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REGIO AND STEREOSPECIFIC SYNTHESIS OF α,β-UNSATURATED ESTERS LACTONES AND ACIDS

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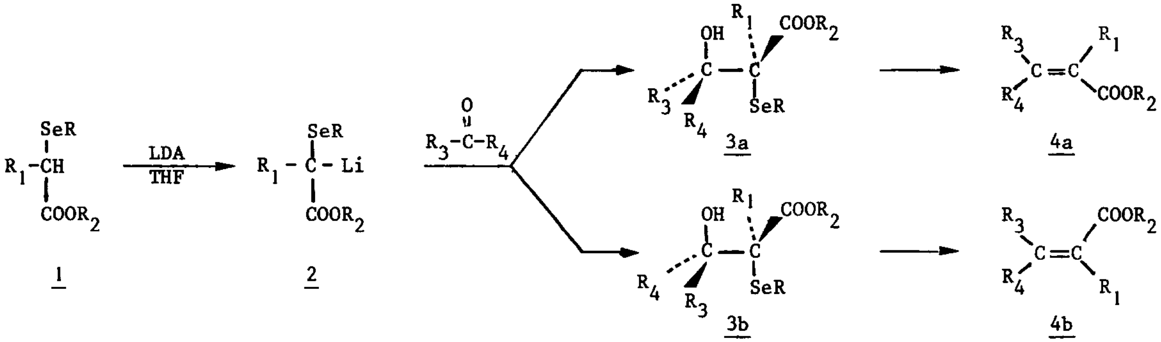
α,β-unsaturated esters, acids and lactones have been recently prepared from α-selenocarbanions, via selenoxide elimination, by Sharpless[1], Grieco[2] and us[3]. Unfortunately the synthesis is not regiospecific when two alkyl groups are directly branched α to the carbonyl group.

We report here a new [C-C] connective and regiospecific synthesis of α,β-unsaturated carbonyl compounds using α-seleno α-lithio esters 2 and carbonyl compounds which take advantage of the known olefin synthesis from β-hydroxyselenides[4,5]



We found that α-selenocarbanions 2 readily obtained according to Sharpless[1] (LDA, THF,-78°C) react at this temperature with aldehydes and ketones producing yet unknown β-hydroxyselenides 3 in high yield. In all the cases studied, mixtures of the two stereoisomers are obtained and their ratio cannot be correlated with the nature of the R_2 group on the ester or the substituant R directly attached to the selenium atom. However, except in the case of terbutyl esters the two isomers are readily separated on thick layer chromatography (ΔRF ∿ 0.1-0.2; ether-pentane 2:8) the 3b isomers being generally the most rapidly eluted.

R	R_1	R_2	R_3	R_4	Yield (%)	$\frac{3b}{3a}$ ratio
C_6H_5	H	Me	C_6H_5	H	88	48/52
C_6H_5	H	Me	C_6H_{13}	H	93	38/62
C_6H_5	H	Me	n-C_3H_7	CH_3	69	58/42
C_6H_5	H	terbutyl	C_6H_5	H	75	-
C_6H_5	n-C_3H_7	Me	C_6H_{13}	H	60	35/65
C_6H_5	H	H	C_6H_{13}	H	97	-
Me	H	Me	C_6H_5	H	87	33/67
Me	H	Me	C_6H_{13}	H	80	32/68
$pClC_6H_4$	H	Me	C_6H_{13}	H	96	44/56

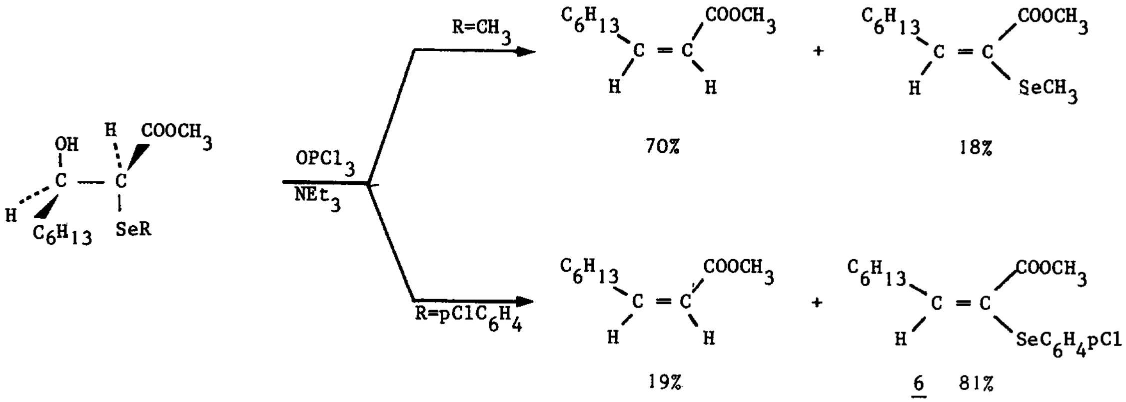
Our attention was then turned around the regio and stereospecific synthesis of the desired α,β-unsaturated carbonyl compounds 4a and 4b from stereochemically pure β-hydroxyselenides 3a and 3b and we decided to use thionyl chloride - triethyl amine method (method A)[8] we found the most successfull in the case of non functionalized β-hydroxyselenides [4b].
The different observations are listed below.

1. In all the cases studied, anti elimination of hydroxyl and selenyl moieties was observed leading to stereochemically pure α,β-unsaturated carbonyl compounds. Probably due to higher nucleophilicity of the selenomethyl group, the elimination occurs more rapidly in the selenomethyl than in the selenophenyl case.
2. Z isomers were obtained at slower rate than the E isomers.Moreover,the yields observed in the E series (86-99%)were always higher than those of their Z analogs (50-70%) and α-chloro α-seleno esters were also isolated in the later case.

These results are somewhat surprising related to our previous work in which even tetrasubstituted olefins were obtained in high yield [4b].

In order to overcome the difficulties uncountered for the synthesis of Z isomers of α,β-unsaturated esters we replaced thionyl chloride by several other reagents both for E and Z series and found phosphorus oxychloride (method B)[8,10]the most interesting : the reaction was cleaner, the solution remaining limpid which is not the case for all other reagents [4,5]; however the yield remained modest for Z disubstituted α,β-unsaturated esters synthesis and in this case α-seleno α,β-unsaturated esters arising from hydroxyl elimination were obtained (instead of the β-chloro α-seleno esters arising from hydroxyl substitution when thionyl chloride was used).

We took advantage of the results disclosed above to synthesize quite specifically from 3b series the compounds depicted in the following scheme.



Thus 1Z-decenoate was formed in 70% yield when the most nucleophilic selenomethyl moiety was present and when phosphorus oxychloride was used. At the opposite 1-(p chloro phenylseleno)1Z-decenoate 6 was obtained in high yield from the corresponding selenide probably due to the lower nucleophilicity of the p-chlorophenylselenyl moiety and its relatively high acidifying effect on the α hydrogen.

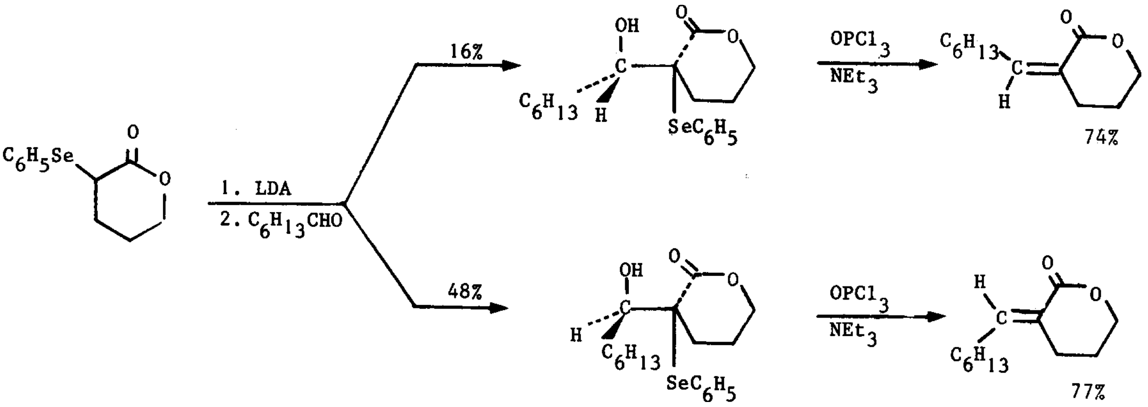
Surprisingly only E α,β-unsaturated esters were always obtained from 3a series whatever is the substituant directly attached to the selenium and the reagent used.

R	R_1	R_2	R_3	R_4	E isomer from pure 3a	Z isomer from pure 3b
CH_3	H	CH_3	C_6H_5	H	99(A)	69(A)
C_6H_5	H	CH_3	C_6H_5	H	92(A)	55(A)
CH_3	H	CH_3	C_6H_{13}	H	99(A)	53(A),70(B)
C_6H_5	H	CH_3	C_6H_{13}	H	86(A),88(B)	55(A)*,45(B)**
$pClC_6H_4$	H	CH_3	C_6H_{13}	H	91(B)	19(B)
C_6H_5	H	CH_3	C_3H_7	CH_3	74(A)	73(A)

* methyl 2-selenophenyl 3-chlorononanoate is also formed in 44% yield

** methyl 2-selenophenyl 2-nonenoate is also formed in 51% yield

Finally using the procedure outlined below, we succeeded the regio and stereospecific synthesis of alkylidene lactones [2,9]



Work is currently in progress for the stereochemical control of the β-hydroxyselenides synthesis, for the generalisation of these reactions and for the synthesis of α,β-unsaturated aldehydes, ketones and lactones using this strategy; the synthesis of obtusilactones is under investigation in our laboratory [11].

References

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6. Typical experiment :
   Methyl selenomethyl acetate (2.10^{-3}m) in THF (3 cc) is rapidly added at -78°C to a lithium diisopropylamide ($2.2\ 10^{-3}$m) solution in THF (2 cc). After 1.5 hr heptanal (2.10^{-3}m) in THF (1 cc) is added dropwise and the resulting solution stirred for 1.5 hr more at -78°C and hydrolysed at 0°C. Usual work up and purification on preparative layer chromatography (TLC, ether:pentane 3:7) lead to 3b (Rf:0.32), 26% and 3a (Rf:0.51), 54%.
7. Using methyl selenophenyl acetate and heptanal, under the condition described above, leads to the formation of corresponding 3 in 93% yield 3b/3a ratio (38/62). However, if the reaction is performed under more dilute conditions (THF, 15 cc overall instead of 6 cc), the yield in 3 is 64% and the 3b/3a ratio (64/36) is reversed. Work is in progress to understand this preliminary result.
8. Typical experiment :
   $SOCl_2$ ($2.2\ 10^{-3}$m) or $OPCl_3$ ($2.2\ 10^{-3}$m) in CH_2Cl_2 (1 cc) is added to a cooled (0°C) solution of β-hydroxyselenide 3 (6.10^{-4} m) in CH_2Cl_2 (5 cc) and triethylamine ($2.4\ 10^{-3}$m). Stirring is continued for 2 to 3 hrs at 0°C and the solution hydrolysed. After usual work up the crude material is purified by PLC (ether pentane 1.5:8.5).
9. The attributions are tentatively presented on the basis of their NMR spectra.
10. In one case, $POCl_3$ was used together with $SnCl_2$ and pyridine for β-hydroxyselenoxide → β-hydroxyselenide reduction (see ref. 5)
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This work will be included in the Ph.D. Thesis of J. Lucchetti.