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A NEW SYNTHESIS OF SQUALENE USING 2-ALKENYLTHIOTHIAZOLINELITHIUM DERIVATIVE

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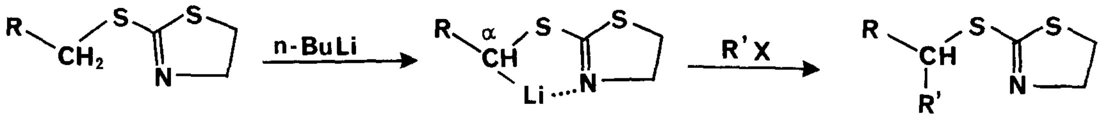
Investigations into new methods for effecting C-C bond formation are one of the main objectives in the field of synthetic organic chemistry. The coupling reaction between an alkyllithium and an alkyl halide is one of such C-C bond formation reactions but this method has its drawbacks due to many side reaction by-products by halogen-metal interconversion.1) In this communication we wish to report a new alkylation reaction and its application to the synthesis of squalene by using 2-alkenylthiothiazolinelithium derivative.

The alkylthiothiazoline (I) was readily prepared from the corresponding alkyl halide and commercially available 2-mercaptothiazoline.2) Treatment of I with n-BuLi formed the corresponding lithium salt (II), which would be stabilized through the contribution of the formation of 5-membered ring containing the sulfur and nitrogen atoms.



I II III

a : $R = H$,
b : $R = C_6H_5$,
c : $R = -\overset{\beta}{CH}=\overset{\gamma}{CH_2}$
d : $R = -CH\underset{(t)}{=}CH{\cdot}C_6H_5$

Chart 1

The following procedure is representative.

A 25-ml flask fitted with an inlet carrying a rubber septum cap, a magneti stirrer, and a pressure-equalized dropping funnel containing 1 x 10^{-2} moles of benzyl chloride was flushed with nitrogen. In the flask had been placed 1 x 10 moles of 2-methylthiothiazoline (Ia) dissolved in 6 ml of tetrahydrofuran at -2 ~ -30°. Then 1 x 10^{-2} moles of n-BuLi in n-hexane was added through syringe t form the lithium salt (IIa). Stirring was continued at the same temperature for thirty minutes to complete the metalation. The benzyl chloride was then added dropwise. The mixture was stirred for another thirty minutes and the temperatur was gradually raised to 0°. Then 30 ml of ice water was added and the mixture w extracted with ethyl acetate. The organic layer was washed with water three tim and dried over $MgSO_4$. Removal of the solvent gave a crude product (IIIa, R'= $C_6H_5CH_2$-), which was purified by silica-gel dry column chromatography. The prod was confirmed as phenethylthiothiazoline [bp 125°/0.2 mm. IR ν_{max}^{film} cm^{-1}: 3030, 1600, 1570 (C=N), 695. NMR$^{3)}$: 3.17-3.45 (2H, almost t.), 4.05-4.32 (2H, almost t.), 2.80-3.40 (4H), ca 7.23 (5H, aromatic). M^+ at m/e 223 ($C_{11}H_{13}NS_2$)] by the comparison with an authentic sample which was prepared from phenethyl chloride a 2-mercaptothiazoline. The experimental results are summarized in Table I.

Table I

R	R'X	Yield % (isolated)	R	R'X	Yield (isolat
a, H	CH_3I	60	b, C_6H_5	$C_6H_5CH_2Cl$	45
a, H	EtBr	45	b, C_6H_5	(p) $CH_3C_6H_4CH_2Cl$	34
a, H	n-BuBr	50	c, $-CH=CH_2$	CH_3I	40
a, H	isoPrBr	25	c, $-CH=CH_2$	$CH_2=CH-CH_2Br$	30
a, H	n-$C_{10}H_{21}Br$	21	c, $-CH=CH_2$	$C_6H_5CH_2Br$	45
a, H	$CH_2=CH-CH_2Br$	40	d, $-CH=CHC_6H_5$	CH_3I	47
a, H	$C_6H_5CH_2Cl$	80	d, $-CH=CHC_6H_5$	$C_6H_5CH_2Br$	45
a, H	(p) $ClC_6H_4CH_2Br$	70	d, $-CH=CHC_6H_5$	isoPrBr	10
b, C_6H_5	CH_3I	60	d, $-CH=CHC_6H_5$	$C_6H_5CH=CH-CH_2Br$	30
b, C_6H_5	$C_6H_5CH_2Br$	45			

In the case of Ic and Id the alkylations were effected at -60° and occurred exclusively at the α position with respect to the sulfur atom (not at the γ position), which would be attributed to a 5-membered chelating ring effect (i.e., II).[4)]

By using this method we succeeded in the synthesis of squalene. 2-Farnesyl thiothiazoline (IV) [IR ν_{max}^{film} cm^{-1}: 1665, 1573 (C=N). NMR δ : 1.60 and 1.70 (CH_3 x 4), 1.90 - 2.20 (8H), 3.20 - 3.55 (2H, almost t.), 4.05 - 4.40 (2H almost t.), 3.80 (2H, d., J=8 Hz), 4.95 - 5.30 (2H, vinyl H), 5.35 (1H, t., J=8 Hz). M^+ at m/e 323 ($C_{18}H_{29}NS_2$). Anal. Calcd. for $C_{18}H_{29}NS_2$: C, 66.84; H, 9.04 N, 4.33; S, 19.79. Found: C, 66.98; H, 9.22; N, 4.33; S, 19.20.] was converted into its lithium salt (V) at -60° and addition of the farnesyl bromide[5)] afforded a squalene derivative (VI) [IR ν_{max}^{film} cm^{-1}: 1665, 1573 (C=N). NMR : 1.62 and 1.72 (CH_3 x 8), 1.90 - 2.50 (18H), 3.20 - 3.50 (2H, almost t.), 4.05 - 4.40 (2H, almost t.), 4.40 - 4.70 (1H, m.), 5.0 - 5.4 (6H, m.). Anal. Calcd. for $C_{33}H_{53}NS_2$: C, 75.10, H, 10.12; N, 2.65; S, 12.13. Found: C, 75.02; H, 10.19; N, 2.78; S, 11.82] in 44% yield. Desulfurization was effected by refluxing with excess Raney nickel in ethanol-tetrahydrofuran (4:1) to afford squalene in 80% yield[6)], which was identical with the natural substance by spectroscopy.

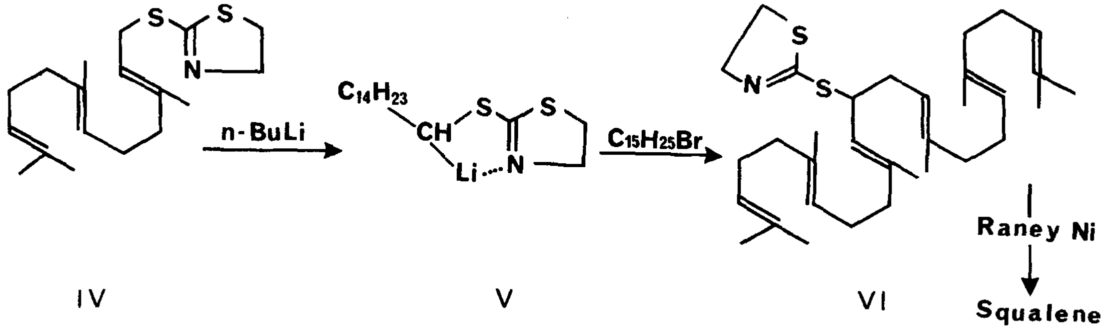


Chart 2

The application of this new alkylation method to the syntheses of the other natural products is now under investigation and the details of the study will be reported in the near future.

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