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# A NEW SYNTHETIC METHOD USING THIAZOLINE DERIVATIVE

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Reactions involving carbon-carbon bond formation are considered to be one of the main objectives in the field of synthetic organic chemistry. This article describes approaches of a new methodology based on thiazoline derivatives to iodomethylation ($-CH_2I$) and *trans*-iodopropenylation ($-CH=CH-CH_2I$) of alkyl halides, synthesis of heterocyclic compounds, and syntheses of natural products squalene and piperovatine.

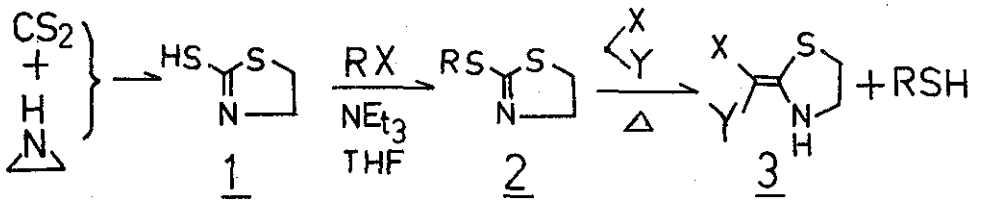
Recently, rapid developments in the field of organic synthesis as well as in theoretical concepts and machine technology have made it possible to synthesize many complicated and strained compounds which were not before imaginable. Besides these pioneering experiments many attempts were made to improve the known methods, and many convenient and versatile reactions have been found. Carbon-carbon bond formation reactions are one of the main objectives in the field of synthetic organic chemistry and the authors attempted to devise improved methods for the elongation of carbon chains, and succeeded in this objective by using thiazoline derivatives. These derivatives could be employed for several other synthetic processes, *e.g.* syntheses of squalene and piperovatine, episulfide formation, and also syntheses of several heterocyclic compounds.

## I. Reaction with Active Methylene Compounds[1]

2-Mercapto-2-thiazoline (1), mp 105°C, is easily prepared from carbon

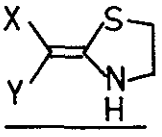
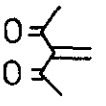
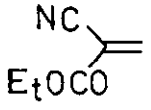
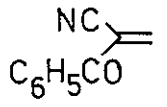
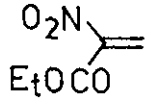
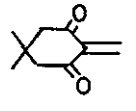
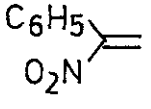
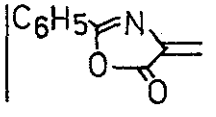
disulfide and ethyleneimine,[2] and is also commercially available. S-Alkyl derivatives (2) are easily prepared by heating 1 with alkyl halides and one equivalent of triethylamine in tetrahydrofuran. Literature describes these derivatives as useful for vulcanization and as insecticides.[3]

Fig.1



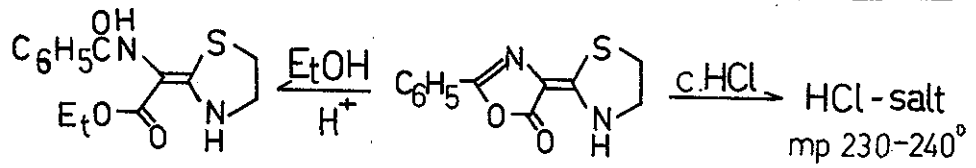

Compound (2) was reacted with active methylene compounds ($<^{X}_{Y}$) to afford thiazolidine derivatives(3) and alkyl sulfide in high yield via an addition-elimination mechanism.[4] Representative thiazolidine derivatives thus obtained are shown in Table 1. The derivatives (3) showed a characteristic $A_2B_2$-type signal ($-S\underline{CH_2}-\underline{CH_2}N-$) in the nmr spectrum ( $\delta$ ) and strongly hydrogen-bonded NH absorption ( 3150 $cm^{-1}$) in the ir spectrum.

Table 1

|  | $A_2$ | $B_2$ |  | 3.92 | 3.05 |
|---|---|---|---|---|---|
|  | 4.05 | 3.40 |  | 4.10 | 3.36 |
|  | 4.10 | 3.25 |  | 3.95 | 3.16 |
|  | 4.10 | 3.25 |  | 3.90 | 3.55 |

The double bond of the thiazolidine derivative (3) (ketene-acetal !) could not be reduced and under drastic conditions 3 decomposed. But in the study of the activity of the double bond of 3, interesting reactions were found. First the azlactone ring of 3g was easily opened by refluxing in ethanol in the presence of a catalytic amount of p-toluenesulfonic acid to give compound (4), mp 180°C.

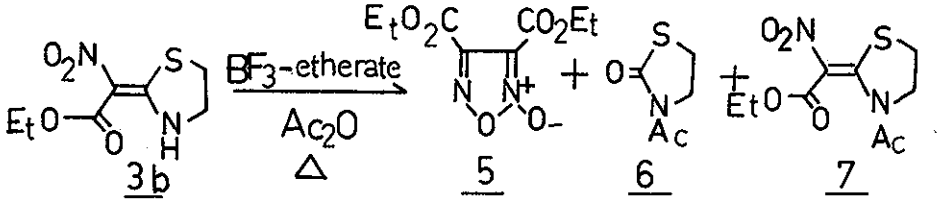
Fig. 2




4 3g

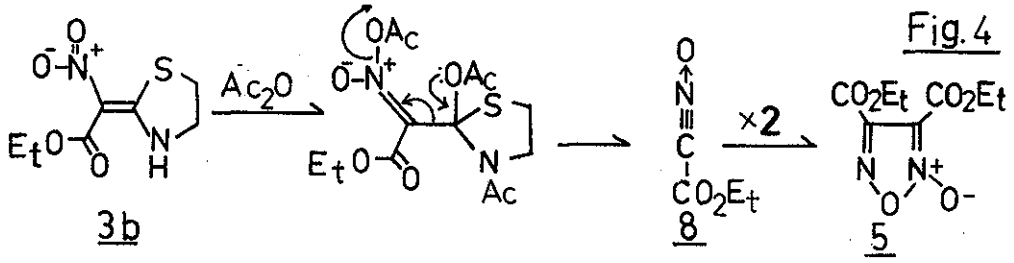
When 3b was heated with boron trifluoride etherate in acetic anhydride, dicarboethoxyfuroxane (5), ir: 1752 $cm^{-1}$, N-acetylthiazolidine-2-one (6) and the N-acetyl derivative of 3b (7) were obtained (Fig.3).

Fig. 3



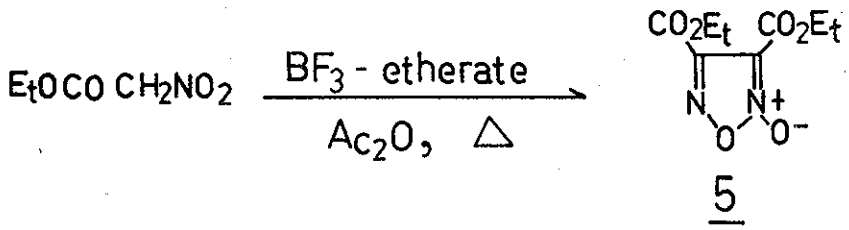

A plausible mechanism for the formation of furoxane derivative (5) is thought to be by dimerization of the nitrile-N-oxide (8) formed by the attack of acetylium cation on the nitro group in 3b as depicted in Fig.4.

Fig. 4



It was deduced from this reaction mechanism that ethyl nitroacetate itself should give the same furoxane derivative (5), and in fact 5 was obtained from ethyl nitroacetate in 60 % yield (Fig.5).

Fig.5

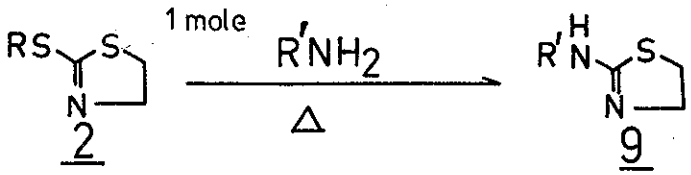



5

II. Reaction with Amines and Amino Acids

S-Alkylthiothiazolines (2) were reacted with amines to give 2-amino-thiothiazoline derivatives (9) as shown in Table 2, and with a 2-azetidinone derivative ( β-lactam ) to give thiazolopyrimidine derivative (10) (Fig.6).[5] Furthermore, amino acids like anthranilic acid (and its ester)

Table 2




2 9

| R | RNH2 | MP(°C) | Yield(%) |
|---|---|---|---|
| H | $C_6H_5NH_2$ | 164 | 27 |
| $CH_3$ | 2-$CH_3$,5-Br$C_6H_3NH_2$ | 142 | 21 |
| Et | $C_6H_5NH_2$ | 164 | 57 |
| Et | p-Cl$C_6H_4NH_2$ | 162 | 52 |
| Et | cyclo-$C_6H_{11}NH_2$ | 165 | 47 |
| Et | $C_6H_5SO_2NH_2$ | 148 | 61 |

gave thiazoloquinazoline derivative (11), mp 157°C, X=H in 70-80 % yield by only heating these two reagents at 150°C for 3-5 h (Fig. 7).

Fig.6

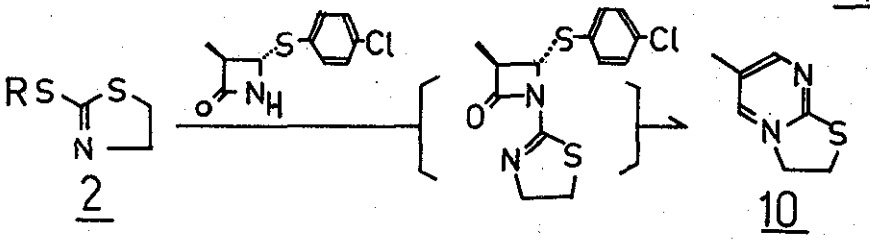
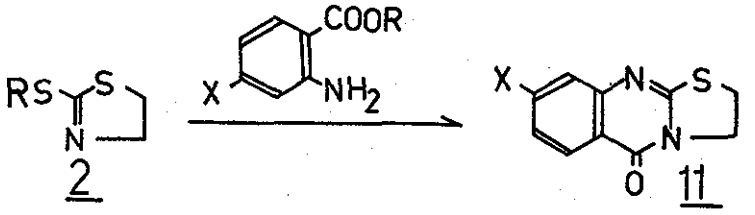


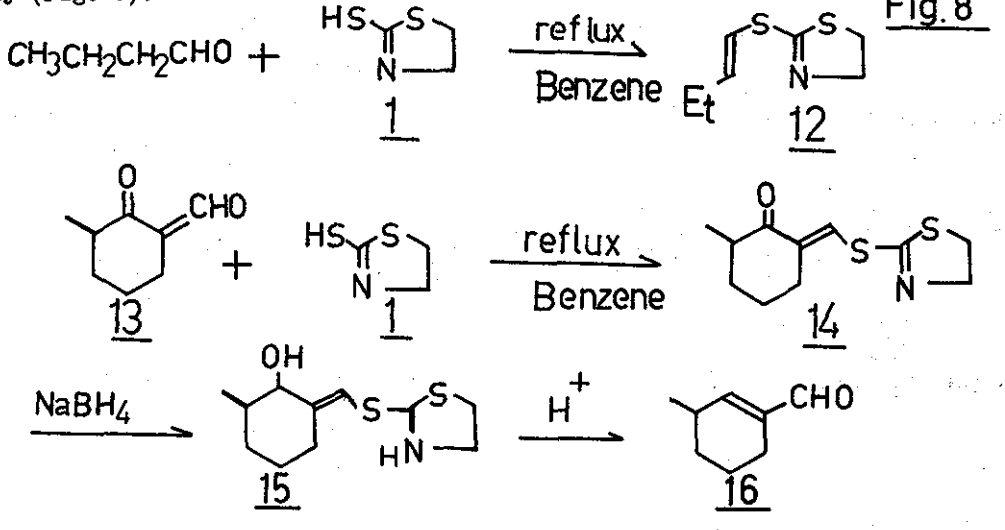
Fig.7



III. Reaction with Aldehydes

2-Mercaptothiazoline (1) was reacted with aldehydes such as butylaldehyde and 13 to give the corresponding vinyl sulfides 12 and 14. In the case of 14 the ketone function was readily reduced to give the corresponding carbinol (15), which was treated with 5 % aq. hydrochloric acid solution in methanol to afford the α,β-unsaturated aldehyde (16) spontaneously (Fig. 8).

Fig.8

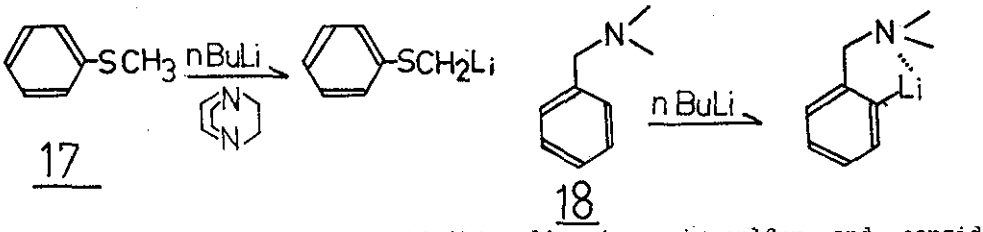


IV. Alkylation Reactions[6]

1). Monoalkylation Reaction

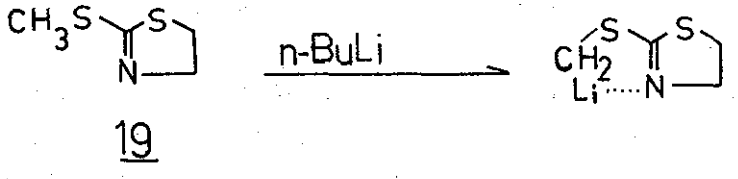
It is well known that thioanisole (17) is converted into its lithium derivative by n-butyllithium/1,4-diazabicyclo[2.2.2]octane,[7] and N,N-dimethylbenzylamine (18) is lithiated specifically at the ortho position ( Fig. 9).[8]

Fig.9



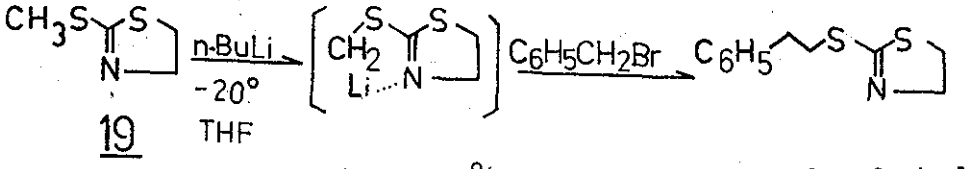

The methyl group of methylthiothiazoline is α- to sulfur, and, considering the above phenomena, the lithiated derivative should be stabilised by a 5-membered chelation effect including the thiazoline nitrogen atom ( Fig. 10).

Fig.10



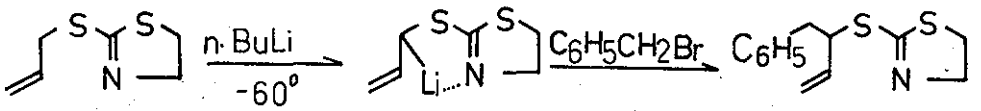

Initially methylthiothiazoline (19) was treated with one equivalent of n-butyllithium in tetrahydrofuran at -20°C, and then addition of benzyl bromide gave phenethylthiothiazoline in 80 % isolated yield (Fig.11). Further when the same reaction was performed using allylthiothiazoline (20)

Fig.11




in tetrahydrofuran(10 % W/V) at -60°C the lithiation occurred exclusively

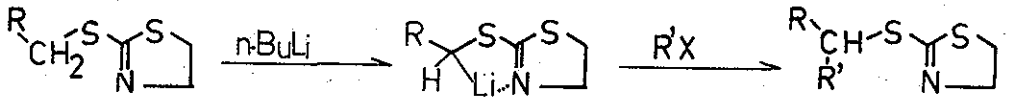
Fig.12




20 21

at the α-position with respect to the sulfur atom (Fig.12). This phenomenon was considered to be due to the strong chelation effect as pointed out before, and the alkylation occurred at that position. Representative examples are shown in Table 3.

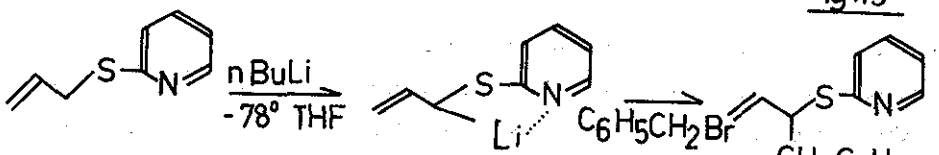
Table 3




| R | R'X | Yield(%) (isolated) | R | R'X | Yield(%) |
|---|---|---|---|---|---|
| H | $CH_3I$ | 75 | $-CH=CH_2$ | $CH_3I$ | 68 |
| H | nBuBr | 70 | $-CH=CH_2$ | $CH_2=CHCH_2Br$ | 60 |
| H | $CH_2=CHCH_2Br$ | 67 | $-CH=CH_2$ | $C_6H_5CH_2Br$ | 78 |
| $C_6H_5$ | $C_6H_5CH_2Br$ | 71 | $-CH=CHC_6H_5$ | $C_6H_5CH_2Br$ | 68 |

This chelation effect was also pointed out independently by Mukaiyama et al in the case of alkylation of 2-pyridyl allyl sulfide (22) (Fig.13).[9]

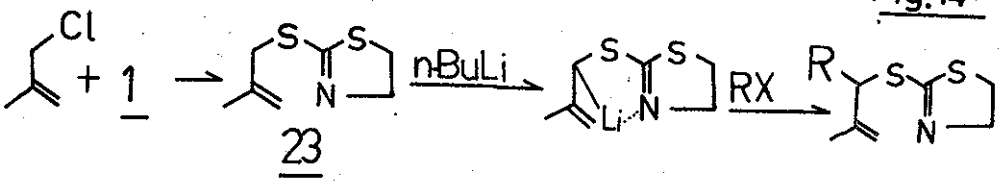
Fig.13




22

In the case of β-methallylthiothiazoline (23) alkylation also occurred exclusively at the α-position under the same reaction conditions (Fig.14).

Fig.14

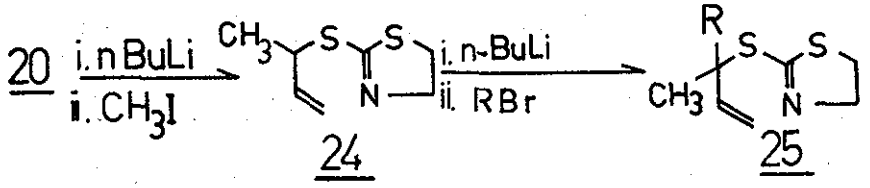


RX : $C_6H_5CH_2Br$ 65%, n-$C_3H_7Br$ 63%, n-$C_{10}H_{21}Br$ 70%

2). Dialkylation

When the above mentioned alkylation was performed twice, different alkyl groups could be introduced into the allylthiothiazoline (21). Thus compound 24 was lithiated with n-butyllithium in tetrahydrofuran and hexamethylphosphortriamide (20:1) at -60°C and then addition of alkyl bromide to this solution gave the dialkylated product (25) as shown in Fig.15.

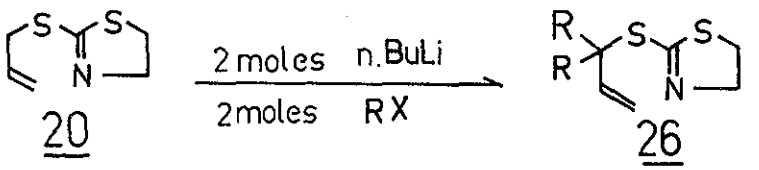
Fig.15



| RBr | Yield % |
|---|---|
| $C_2H_5Br$ | 42 |
| n-$C_{10}H_{21}Br$ | 56 |
| $C_6H_5CH_2Br$ | 40 |

If the alkylation was attempted using two mole equivalents of n-butyllithium and alkyl halide at -60°C in tetrahydrofuran, dialkylation occurred at the α-position to give the dialkylated product (26) in about 40 % yield (Fig.16).

Fig.16

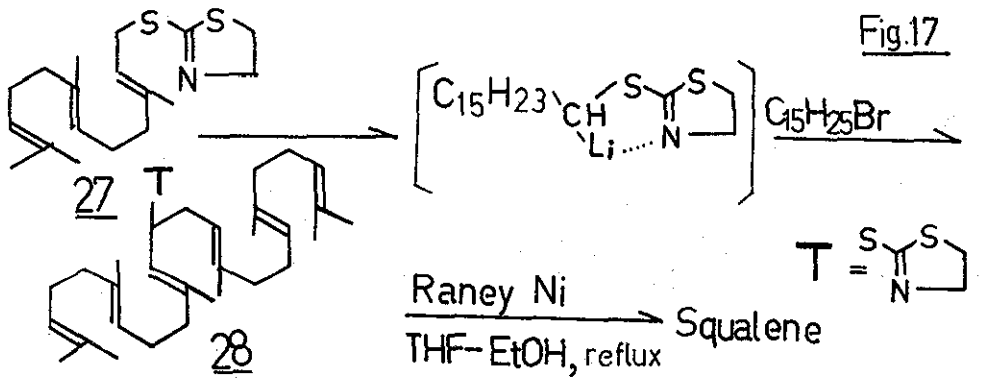



RX : EtBr 40%, nPrBr 35%

V. Application to the Synthesis of Squalene[6]

This regiospecific alkylation reaction was applied to the synthesis of squalene. Farnesylthiothiazoline (27) was lithiated in the usual way, and to this was added farnesyl bromide to afford squalene derivative (28) in 45 % yield. The squalene derivative thus obtained was easily desulfurized by Raney nickel to give squalene in 80 % yield (Fig. 17).

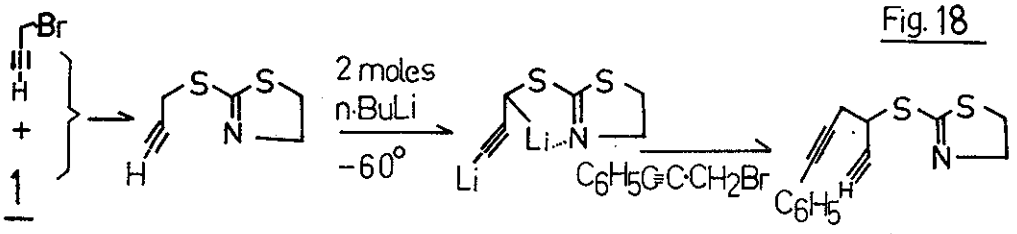
Fig.17




VI. Application to Acetylenic Compounds[10]

Propargylthiothiazoline (29) was easily prepared from propargyl bromide and mercaptothiothiazoline (1). Compound (29) was treated with two equivalents of n-butyllithium at -60°C in tetrahydrofuran to give a white precipitate of the di-lithium salt (30). To this salt was added phenylpropargyl bromide to give the product (31) in 70 % yield, which was derived from alkynylation at the α-position with respect to the sulfur atom.

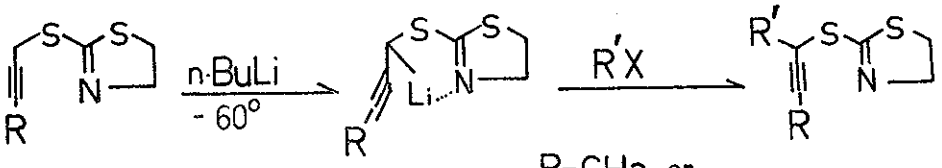
Fig. 18




29 30 31

This is a general method for the formation of 1,5-diyne derivatives, and some examples are shown in Table 4. The carbanion which was generated between the sulfur atom and the triple bond was fixed and thus gave no

Table 4




R=$CH_3$ or

R = H (nBuLi : two equivalent) $C_6H_5$ (nBuLi : one eq.)

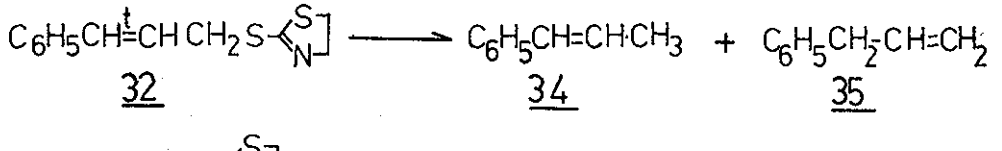
| R | R'X | Yield (isolated) | R | R'X | Yield |
|---|---|---|---|---|---|
| a. H | $C_6H_5C{\equiv}CCH_2Br$ | 60% | f. $CH_3$ | $C_6H_5CH_2Br$ | 48 % |
| b. H | $HC{\equiv}CCH_2Br$ | 50 | g. $CH_3$ | $C_6H_5C{\equiv}CCH_2Br$ | 48 |
| c. H | $C_6H_5C{=}CCH_2Br$ | 50 | h. $C_6H_5$ | $HC{\equiv}CCH_2Br$ | 45 |
| d. H | $CH_3I$ | 60 | i. $C_6H_5$ | $C_6H_5CH_2Br$ | 50 |
| e. H | $C_6H_5CH_2Br$ | 65 | j $C_6H_5$ | $C_6H_5C{=}CCH_2Br$ | 48 |

allenic type compound. This is also due to the strong 5-membered chelation effect as shown in the case of allylthiothiazoline (20).

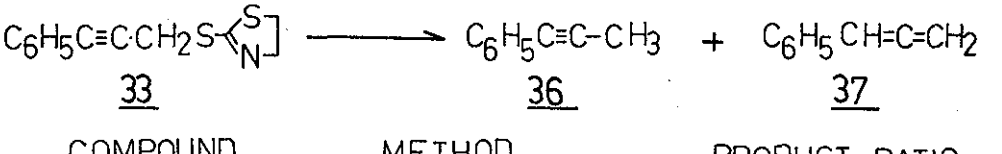
VII. Desulfurisation Reactions[10]

It is necessary to desulfurise the alkylated thiazoline derivative to isolate the hydrocarbon part. For this purpose, in model experiments several methods were checked with compounds 32 and 33, and it was found that Raney nickel ( refluxing in ethanol), zinc, aluminum, and aluminum amalgam were all effective for this purpose. The results are shown in Table 5.

Table 5



32 → 34 + 35

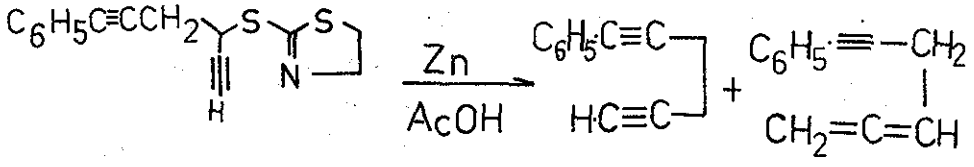


33 → 36 + 37

| COMPOUND | METHOD | PRODUCT RATIO |
|---|---|---|
| 32 | Zn in AcOH at r.t. | 34 : 35 = 78 : 22 |
| 32 | Al-Hg in 10% aq. THF at r.t. | 34 : 35 = 42 : 58 |
| 32 | Raney Ni in refluxing EtOH | 34 > 95 % |
| 33 | Zn in AcOH at r.t. | 36 : 37 = 72 : 28 |
| 33 | Al in AcOH at 100° | 36 : 37 = 73 : 27 |
| 33 | Al-Hg in 10% aq. THF at r.t. | 36 : 37 = 42 : 58 |
| 33 | Raney Ni in refluxing EtOH | 36 : 37 = 86 : 14 |

Under zinc-acetic acid conditions ( room temperature for 1 h ) the 1,5-diyne derivative (31) was desulfurised quantitatively to give 38 and the allene (39) (1:8). These products were separated easily by silica gel chromatography. 38: ir, 3320, 2220, 2100, 1600 and 755 $cm^{-1}$. 39: ir, 2200, 1960, 1600, 850 and 755 $cm^{-1}$.

Fig. 19

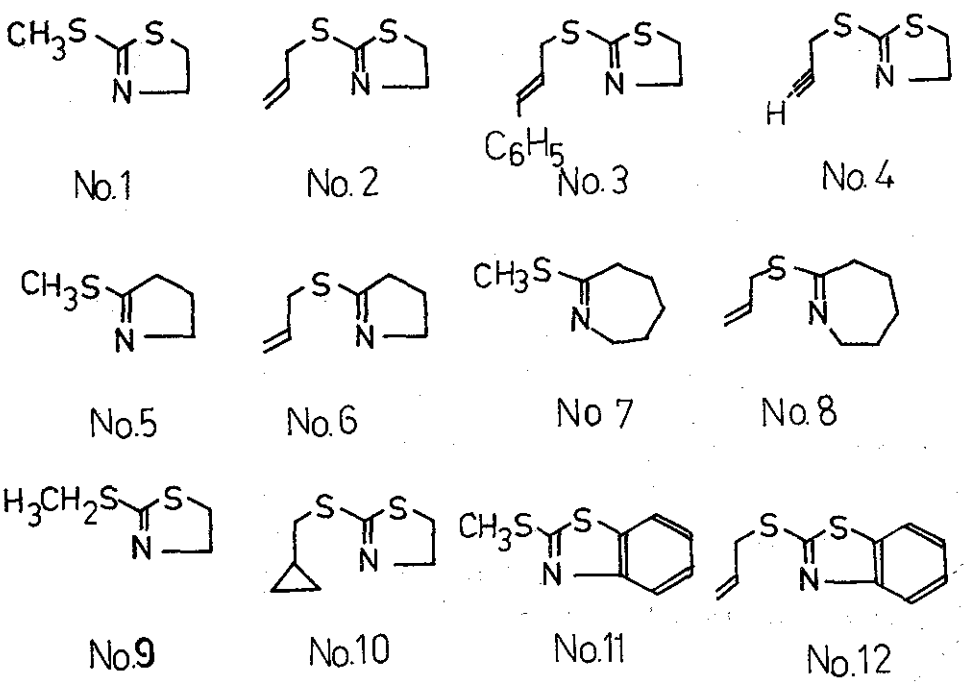



31 38 39

VIII. Limitation of the Alkylation

Several thiazoline derivatives and analogous compounds were checked in the alkylation reaction. Under the described reaction conditions ( n-butyllithium in tetrahydrofuran, -60°C) the compounds No. 1-4 were easily alkylated and those No. 5-8 not so easily ( probably because of the instability of the product). No. 9-12 could not be alkylated under these reaction conditions (Fig.20).

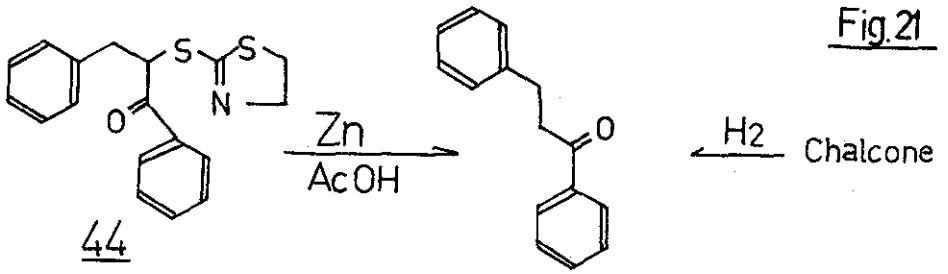
Fig. 20



## IX. Reactivity of α-Thiothiazolinoketones

α-Thiothiazolinoketones (41) are readily prepared by mixing 1 and α-haloketones and base treatment of the adduct. After being treated with sodium hydride in tetrahydrofuran-dimethylformamide these α-thiothiazolinoketones react with alkyl halides at room temperature to give keto-derivatives (42) when the alkyl halide is benzyl bromide or methyl iodide, and enol-derivative (43) when the alkyl halide is n-butyl bromide or n-amyl bromide under reflux as shown in Table 6 in the next page. The keto derivative (44) thus obtained was readily desulfurised quantitatively with zinc-acetic acid to give dihydrochalcone (Fig. 21).

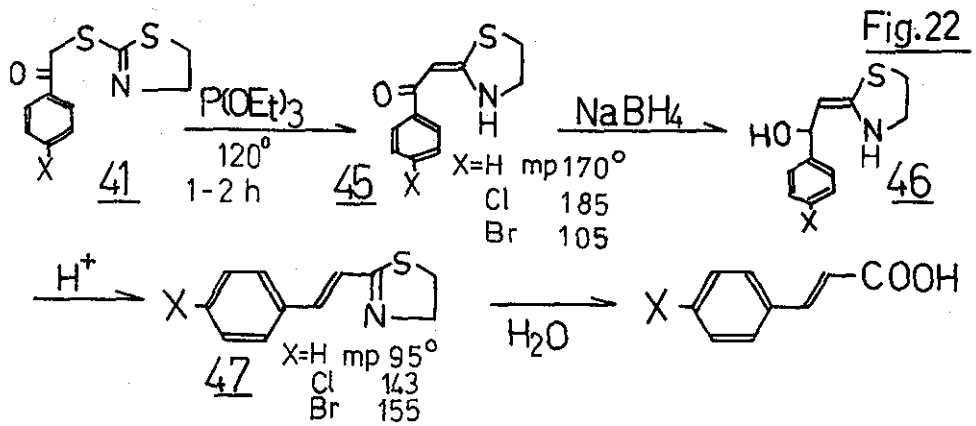
Fig.21




44

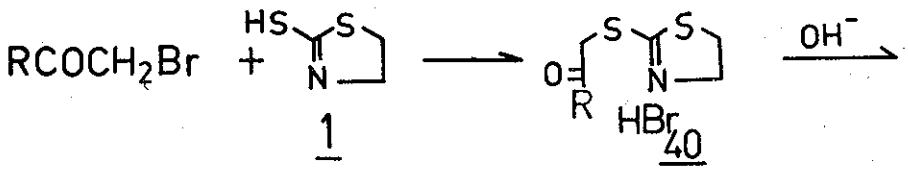
The sulfur atom in α-thiothiazolinoketones (41) was extruded in high yield by heating at 120°C for 1-2 h in triethylphosphite[11] to afford the corresponding thiazolidine derivative (45), which was further reduced by sodium borohydride to the corresponding carbinol(46); acid treatment of the carbinol gave the thiazoline derivative (47). Acid hydrolysis of these compounds (47) gave the corresponding cinnamic acids in low yield.

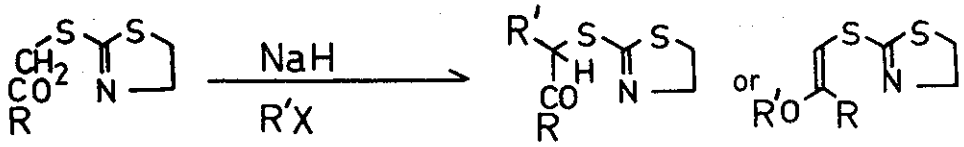
Fig.22




41 45 46 47

## Table 6

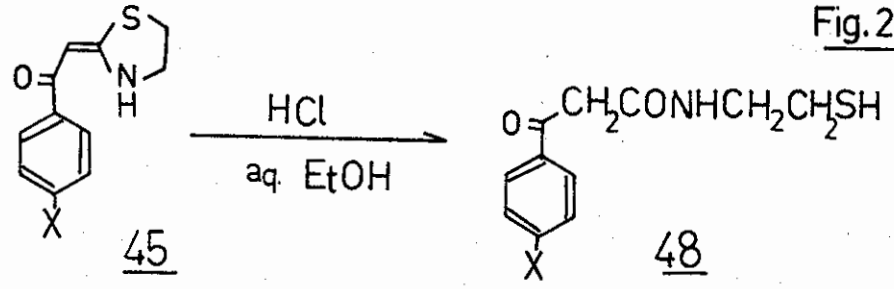




| R | R'X | 42(keto) Yield (%) | 43(enol) Yield (%) | |
|---|---|---|---|---|
| $C_6H_5$- | $CH_3I$ | 52 | — | r.t. |
| | p-$ClC_6H_4CH_2Br$ | 43 | — | r.t. |
| | $C_6H_5CH_2Br$ | 42.5 | — | r.t. |
| | n-BuBr | — | 30 | reflux |
| | n-AmBr | — | 25 | reflux |
| p-$ClC_6H_4$- | $C_6H_5CH_2Br$ | 51 | — | r.t. |
| | n-BuBr | — | 28 | reflux |
| $CH_3$- | $C_6H_5CH_2Br$ | 43 | — | r.t. |
| | $CH_3I$ (2 moles) | 45 (  ) | — | r.t. |
| EtO- | $C_6H_5CH_2Br$ | 52.5 | — | r.t. |
| | $CH_3I$ | 48 | — | r.t. |

However the sulfur-extruded products (45) were hydrolysed under the same reaction conditions to give the corresponding β-ketocarboxylic acid derivative (48) in about 50 % yield ( Fig. 23 ).

Fig. 23

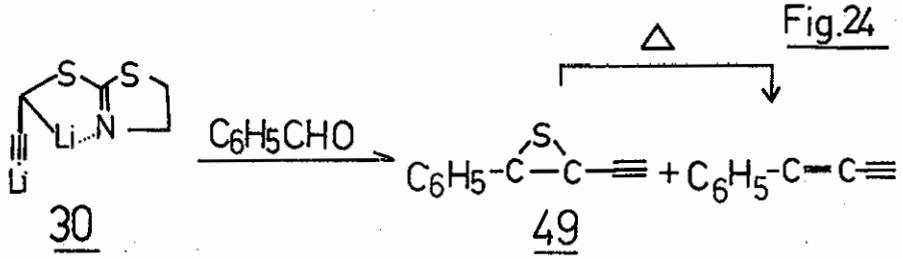



45 48

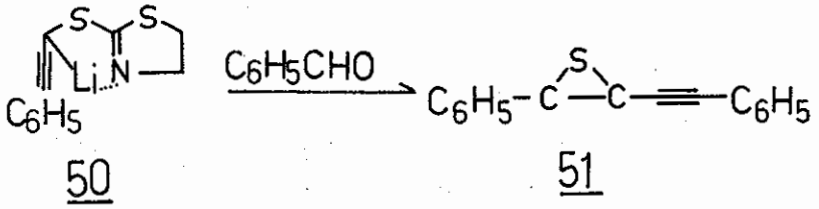
X. Synthesis of Episulfide Derivatives[12]

The dilithium salt (30) was reacted with benzaldehyde to afford the corresponding episulfide (49) in 20 % yield and in the case of the phenyl propargylthiothiazoline lithium (50) the product was the corresponding episulfide (51) ( Fig.24 ).

Fig. 24



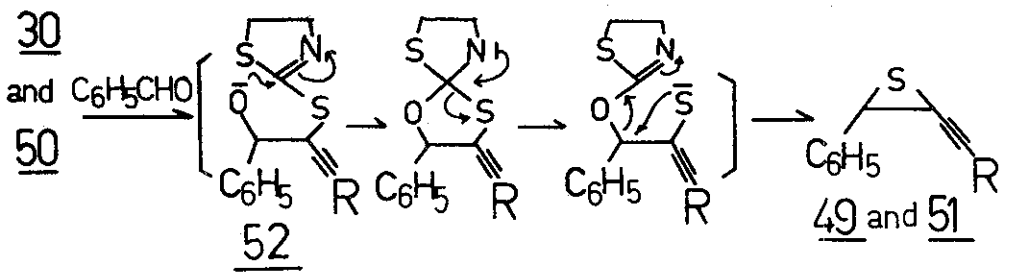

30 49




50 51

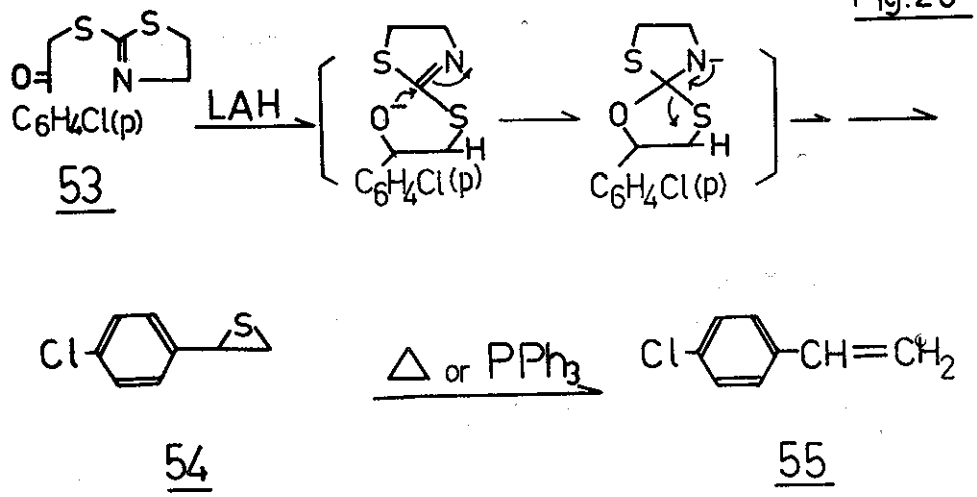
The proposed mechanism for the formation of these episulfides is depicted in Fig.25. The suggested intermediate carbinol anion (52) was alternatively generated by reduction of α-thiazolino-ketone (53) with

Fig.25




Lithium aluminum hydride and the product was kept standing in chloroform at room temperature to give the expected episulfide (54) in 60 % isolated yield. This episulfide gave the styrene derivative (55) by heating or triphenylphosphine treatment ( Fig. 26 ).

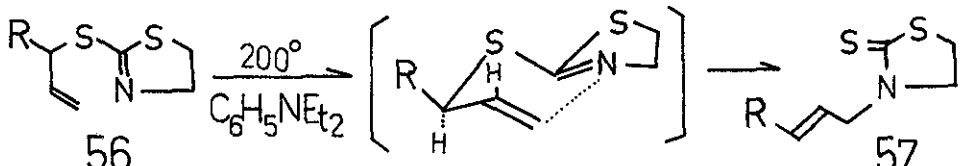
Fig.26




XI. Thermal Rearrangement

The alkylated thiazoline derivative (56) gave trans-2-thione derivative (57) by heating about 200°C in diethylaniline (i.e. 3,3-sigmatropic rearrangement )(Fig.27). In general the compounds such as 56 give a strong $\nu_{C=N}$ band at about 1570 $cm^{-1}$ in the ir spectrum, while the rearranged products (57) show a uv maximum at about 270 nm. From these characteristic data the structures were determined easily.

Fig.27

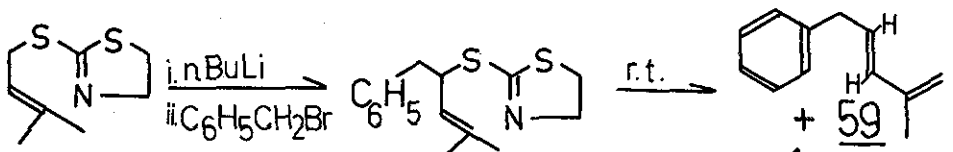



56 57

| | Yield | | |
|---|---|---|---|
| R=H | 95 % | $CH_2=CHCH_2$ | 85 % |
| $C_6H_5CH_2$ | 76 | $nC_4H_9$ | 72 |

The other example of the thermal rearrangement is shown in Fig. 28. The coupling constant between the two vinylic protons in 59 is 15.5 Hz.

Fig.28



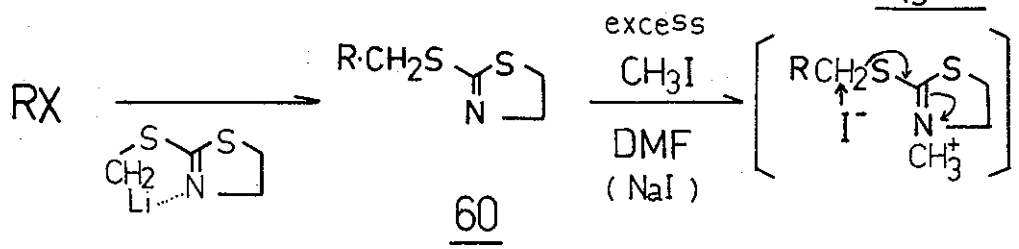

58 1 + 59

These thermal experiments show that for the purification of the alkylated product (56) it is necessary not to overheat it in order to avoid these sigmatropic rearrangement (i.e. distillation is not so good for the purification of alkylated product (56)).

XII. Iodomethylation and trans-Iodopropenylation Reactions[13]

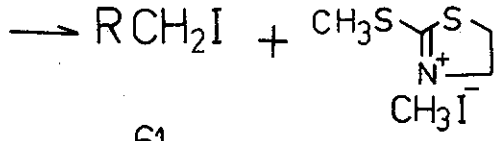
Compound (60) which is readily prepared from the alkyl halide and methylthiothiazoline lithium was treated with excess methyl iodide in dimethylformamide at room temperature, or methyl iodide in dimethylformamide in the presence of sodium iodide at room temperature overnight, or by heating at 70–80°C for 1–2 h[14] to give one-carbon homologue (61) as shown in Fig.29 (Iodomethylation). In the case of allylic derivatives (Fig.30) allylic rearrangement occurred and three-carbon elongated trans-allyl iodide derivatives (63) were obtained in 70–80 % yield (trans-Iodopropenylation).

Fig 29




60

Yield (60→62)

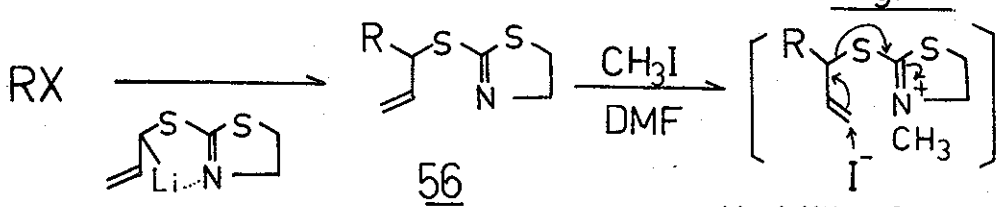



| | |
|---|---|
| R = $C_6H_5$ | 82 % |
| $C_6H_5CH_2$ | 75 |
| n·$C_9H_{19}$ | 68 |

61 62

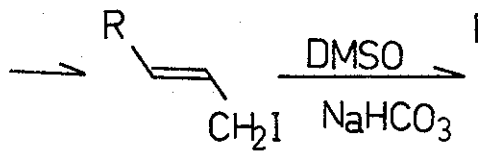
In both reactions N-methylthiazoline-2-thione was formed as by-product but this forms a crystalline methiodide salt (62), mp 130°C, which precipitates in the reaction mixture. Thus the formation of this salt be-

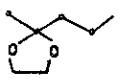
Fig.30




56

Yield(56→63) %



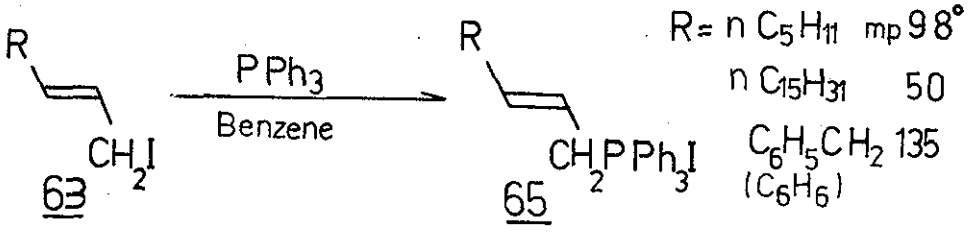

| | |
|---|---|
| R = $C_6H_5CH_2$ | 65.8 |
| n$C_{10}H_{21}$ | 72 |
| $C_6H_5CH_2CH_2$ | 70 |
|  | 76 |
|  | 72 |

63 64

comes an indicator of the reaction progress, and when the reaction was complete the products (61 and 63) were extracted with ether and merely washing the organic layer with water ( and also with 1 % aq. sodium thiosulfate solution ) gave almost pure samples of iodomethylated (61) or trans-iodopropenylated (63) product ( if necessary preparative silica gel thin layer chromatography is effective for the purification of the products, 61 and 63, solvent system : n-hexane ).

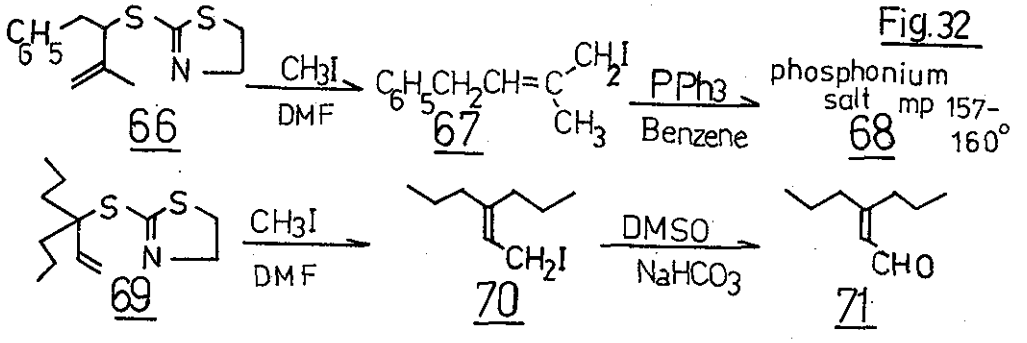
Compound 63 thus obtained was easily converted into the corresponding trans α,β-unsaturated aldehyde by the Kornblum reaction ( dimethyl sulfoxide/ sodium bicarbonate, 130-140°C, 3-5 min)[15] as shown in Fig. 30, or could be treated with triphenylphosphine to afford the triphenylphosphonium salt (65) which is useful for the Wittig reaction (Fig. 31).

Fig. 31




In the case of 66 and 69 the same type of allylic rearrangement reaction occurred to give the corresponding products such as 67 and 70, but the product (67) was a mixture of two isomers (cis- and trans-). The compounds 67 and 70 were easily converted to the phosphonium salts (68) and the corresponding α,β-unsaturated aldehyde (71) under Kornblum reaction conditions.

Fig. 32

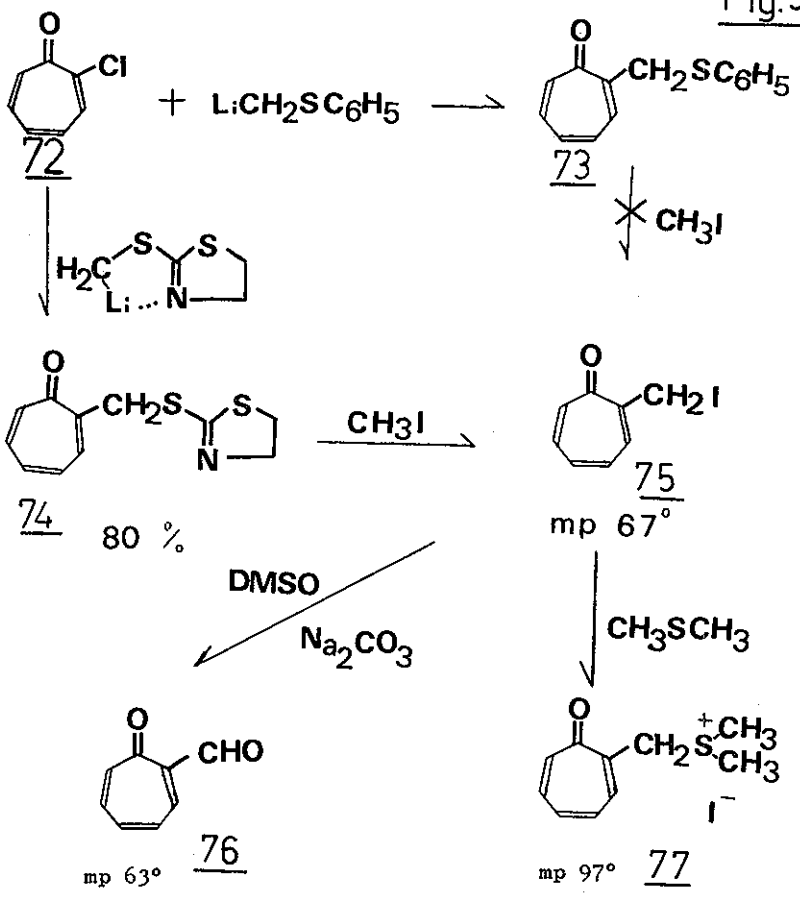


XIII. Applications of the Iodomethylation and trans-Iodopropenylation Reaction

1). Synthesis of 2-Iodomethyltropone[16]

Y. Sugimura applied the iodomethylation reaction to chlorotropone (72) and obtained thiazolinothiomethyltropone (74) in 80 % yield. Iodomethyltropone (75) was obtained by treating 74 with methyl iodide in dimethylformamide. Iodomethyltropone (75) thus obtained gave formyltropone (76) by the Kornblum reaction and sulfonium salt (77) by treating with dimethyl sulfide (Fig.33).

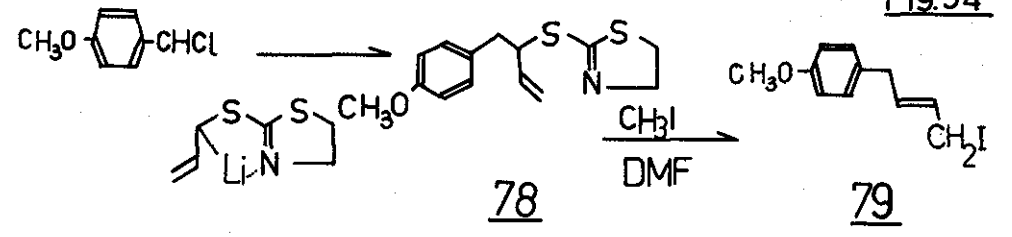
Fig.33

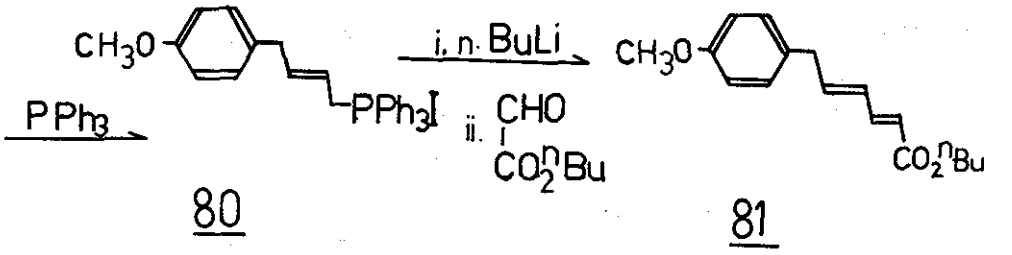


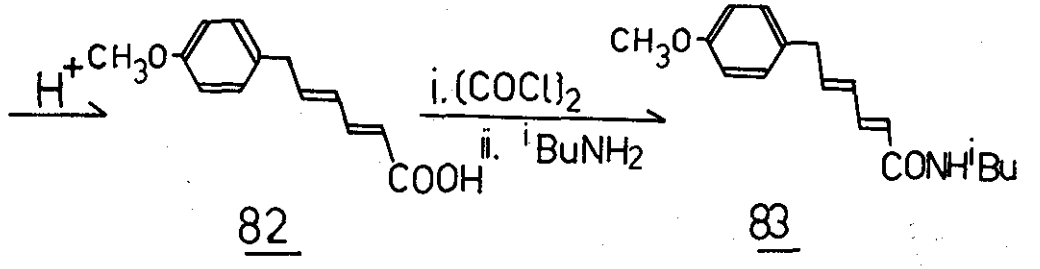
2). Synthesis of Piperovatine[17]

Piperovatine (83) is an ingredient of Piper ovatum and is reported to be active as a temporary nerve depressant. This material was synthesized using the trans-iodopropenylation reaction (Fig.34). The thiazoline derivative (78) was obtained from p-methoxybenzyl chloride and the allylthiothiazoline lithium derivative in 75 % yield in the usual way, and then treated with methyl iodide in dimethylformamide to give the expected trans-iodopropenylated product (79). This product was treated in benzene with one equivalent of triphenylphosphine to afford the crystalline triphenylphosphonium salt (80), mp 123-127°C. The ylid which is generated by treat-

Fig.34



ing this phosphonium salt with n-butyllithium in tetrahydrofuran was reacted with n-butyl glyoxalate to give α,β,γ,δ-unsaturated carboxylate (cis : trans =1:1) quantitatively. The mixture was separated easily by silica gel chromatography, and the trans-isomer (81), $\lambda_{max}$ 264 nm was hydrolyzed under acidic conditions to give α,β,γ,δ -unsaturated acid (82) mp 116°C. This acid is known and by the usual method, chlorination by oxalyl chloride and then isobutylamine treatment it was already transformed into piperovatine (83)[18].

XIV. Miscellaneous

2-Mercaptothiazoline was reacted with methylene iodide or methylene bromide in tetrahydrofuran in the presence of triethylamine at 88°C ( bath temperature) to give 1,3-dithiane derivative (84), mp 46°C. If the reaction temperature is relatively high and reaction time is long the product is 1,3-diaza compound (85), mp 162°C, which is also obtained from 84 by heating about 100°C for more than five hours. This 1,3-dithiane derivative ( 84) was reacted with alkyl halide after treating it with n-butyllithium to give the expected alkylated product (86). The utility of the reagent 84 is now under investigation. On the other hand the reaction product of 1 with methoxymethyl chloride was the N-methoxymethylated product (87), mp 33°C (Fig.36).

Fig.35

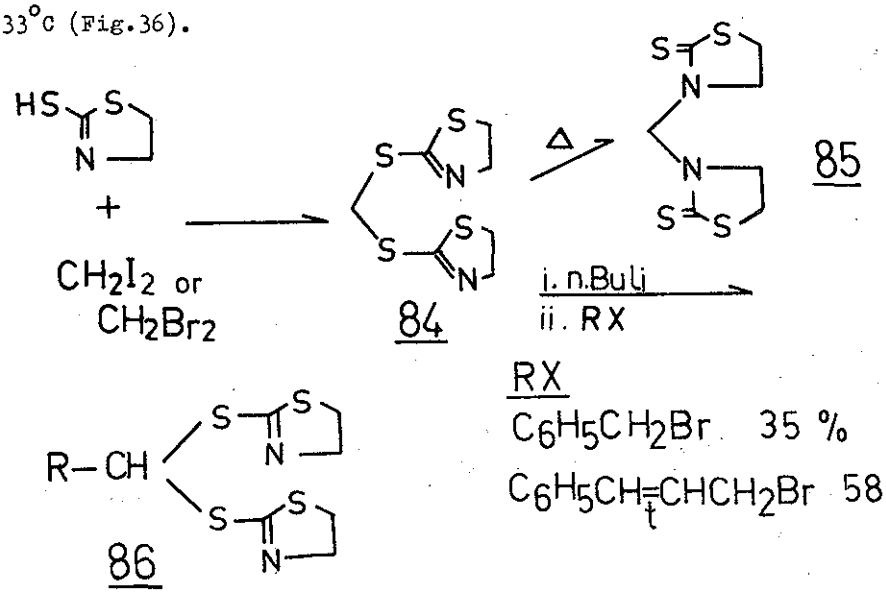
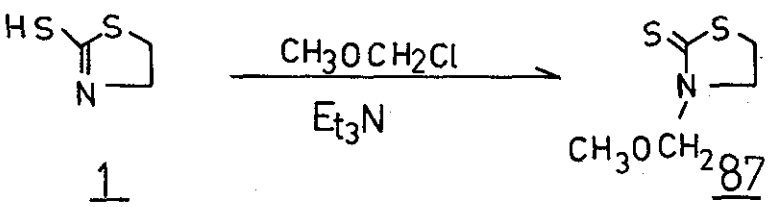


Fig.36




1 87

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REFERENCES

1 K. Hirai, H. Matsuda, and Y. Kishida, Chem. Pharm. Bull.(Tokyo), 1972, 20, 97.

2 S. Fruton in Elderfield's "Heterocyclic Compounds," I, 1950, p.61.

3 For example: C.A. 36, 1808[2]; 45, 810[c]; 47, 1698[h].

4 T. Nakai and M. Okawara, Bull. Chem. Soc. Japan, 1970, 43, 3528.

5 K. Hirai, H. Matsuda, and Y. Kishida, Chem. Pharm. Bull.(Tokyo), 1973, 21, 1305.

6 K. Hirai, H. Matsuda, and Y. Kishida, Tetrahedron Letters, 1971, 4359.

7 E.J. Corey and D. Seebach, J. Org. Chem., 1966, 31, 4097.

8 F. N. Jones, M. F. Zinn, and C.R. Hauser, J. Org. Chem., 1963, 28, 663.

9 T. Mukaiyama, K. Narasaka, K. Maekawa, and M. Furusato, Bull. Chem. Soc. Japan, 1971, 44, 2285.

10 K. Hirai and Y. Kishida, Tetrahedron Letters, 1972, 2117.

11 M. Roth, P. Dubs, E. Götschi, and A. Eschenmoser, Helv. Chim. Acta, 1971, 54, 710.

12 K. Hirai, H. Matsuda, and Y. Kishida, Chem. Pharm. Bull. (Tokyo), 1972, 20, 2067.

13 K. Hirai and Y. Kishida, Tetrahedron Letters, 1972, 2743.

14 E.J. Corey and M. Jautelat, Tetrahedron Letters, 1968, 5787.

15 A.P. Johnson and A. Pelter, J. Chem. Soc., 1964, 520.

16 Y. Sugimura, private communication.

17 K. Hirai and Y. Kishida, The 93rd Annual Meeting of Pharmaceutical Society of Japan, 1973 (Tokyo). Abst. II, p.100.

18 S.J. Price and A.R. Pinder, J. Org. Chem., 1970, 35, 2568

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