

SYNTHESES VIA DIHYDRO-1,3-OXAZINES. XI.

A SYNTHESIS OF FUNCTIONALLY SUBSTITUTED ALDEHYDES

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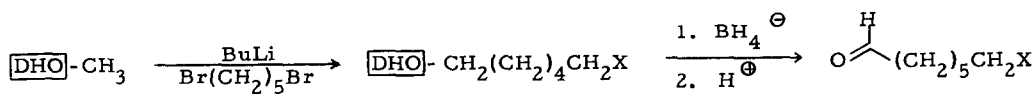
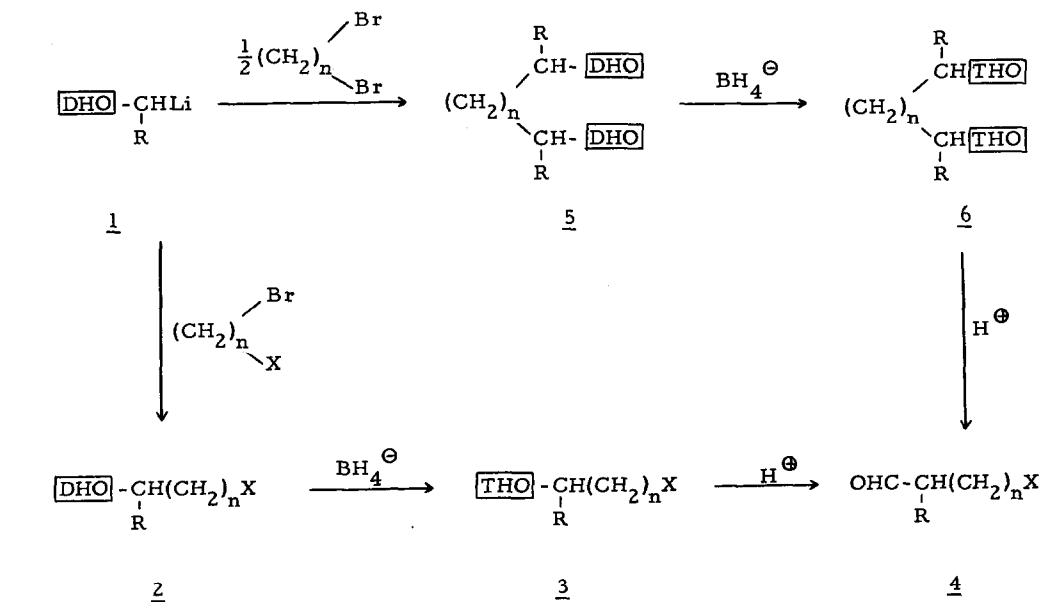
The use of dihydro-1,3-oxazines in synthesis has been demonstrated with respect to obtaining aldehydes,¹ ketones,² and acids³ of varied structure. We now report our preliminary results regarding the formation of halo, cyano, hydroxy, and keto-substituted aldehydes along with dialdehydes by simple manipulation of the dihydro-1,3-oxazine system and readily available materials.

The lithio salt¹ of the 2-methyldihydro-1,3-oxazine 1 (R=H) was converted to the chlorobutyl derivative 2 (R=H, n=3, X=Cl) by treatment with 1-chloro-3-bromopropane at -78°. The crude product (92%) was reduced¹ without purification to the corresponding tetrahydro-1,3-oxazine (THO) 3 using aqueous sodium borohydride, which was cleaved (oxalic acid) to 5-chloropentanal 4a in 51% yield (Table I). In a similar fashion the 2-benzylidihydro-1,3-oxazine, through its lithio salt 1 (R=Ph) was monoalkylated with 1,4-dibromobutane in 94% crude yield to 2 (R=Ph, n=4, X=Br) which was reduced and cleaved to 6-bromo-2-phenylhexanal 4b in 60% yield. This sequence adequately exemplifies the utility of this method in obtaining ω -haloaldehydes of various chain lengths.

The selectivity of the lithio salt 1 (R=Ph) toward substituted halides (5-bromovaleronitrile) was illustrated by a 92% conversion to 2 (R=Ph, n=4, X=CN) without appreciable attack at the other reactive centers. The usual reduction with sodium borohydride followed by acid cleavage of 3 afforded 6-cyano-2-phenylhexanal (4c). Attempts to duplicate this sequence employing 1 (R=H) resulted in proton abstraction, addition to the cyano group, along with bromide displacement. The poor selectivity of the anion of the 2-methyl-DHO was

overcome by a slight modification in procedure discussed later (7 \rightarrow 8a \rightarrow 8b).

The synthesis of dialdehydes followed from this scheme by utilizing 2 eq of the lithio salt 1 (R=Ph) and 1 eq of 1,4-dibromobutane to form the α, ω -bis (dihydro-1,3-oxazinyl) alkane 5 (R=Ph, n=4). Reduction with the requisite amount of borohydride solution cleanly reduced the C=N link in both oxazine rings (6) which was then hydrolyzed in oxalic acid to 2,7-diphenyloctanedial (4d).



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- 8a, X=Br
8b, X=CN
8c, X=MgBr
8d, X=D
8e, X=PhCHOH
8f, X=PhCO
8g, X=CO₂Et

- 9a, X=CN
9b, X=D
9c, X=PhCHOH
9d, X=PhCO

To further demonstrate the wide scope of this method for obtaining substituted aldehydes, a scheme starting with 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (DHO-CH₃) 7 and 1,5-dibromopentane was investigated. The 6-bromohexyl derivative, 8a (90%, 1658 cm⁻¹) was transformed into the corresponding nitrile 8b (95%, 2240, 1658 cm⁻¹) by treatment with 1.8 eq sodium cyanide in DMSO (55°, 2 hr). This procedure, therefore, overcomes the poor selectivity of 1 (R=H) with halonitriles. Reduction and cleavage of 8b gave 7-cyano-heptanal 9a (Table 2). The bromohexyl oxazine 8a could also be converted to the Grignard reagent 8c (THF, 66°, 3 hr)³ treated with deuterium oxide, and ultimately converted to 7-deuterioheptanal 9b. The Grignard reagent 8c was also treated with benzaldehyde (MgBr₂) producing the alcohol 8e (55%, 3225, 1658 cm⁻¹) which subsequently gave the 8-hydroxy-8-phenylaldehyde 9c. Reaction of 8c with ethyl chloroformate proceeded normally giving rise to the 6-carboethoxy oxazine 8g (40%, 1660, 1735 cm⁻¹). The latter was formed in higher yield (83%) from the nitrile 8b using ethanolic hydrogen chloride. The successful introduction of the carboethoxy group is significant due to the fact that the anion of 7 (1 R=H) is poorly selective in its reaction with ω-bromoesters. Finally, the addition of phenylmagnesium bromide to the 6-cyanoethyl oxazine, 8h, produced the 6-benzoylhexyl derivative, 8f (90%, mp 28-30, 1675, 1658 cm⁻¹). The C=N link was reduced (-45°) without affecting the carbonyl group and the tetrahydro-1,3-oxazine hydrolyzed to the ketoaldehyde 9d.

Although the transformations described are of the standard type, they are reported here to illustrate the unique stability of the dihydro-1,3-oxazine toward a variety of conditions.

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REFERENCES

1. H.W. Adickes, I.R. Politzer, and A.I. Meyers, *J. Am. Chem. Soc.*, 91, 2155 (1969); *Tetrahedron Letters*, 1783 (1969).
2. A.I. Meyers and E.M. Smith, *ibid.*, 92, 1084 (1970).
3. A.I. Meyers, I.R. Politzer, B.K. Bandlish, and G.R. Malone, *ibid.*, 91, 5886 (1969).

TABLE I. Substituted Aldehydes (4) - $\text{OHC}-\underset{\text{R}}{\text{CH}}(\text{CH}_2)_n\text{X}$

Compound	R	n	X	% yield ^a	ir (cm ⁻¹)	δppm(CHO)	2,4-DNP
<u>4a</u>	H	3	Cl	51	1722	9.76	106-108 ^b
<u>4b</u>	Ph	4	Br	60	1725	9.63	136-138
<u>4c</u>	Ph	4	CN	71	1720, 2243	9.66	116-117
<u>4d</u>	Ph	4	$\text{Ph}\underset{\text{I}}{\text{C}}\text{HCHO}$	63 ^c	1716	9.61	210-213

a) All new compounds gave satisfactory elemental and/or mass analyses; b) Y. Ban and T. Orshi, Chem. Pharm. Bull., 11, 446 (1963); c) Mp 37-39^o

TABLE II. Substituted Heptaldehydes (9)

Compound	X	% yield	ir (cm ⁻¹)	δppm (CHO)	2,4-DNP
<u>9a</u>	CN	47	1718, 2240	9.71	76-77 ^a
<u>9b</u>	D	55 ^b	1724, 2178	9.73	108-109
<u>9c</u>	PhCHOH	44	1720, 3400	9.70	
<u>9d</u>	$\text{Ph}\underset{\text{I}}{\text{C}}=\text{O}$	49	1720, 1680	9.69	84-85 ^c

a) M. Ohno, N. Naruse, S. Torimitsu, I. Teresawa, J. Am. Chem. Soc., 88, 3168 (1966);
 b) Mass spectral analysis indicated that deuteration was quantitative; c) Mp of corresponding keto acid [T. Weil and D. Ginsburg, J. Chem. Soc., 1291 (1957)], which was obtained by oxidation with chromic acid.

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