

The Synthesis of Aldehydes from 2-Methyl-2-Thiazoline

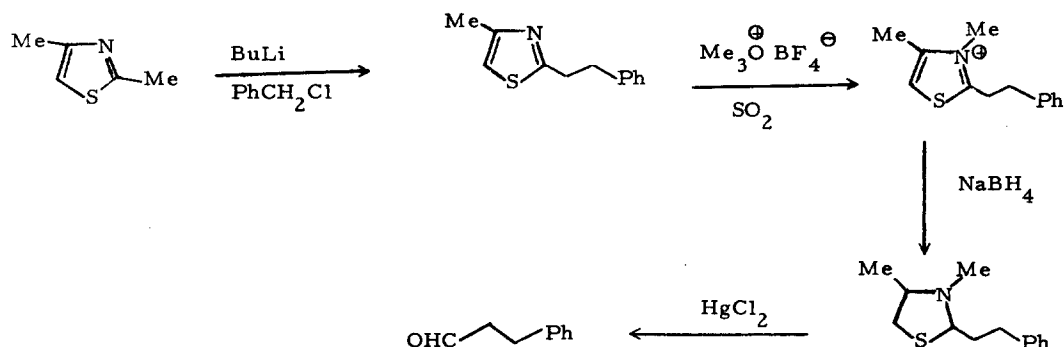
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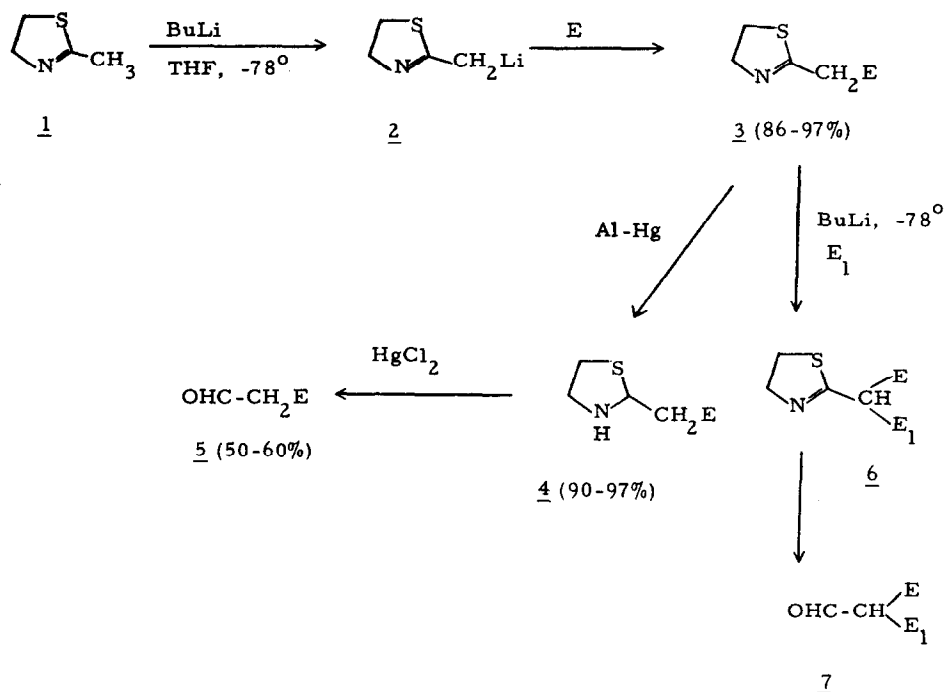
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A recent report² described the use of 2,4-dimethyl thiazole as a source of aldehydes (Scheme 1) based upon the principle of the oxazine-aldehyde synthesis². The major advantage of the thiazole route lies in the neutral method of aldehydic release from the thiazolidine intermediate.

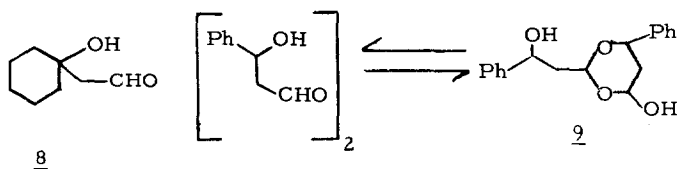
Scheme 1



We wish to report our own results in this area which began in 1967 using the simpler system; 2-methyl-2-thiazoline. A solution of 1 was smoothly transformed into its lithio salt 2 at -78° using n-butyllithium and treated with a variety of electrophilic agents (E) at the low temperature. Isolation produced the elaborated thiazolines in high yield which were then reduced (as the crude product) with aluminum amalgam⁴ in moist ether to the thiazolidine, 4. The latter was cleaved to the aldehyde by treatment with mercuric chloride in aqueous acetonitrile at room temperature. In this fashion the aldehydic products were isolated in 50-60% overall yield from 1 (Table I). The products obtained when carbonyl compounds were added to the lithio thiazoline and ultimately reduced and cleaved to the aldehydes, were the β -hydroxy derivatives 8 (oil, $3600-3100\text{ cm}^{-1}$, $2740, 1720$, nmr (CDCl₃) δ 10.0 (t, 1, J=0.5 Hz), 3.5 (l, exchangeable with D₂O), 2.6



(d, $J=0.5$, 2), 1.6 (m, 10) and the dimer **9** (oil, 3400 cm^{-1} , nmr (CCl_4) δ , 7.4-7.0 (m, 10); 4.8-4.1 (m, 4); 2.7-1.0 (m, 6; 2 protons exchanged with D_2O). In both instances (**8** and **9**) the 2,4-DNP derivative was that of the dehydrated aldehyde; cyclohexylidene acetaldehyde and cinnamaldehyde respectively.^{5,6} Of further interest is the fact that the initially elaborated thiazoline **3** ($\text{E}=\text{CH}_2\text{Ph}$) could be alkylated again (EtI)



in 91% yield to **6** ($\text{E}_1=\text{Et}$, $\text{E}=\text{CH}_2\text{Ph}$) which reduced and cleaved to 2-benzylbutyraldehyde **7** (2,4-DNP 112-113⁰) in 50% overall yield. The degree of polyalkylation of **1** (or **3**) with the electrophiles employed did not exceed 5% (vpc) thus rendering this method synthetically

quite useful.

The preparation of 2-(1-hydroxy) cyclohexylacetaldehyde, 8, serves as a typical example. A solution of 10.0 g of 1 in 90 ml THF was cooled under nitrogen to -78° after which 1.05 equiv of n-butyllithium was added (15-20 min). After 15 min, a pale yellow suspension (indicative of salt formation) appeared and was stirred for 1.5 hr. A solution of cyclohexanone (1.02 equiv) in 25 ml THF was added at -78° and the mixture slowly allowed to warm to ambient, at which time it was quenched in 150 ml cold water, acidified (pH~2) and extracted with pentane. The extracts were discarded and the solution neutralized with dilute alkali. The separated oil was removed by several ethereal extractions, dried (K_2CO_3) and concentrated, leaving the elaborated thiazoline (crude yield 94%, purity > 95%, mp $92-94^{\circ}$). Reduction was performed using 5g of above in 200 ml ether (previously shaken with water) and aluminum-amalgam prepared as follows: aluminum powder (8.5g, 8-20 mesh) was etched with 5% KOH until vigorous evolution of hydrogen occurred. The aqueous solution was decanted and the residue washed with water. After decanting, a solution of 0.5% $HgCl_2$ (175 ml) was added to the aluminum powder and shaken for 2-3 min. and decanted again. Water was added to wash the amalgam and the entire process of adding $HgCl_2$ solution was repeated. The amalgam was then washed initially with ethanol and finally with ether. An ethereal solution of the thiazoline containing the amalgam was heated to reflux for 1.5-2 hr and then the salts were filtered and the ether solution dried and concentrated. The residue, mp $78-81^{\circ}$ (purity > 90%) was used without further purification. Cleavage to the aldehyde was accomplished by treating 4.2 g of thiazolidine with 30 ml of 20% aqueous acetonitrile to which 8.3 g $HgCl_2$ had been dissolved. The mixture, containing a precipitate, was stirred at room temperature for 2 hr, water added (25 ml), and filtered. The filtrate was extracted with ether-pentane (1:1), the latter dried (K_2CO_3) and concentrated affording the hydroxy aldehyde 8 (purity > 95%).

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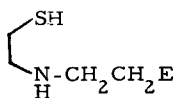
Table I. Alkylation, Reduction and Cleavage of 1 to Aldehydes

<u>E(electrophile)</u>	<u>% 3</u>	<u>% 4</u>	<u>% 5 (ECH₂CHO)</u> <u>Overall from 1</u>	<u>2,4-DNP</u>
PhCH ₂ Cl	97 ^a	88 ^d	59.8	152-154
PhCH ₂ CH ₂ Br	89 ^b	82 ^d	48	95-97
PhCHO	87 ^d	86 ^e	49.6	251-252 ^h
Cyclohexanone	94 ^c	97 ^f	51	193-195 ⁱ
Styrene Oxide	93 ^d	85 ^g	49.7	104-106 ^j

a) bp 135-137° (2.8 mm); b) bp 153-156° (2.4 mm); c) mp 92-94°; d) viscous oil; e) mp 81-82°; f) mp 76-79°; g) mp 105-106°; h) Corresponds to derivative of cinnamaldehyde; i) corresponds to derivative of cyclohexylidene acetaldehyde; j) aldehyde exists in cyclic hemiacetal form; H. W. Adickes, I. R. Politzer, and A. I. Meyers, J. Amer. Chem. Soc., 91, 2155 (1969).

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4. The reduction of the 2-thiazolines 3 to their corresponding thiazolidines 4 was studied using sodium borohydride and sodium cyanoborohydride under a variety of conditions. In all cases there was obtained along with the desired product, various quantities of the open chain mercapto amines;



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7. Purchased from Columbia Organic Chemicals, Columbia, S. C.