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CONTROLLED REGIOSPECIFIC ADDITION OF 1-LITHIO 1-SELENO ACETATES TO α,β-UNSATURATED KETONES

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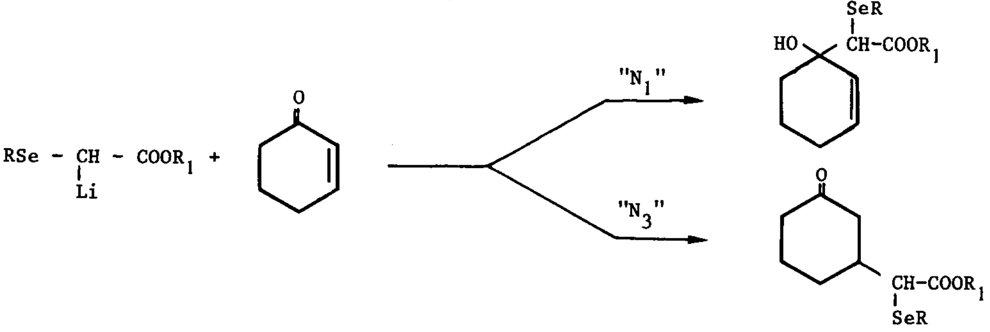
Numerous reports deal with the reactions of "carbanions" with α,β-unsaturated ketones. Sometimes, both 1-2 and 1-4 additions are simultaneously observed. Sometimes control of the regioselectivity was achieved by proper choice of experimental conditions [1]. Of course, the nature of the carbanion [2] and the counterion [3], the structure of the carbonyl [4] compound and the solvent choice [5] have been accounted for the specificity sometimes observed.
The specificity has been discussed in terms of frontier orbitals [4] or in terms of chelation of the metal with the carbonyl group [6] which allows the proximity of the carbanionic center near the C_1 (N_1 reactivity) [7] or the C_3 (N_3 reactivity)[7] center of the unsaturated system.

We present here our preliminary results for the reaction of 1-selenoalkyl (or phenyl) 1-lithio acetates with cyclohexenone.

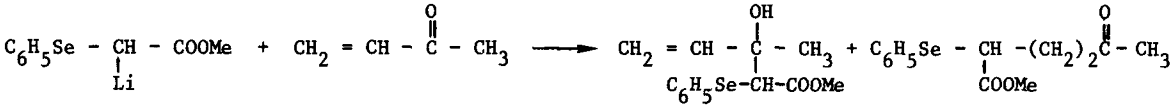
We found that these derivatives add kinetically 1-2 to cyclohexenone in THF at -78°C (N_1/N_3 : 95/5) (method A)[9a]. These results have been observed even after 6 hrs of reaction at this temperature.

We also found that the lithio alcoholate can be transformed to the more stable 1-4 adduct by simply rising the temperature to 25°C for only one hour (N_1/N_3 : 5/95)[10b] or by addition of HMPT to the medium at -78°C (N_1/N_3 : 20/80).Higher specificity was also observed in the later case when the reaction is conducted for the same time but at higher temperature (-45°C) (N_1/N_3 : 5/95)[10a]. Similar results were obtained if the reaction is directly performed in THF-HMPT at -78°C (N_1/N_3 : 20/80) (method B)[9b] or at -45°C (N_1/N_3 : 5/95) (method C)[9c].



R	R_1	Solvent		Yield	N_1	N_3
CH_3	CH_3	THF	(A)	57	95	5
C_6H_5	CH_3	THF	(A)	64	72	28
C_6H_5	CH_3	THF/HMPT	(B)	67	19	81
C_6H_5	CH_3	THF/HMPT	(C)	73	5	95
ClC_6H_5	CH_3	THF	(A)	53	94	6
ClC_6H_5	CH_3	THF/HMPT	(B)	72	15	85
ClC_6H_5	tC_4H_9	THF	(A)	76	96	4
ClC_6H_5	tC_4H_9	THF/HMPT	(B)	88	25	75
ClC_6H_5	tC_4H_9	THF/HMPT	(C)	55	5	95

Similar observations were done when methyl vinyl ketone was reacted instead of cyclohexenone.



$$C_6H_5Se-\underset{Li}{CH}-COOMe + CH_2=CH-\overset{O}{\overset{\|}{C}}-CH_3 \longrightarrow CH_2=CH-\underset{C_6H_5Se-CH-COOMe}{\overset{OH}{C}}-CH_3 + C_6H_5Se-\underset{COOMe}{CH}-(CH_2)_2\overset{O}{\overset{\|}{C}}-CH_3$$

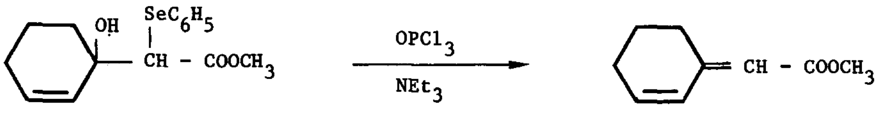
THF	(method A)	45% overall	81%	19%
THF/HMPT	(method B)	44% overall	15%	85%

A question requires an answer : Why these carbanions react regiospecifically N_1 in THF (-78°C, 6 hrs) whereas closely related 1-selenophenyl 1-lithio octanenitrile[5d] or 2-thiophenyl 2-lithio propionate react regiospecifically N_3 in the same solvent at -78°C ?

Both the intime structure of the carbanion [6,8] and the stabilization of the negative charge by the different groups directly attached to the carbanionic center should account for these results [11].

Several experiments are designed to understand the first results presented here (only few examples of solvent dependent N_1/N_3 regiospecificity have been already described) [5a-c].

Nevertheless, we have already used the adduct 1 for the regiospecific synthesis of dienoic ester 2 [16].



1 2 56%

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2. The structure of"*carbanions*"α to an ester or a nitrile group can be:sp^3 charge localized carbanion which has been suggested to react under coulombic control or planar sp^2 enolate which is suspected to react under orbital controlled process. The presence of the electronegative chlorine atom in 1-chloro acetate or acetonitrile was suggested to favor the sp^3 structure but the presence of an extra stabilizing group (such as a phenyl) in such a molecule seems to favor the enolate structure.
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   b) 2-phenyl 2-lithio dithiane adds reversibly to cyclohexenones largely N_1 in hexane- THF at -78°C but substantial amounts of N_3 adduct are formed irreversibly in THF at -78°C or better at 20°C, P.C. Ostrowski and V.V. Kane, Tet. Lett., 3549 (1977)

   c) (1-lithio isobutyl) phenyl sulfide, prepared by C-Se bond cleavage in mixed 1-thiophenyl 1-selenophenyl 2-methyl propane adds regiospecifically N_1 (50%) in THF , (W.Dumont and A. Krief, results to be published)and N_3 in THF-HMPT, (T.M . Dolak and T.A. Bryson, Tet. Lett., 1961 (1977))
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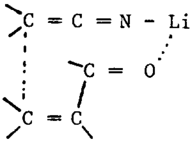
8.



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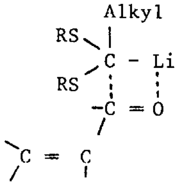

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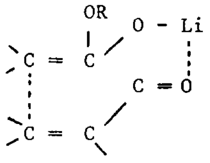

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9. a) Method A
α-selenoacetate (10^{-3} m) in THF (1 cc) is added to a lithiumdiisopropylamide (LDA) (10^{-3} m) solution in THF (1 cc) at -78°C and stirred for 1.5 hr at this temperature. Cyclohexenone (10^{-3} m) in THF (1 cc) is then added dropwise and the resulting solution stirred for 6 hrs at this temperature. Hydrolysis at -78°C is followed by usual work up. All the yields are given for purified products (PLC, ether-pentane : 3:7, rf : 0.4 (N_1) (two stereoisomers); rf : 0.2 (N_3)).

b) Method B
α-selenoacetate (10^{-3} m) in THF (1 cc) is added to a LDA (10^{-3}m) solution in THF (1 cc at -78°C and stirred for 1.5 hr at this temperature. HMPT (1 cc) is then added (at -78°C) followed by cyclohexenone (10^{-3} m) in THF (1 cc) and the resulting solution is stirred for 6 hrs at this temperature. Hydrolysis at -78°C is followed by usual work u

c) Method C
α-selenoacetate (10^{-3} m) in THF (1 cc) is added to a LDA (10^{-3} m) solution in THF (1 cc) at -78°C and stirred for 1.5 hr at this temperature. HMPT is added prior to the heating of the solution at -45°C. Cyclohexenone (10^{-3} m) in THF is added at this temperature and the resulting solution is stirred at -45°C for 6 hrs prior to hydrolysis at this temperature.

10. a) Cyclohexenone is added to the preformed methyl 1-lithio 1-selenophenyl acetate at -78°C After 1 hr : half of the solution is removed and hydrolysed at this temperature leading to 71% reaction (N_1/N_3 : 95/5). HMPT (1 cc per 10^{-3} m of product) is added to the other half and the temperature is raised to -45°C; hydrolysis was performed after 4.5 hrs. We have 70% yield (N_1/N_3 : 5/95)

b) Same kind of reaction except that half of the reaction is heated at 25°C for one hour before hydrolysis (yield, 72%, N_1/N_3 : 5/95).

11. By calculation [12] in gas phase it was suggested that selenyl moieties better stabilize an α-carbanion than the corresponding sulfur analog. However, several experimental result in different solvents THF [13,14], DMSO [15], lead to reverse observations.

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This work will be included in the Ph.D. Thesis of J. Lucchetti.