectrum: 0.83 s (9H, t-Bu), 2.63 t of t (1H, $J_{1,2a}$ = 5, $J_{1,2e}$ = 2.5 Hz, H^1), 3.68 s (3H, $COOCH_3$).

The ester (II) was prepared in an analogous manner, purity 98% (capillary GLC). PMR spectrum: 0.83 s (9H, t-Bu), 2.11 t of t (1H, $J_{1,2a}$ = 17.5, $J_{1,2e}$ = 4 Hz, H^1), 3.66 s (3H, $COOCH_3$).

Methyl Esters of 4-Tert-Butylcyclohexaneselenocarboxylic Acids (III) and (IV). A solution of 0.228 g (1.14 mmole) of (I) in 3 ml of ether was treated with 0.68 ml of a 2 N solution of $Me_2AlSeMe$ in toluene (1.37 mmole); the mixture was stirred for 10 h at 20°C, an excess of $Na_2SO_4 \cdot 10H_2O$ was added, the precipitate was removed by filtration and washed with chloroform. The solvent was removed by evaporation and the residue was chromatographed on silica gel (petroleum ether–ether). Yield 0.273 g (92%) of (III), purity > 99% (capillary GLC). PMR spectrum: 2.19 s (3H, COSeMe), 2.27 m (1H, $J_{1,2a}$ = 5, $J_{1,2e}$ = 2.5 Hz, H^1).

Reaction of an Equimolar Mixture of Esters (I) and (II) with $Me_2AlSeMe$. A mixture consisting of 0.098 g (0.5 mmole) of (I) and 0.098 g (0.5 mmole) of (II) in 1 ml of CH_2Cl_2 was treated with 0.3 ml of a 2 N solution of $Me_2AlSeMe$ in toluene (1.2 equiv); the mixture was stirred 2 h at 20°C, and then an excess of $Na_2SO_4 \cdot 10H_2O$ was added. The precipitate was filtered, washed with chloroform, and the solvent was evaporated to give a residue which was dissolved in 2 ml of a 1:1 MeCN–H_2O mixture. This mixture was treated with 0.4 g of $HgCl_2$ and 0.35 g of HgO and stirred 1 h at 20°C. The mixture was diluted with water and extracted with petroleum ether. The organic layer was washed with bicarbonate solution, water, and evaporated to dryness. The residue was subjected to microdistillation. Yield 0.088 g (90%) of (I), bp 65-67°C (0.2 mm).

Reaction of $Me_2AlSeMe$ with Diester (V). A solution of 0.606 g of (V) (2.86 mmole) in 5 ml of ether was treated with 1.5 ml of a 2 N solution of $Me_2AlSeMe$ (3 mmole, 0.5 equiv) under an argon atmosphere and then stirred 12 h at 20°C. The mixture was decomposed with an excess of $Na_2SO_4 \cdot 10H_2O$, the precipitate was washed with chloroform, and the solvent was evaporated; the residue was subject to chromatography on silica gel (benzene). Yield 0.532 g (67.5%) of (VI), 0.153 g (15.8%) of (VII). PMR spectrum (V): 3.22 d of d of d (1H, $J_{1,2}$ = 5.5, $J_{1,6}$ = 4.2, $J_{1,7}$ = 2 Hz, H^1), 2.83 d of d (1H, $J_{2,3}$ = 1.7, H^2), 3.68 s (3H, COOMe at C^1), 3.71 s (3H, COOMe at C^2). ^{13}C-NMR spectrum: 51.7 and 51.9 (C^1 and C^2), 41.8 (C^3), 28.9 (C^4), 24.35 (C^5), 40.3 (C^6), 38.2 (C^7), 49.55 and 48.8 (COOMe), 173.9 and 175.1 (COOMe).

PMR spectrum of (VI): 3.23 d of d of d (1H, $J_{1,2}$ = 5.5, $J_{1,6}$ = 4.2, $J_{1,7}$ = 2 Hz, H^1), 3.13 d of d (1H, $J_{2,3}$ = 1.7 Hz, H^2), 3.72 s (3H, COOMe on C^1), 2.21 s (3H, COSeMe on C^2). ^{13}C-NMR spectrum: 49.4 (C^1), 61.4 (C^2), 42.6 (C^3), 28.8 (C^4), 24.5 (C^5), 40.2 (C^6), 38.05 (C^7), 51.8 (COOMe), 4.8 (COSeMe), 173.4 (COOMe), 167.1 (COSeMe).

PMR spectrum of (VII): 3.52 d of d (1H, $J_{1,2}$ = 5.5, $J_{1,6}$ = 4.2, $J_{1,7}$ = 1.7 Hz, H^1), 3.18 d of d (1H, $J_{2,3}$ = 1.7 Hz, H^2), 2.26 s (3H, COSeMe on C^1), 2.21 s (3H, COSeMe on C^2). ^{13}C-NMR spectrum 60.25 (C^1), 61.6 (C^2), 42.7 (C^3), 28.85 (C^4), 23.8 (C^5), 41.55 (C^6) 37.9 (C^7), 4.97 and 4.85 (COSeMe), 167.1 and 167.4 (COSeMe).

Reaction of n-Butyl, sec-Butyl, and tert-Butyl Esters of Butyric Acid with $Me_2AlSeMe$. The above-mentioned esters were prepared by the reaction of butyric anhydride with n-butanol, sec-butanol, and tert-butanol, respectively, in CH_2Cl_2 in the presence of Et_3N and 4-dimethylaminopyridine, followed by vacuum distillation. Respective bp: n-butyl ester, 56-57°C (11 mm); sec-butyl ester, 54-55°C (18 mm); tert-butyl ester, 58-59°C (38 mm).

To 0.5 ml of a toluene solution containing 0.356 mole of the butyric acid esters and 20 mg of n-dodecane (internal standard) was added 1 ml of solvent ($PhCH_3$, CH_2Cl_2, Et_2O, THF), followed by 0.2 ml of 2 N solution of $Me_2AlSeMe$ in toluene (1.15 equiv). The mixture was maintained at 20°C for 48 h (monitored by capillary GLC).

Reaction of Esters (VIII), (X), and (XII) with $Me_2AlSeMe$. A mixture of equimolar amounts of esters (VIII), (X), and (XII) in 0.5 ml of toluene was treated with 1 ml of solvent ($PhCH_3$, CH_2Cl_2, Et_2O, THF), 20 mg of tridecane (internal standard) and 0.19 ml of a 2 N solution of $Me_2AlSeMe$ in toluene (1.1 equiv, 0.385 mmole). The mixture was stirred at 20°C for 48 h (monitored by capillary GLC). Mass spectra (m/e, %): (IX), 220 (1.7), 218 (1), 125 (90), 97 (100), 83 (33): (XI), 111 (90), 83 (100): (XIII), 220 (1), 218 (0.6), 125 (90), 97 (100).

CONCLUSIONS

The rules governing the reaction of mixed carboxylic acid esters with dimethylaluminum methyl selenide have been investigated; it was found that the nature of the solvent and the structure of the precursor ester both exert significant effects on the selectivity of seleno-ester formation.

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