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# SELENOESTERS IN ORGANIC SYNTHESIS. 1. A NOVEL SYNTHESIS OF KETONES.

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Abstract. A mild and efficient esters into ketones transformation via selenoesters have been described.

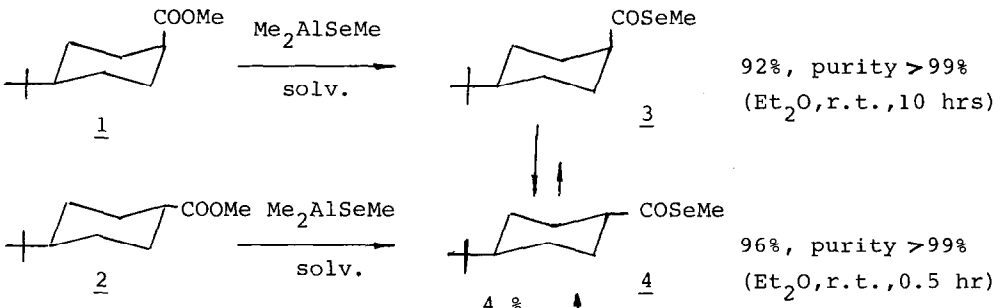
During the realization of synthetic programme directed to macrolide antibiotics construction we needed in mild and efficient ester to ketone transformation. Traditional sequence including ester cleavage, preparation of active acyl-transfer derivative followed by reaction with appropriate organometallics have some disadvantages for natural products synthesis since may affect position $\alpha$ to carboxylic group. Therefore we are interested in more mild and straightforward synthesis of active acyl-transfer derivatives. Recently the procedure for direct transformation of esters into selenoesters by treatment with $Me_2AlSeMe$ was proposed[1] and selenoesters were shown to be active acyl-transfer reagents in heavy metal assisted reactions[1,2].

We now describe a new, mild and efficient esters into ketones transformation using selenoesters.

For projected stereospecific synthetic procedure the behavior of esters bearing labile chiral centre in $\alpha$-position to carbalkoxy group is of special interest. Therefore the interaction of methyl cis(1)- and trans-4-tert-butylcyclohexylcarboxylates (2) with $Me_2AlSeMe$ in different solvents has been investigated. For 1 ⟶ 3 convertion the results are presented at figures 1 and 2.

The nature of solvent was found to be critically important for reaction rate as well as for isomerisation of axial selenoester 3 into equatorial isomer 4. Use of noncoordinating solvents ($PhCH_3$,$CH_2Cl_2$) leads to essential isomerisation of 3 into 4, probably due to dimethylaluminium methoxide (appearing during the reaction) and other Lewis acids, which can arise as a result of side reactions or impurity of reagents[3]. Ether is solvent of choise providing the high reaction rate ($\tau^{rel}_{20\%}$ $Et_2O$:$PhCH_3$:$CH_2Cl_2$ ~1:2:8) and stereochemical purity

of the process. More basic solvents (THF, dioxane) suppress the isomerisation, but reaction rate is strongly decreased.



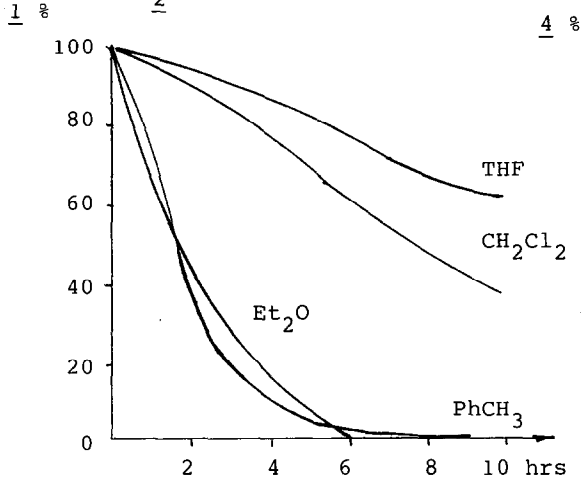




Fig.1 Conversion of 1 under the action of $Me_2AlSeMe$ in different solvents.

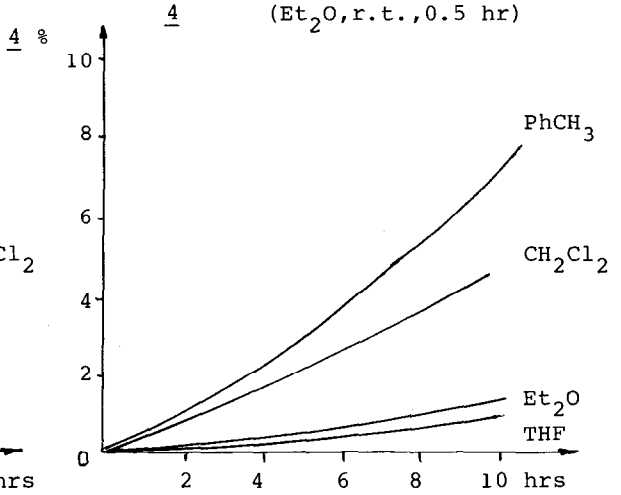
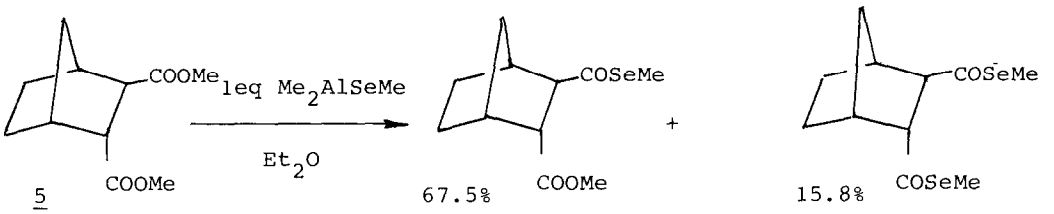



Fig.2 Formation of 4 during the reaction between 1 and $Me_2AlSeMe$ in different solvents.

Conversion of esters into selenoesters appears to be very sensitive to steric factors allowing to perform selective transformation of one ester group in presence of the others. For example, convertion of 2 into selenoester completed for 1 hr($CH_2Cl_2$,room temperature), whereas axial isomer 1 demands over 30 hrs for full transformation. This rate difference can be used for effective kinetic separation of isomeric methyl 4-tert-butylcyclohexylcarboxylates, e.g. reaction between 1, 2 and $Me_2AlSeMe$ (molar ratio 1:1:1.2,$CH_2Cl_2$,r.t.,2 hrs) followed by hydrolysis ($HgCl_2$-HgO/$CH_3CN$-$H_2O$,r.t.,1 hr) and mild alkali extractive work-up affords pure 1 in 90% yield (purity >99% by capillary GLC).

Considerable selectivity of the reaction can be demonstrated by preferential equatorial ester group conversion in trans-dicarbomethoxynorbornane 5 known to be poorly differentiated system:

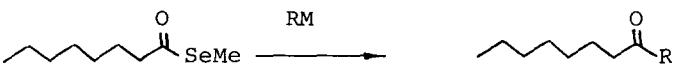



The structure of acyl and alkoxy groups of esters has the essential influence on the reaction rate. The competitive reaction of equimolar amounts of butyl butyrate, sec-butyl butyrate and $Me_2AlSeMe$ shows remarkable(≈100:1) primary vs. secondary alkoxy group replacement selectivity[4]; tert-butyl ester (cf ref.1) as well as TMS-esters do not react practically at all.

Influence of acyl group structure is expressed not so strongly. Thas, according to the data obtained from competitive reactions of mixture of methyl cyclohexylacetate, cyclohexylcarboxylate and 1-methylcyclohexylcarboxylate with $Me_2AlSeMe$ (molar ratio 1:1:1:1) relative reactivity is about 10:5:1 respectively, and only slightly varied in different solvents.

The high yield of selenoesters, mild reaction conditions, selectivity as well as stability and high reactivity[1,2] of selenoesters make this compounds the very promising class of acyl transfer reagents.

We found the selenoesters smoothly react with organocuprates and some other organometallics to produce ketones in excellent yield. Results are summarized in Table:




6

| Reagents | Amount (equv.) | T°C | Time (hours) | Yield, % |
|---|---|---|---|---|
| 1. $Me_2CuLi$ | 1.1 | -78 | 0.08 | 98 |
| 2. $Bu_2CuLi$ | 1.5 | -78 | 0.25 | 96 |
| 3. t-BuCuSPhLi[5] | 1.5 | -78 | 1 | 98 |
| 4. $Bu_4BCu$[6] | 1.5 | 20 | 2 | 96 |
| 5. BuMnCl[7] | 3 | 0 | 3 | 98 |
| 6. $Me_2Cd$ | 2 | up to 100 | 4 | 10 |
| 7. PrHgBr | 4 | up to 80 | 4 | 0 |

Reactions of selenoester 6 with homo- and heterocuprates proceeded in very mild condition and afforded ketones in nearly quantitative yields (runs 1-3).

A number of other organometallics also transform selenoesters into ketones. For example, butylmanganese chloride[7] reacts with 6 to afford dodecanone-5, but 3 eq of the reagent is required to complete the reaction (run 5).

Reaction of copper(1)tetraalkylboronates[6] giving rise to ketones in high yield, sometimes can be useful (run 4).

On the other hand, selenoesters poorly react with $Me_2Cd$ (run 6) in contrast to acylchlorides; PrHgBr does not react at all (run 7).

The presented procedure provides mild and efficient ester into ketone transformation particularly suitable for natural products syntheses.

## REFERENCES AND NOTES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2. A.P.Kozikowsky, A.Ames, J.Amer.Chem.Soc., 102, 860 (1980).
3. The isomerisation can be initiated particularly by dimethylaluminium halides presented in trace amounts in trimethylaluminium, or arised when $CH_2Cl_2$ was used without special purification (distillation from $CaH_2$ under argon).
4. The slow alkoxide exchange

   $C_3H_7COOBu\text{-}sec + Me_2AlOBu \longrightarrow C_3H_7COOBu + Me_2AlOBu\text{-}sec$

   have been observed when ether used as a solvent.
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