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A NEW SYNTHETIC METHOD USING THIAZOLINE DERIVATIVE. VI.[1)]
C_2-UNIT ELONGATION REACTIONS : ALKOXYCARBONYLMETHYLATION ($-CH_2CO_2R$) AND ALKOXYCARBONYLIODOMETHYLATION ($-CHICO_2R$) REACTIONS

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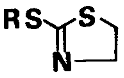
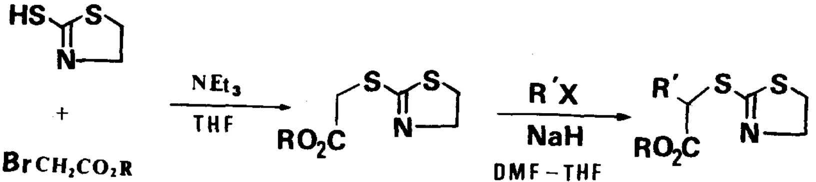
In the course of our study on the synthetic utility of thiazoline derivatives (Ia,b) we have found the iodomethylation ($RX \longrightarrow RCH_2I$: C_1-unit elongation) and the iodopropenylation reactions ($RX \longrightarrow RCH\overset{t}{=}CH\text{-}CH_2I$: C_3-unit elongation) of an alkyl halide using these derivatives (Ia,b)[2)]. With the above success in hand we considered it relevant to explore the C_2-unit elongation (alkoxycarbonylmethylation : $-CH_2CO_2R$ and alkoxycarbonyliodomethylation : $-CHICO_2R$) of an alkyl halide using another type of thiazoline derivatives such as alkoxycarbonylmethylthiothiazolines (IIa,b).

The reagents IIa,b were easily prepared from alkyl bromoacetate and 2-mercaptothiazoline in the presence of one equivalent of NEt_3 in THF (IIb : bp 150-1°/ 6 mm). Using IIa,b and alkyl halide (RX, 1.1 eq.) the alkylation reaction was performed successfully at r.t. with NaH (1 eq.) in DMF : THF (1:1) solution [Procedure <u>A</u>]. The representative examples are shown in Table 1.



I a : R = CH_3
b : R = $CH_2CH{=}CH_2$



II a,b **III a,b**

a : R = CH_3 **b** : R = Et

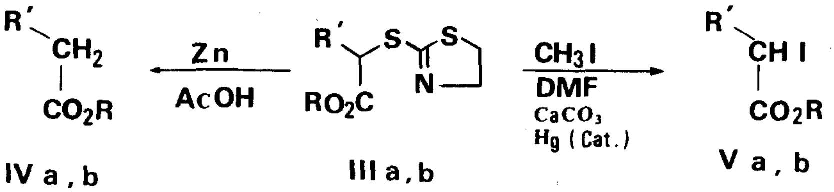
Table 1. Isolated Yield of III, IV and V (a : R = CH_3, b : R = Et)

II	R'X	III	(III→) IV	(III→) V
a.	CH_3I	a. 48 %[3]	a. 78 %	a. 52 %
b.	$C_6H_5CH_2Br$	b. 68.2	b. 83	b. 75.2
b.	$CH_2{=}CHCH_2Br$	b. 68 [3]	b. 72	
b.	$n\text{-}C_4H_9Br$	b. 61.2	b. 75	b. 68
b.	$n\text{-}C_{10}H_{21}Br$	b. 34	b. 68.5	b. 72

IIb → Vb (R=H) : 85 %

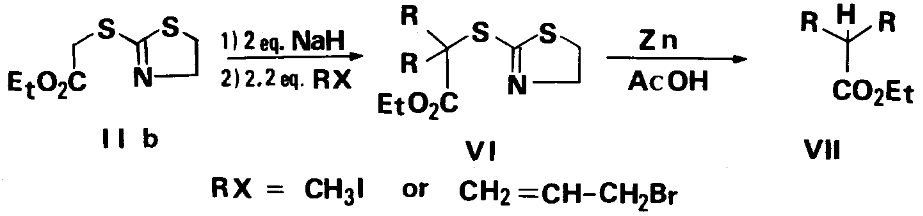
Next step is how to remove or exchange the thiothiazoline part. Fortunately this part is efficiently removed by Zn in acetic acid at r.t. for one hour to give the desired alkoxycarbonylmethylated products (IV) [Procedure B]. The representative examples are also summarized in Table 1.

Furthermore the thiothiazoline part was exchanged by iodine atom under essentially the same conditions as in the iodomethylation or iodopropenylation reaction[2),4)] (excess CH_3I in DMF, in the presence of $CaCO_3$ and Hg (cat.) at 70-75° for 5 hours) [Procedure C]. These alkoxycarbonyliodomethylated products are thought to be important as the starting materials for the Wittig type of reactions, and easily dehydroiodinated to afford the corresponding α,β-unsaturated carboxylate (See Procedure C).

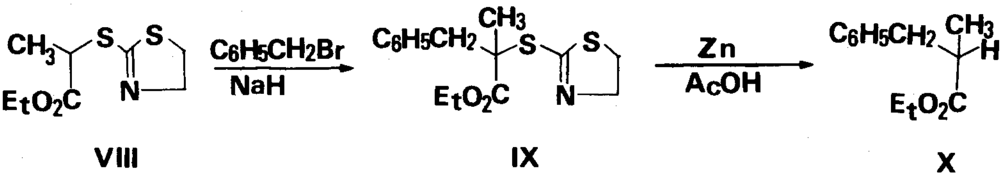


a : R = CH_3 b : R = Et

It is noteworthy that dialkylation was easily achieved when an active halide such as allyl bromide or methyl iodide was used in 2.2 equivalent amount in the presence of 2 eq. NaH in DMF : THF (1 : 1) at r.t. for 2 hours. Yield of VII : 68 % (RX = CH_3I), 72 % (RX = $CH_2{=}CHCH_2Br$).



Using VIII (= IIIb, R'= CH_3), which was alternatively prepared from ethyl α-bromopropionate and 2-mercaptothiazoline, benzylation was achieved to give IX under the same conditions of the procedure A in 72 % yield and the product (IX) was easily desulfurized to afford α-methyl-β-phenyl propionate X.



The following procedures are representative ------ A]. To a solution of 615 mg (3 m mole) of ethoxycarbonylmethylthiothiazoline in 12 ml of DMF : THF (1:1) is added 160 mg of 50 % NaH and the mixture is stirred for 15 min., and then 530 mg (3.1 m mole) of benzyl bromide is added. The temperature is observed to rise to ca. 50°, and the whole mixture is stirred for additional 2 hours under N_2 atmosphere. Ethyl acetate is added and the organic solution is washed with water three times and dried over $MgSO_4$. After evaporation of the solvent the crude product is purified by prep. TLC5)to give 603.6 mg of the benzylated product (IIIb, R' = $CH_2C_6H_5$), yield 68.2 %. Rf = 0.58 (Ben. : EtOAc = 10 : 1). IR $\nu_{max.}^{liq.}$ 1730, 1570 cm^{-1}. NMR6)($CDCl_3$) δ : 1.12 (3H, t., J=7 Hz), 3.20 (2H, d., J=7.5 Hz), 3.32 (2H, t., J=7.8 Hz), 4.08 (2H, q., J=7 Hz), 4.15 (2H, t., J=7.8 Hz), 4.66 (1H, t., J=7.5 Hz), 7.23 (5H, br. s.). Anal. Calcd. for $C_{14}H_{17}NO_2S_2$: C, 56.92 ; H, 5.80 ; N, 4.74. Found : C, 57.11 ; H, 5.99 ; N, 4.61 .

B]. To a solution of 200 mg of above product (IIIb, R'= $CH_2C_6H_5$) in 2 ml of acetic acid is added 400 mg of Zn powder at r.t. under vigorous stirring. After one hour the starting material (IIIb, R'=$CH_2C_6H_5$) disappears and 2-

mercaptothiazoline is detected on TLC under UV-lamp irradiation. Ethyl acetate is added and the organic solution is washed successively with water, 5 % aq. NaOH (to remove 2-mercaptothiazoline) and water. After drying over $MgSO_4$ the solvent is evaporated to give the desired crude product, which is purified by prep. TLC to give 100.2 mg (83 %) of the desulfurized product (IVb, R'= $CH_2C_6H_5$), which is identical with the standard ethyl β-phenylpropionate.

C). To a solution of 400 mg of the benzylated product (IIIb, R'=$CH_2C_6H_5$) in 1.3 ml of DMF is added 1.5 ml of CH_3I, 100 mg of $CaCO_3$ and Hg (cat.). The whole mixture is stirred at 70-75° for 5 hours under N_2 atmosphere. After cooling ethyl acetate is added and the organic solution is washed successively with 1 % aq. sodium hydrosulfite solution and water, and dried over $MgSO_4$. Evaporation of the solvent gives the crude product which is purified by prep. TLC ; Rf = 0.76 (Ben.: EtOAc = 30 : 1) to give 310 mg of ethyl α-iodo-β-phenylpropionate (Vb, R'= $CH_2C_6H_5$). Yield 75.2 %. IR $\nu_{max.}^{liq.}$ 1732 cm^{-1}. NMR ($CDCl_3$) δ : 1.15 (1H, t., J=7 Hz), 3.26 (1H, d. of d., J=14 and 8 Hz) 3.44 (1H, d. of d., J=14 and 8.5 Hz), 4.14 (2H, q., J=7 Hz), 4.55 (1H, d. of d., J=8.5 and 8 Hz), 7.3 (5H, br.s.). This iodinated product (Vb, R'= $CH_2C_6H_5$) is dissolved in benzene and treated with DBN for 30 min. at r.t. to give ethyl cinnamate in 90 % isolated yield, which is identical with an authentic sample.

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REFERENCES

1. Part V : K. Hirai and Y. Kishida, Yuki Gosei Kagaku Kyokai Shi (Japanese), 32 20 (1974), Heterocycles, 2 185 (1974).
2. K. Hirai and Y. Kishida, Tetrahedron Letters, 2743 (1972).
3. About 10 % dialkylated products (VIIa,b) were also isolated.
4. E.J. Corey and M. Jautelat, Tetrahedron Letters 5787 (1968).
5. (Preparative) thin layer chromatography (TLC) was carried out on Merck TLC-plate, silica gel, F_{254} pre-coated, layer thickness :(2 mm) 0.25 mm .
6. The NMR (60 MHz) spectra were taken in $CDCl_3$ solution and calibrated to internal standard of TMS. s.,singlet;d.,doublet;t.,triplet;q.,quartet;br.,broad.