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ALDEHYDES FROM DIHYDRO-1,3-OXAZINES. V.
A THREE CARBON CHAIN EXTENTION LEADING TO α,β-DISUBSTITUTED PROPIONALDEHYDES

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The 2-alkyldihydro-1,3-oxazine system has been shown to be a fundamental building block for a variety of substituted acetaldehydes and their C-1 deuteriated derivatives.[1] We now wish to introduce a further oxazine, 1, which we have successfully utilized for obtaining propionaldehyde derivatives, 2, substituted at C-2 and C-3 by alkyl, alkenyl, and aryl groups.

When a solution of 1 and an alkyl halide (1.1-1.5 eq) in THF was cooled (-40 to -60°) and treated with a typical Grignard reagent (2.0-2.2 eq) the doubly alkylated oxazine, 3, was formed (Table I) along with polymer derived from the vinyl oxazine.[2] The use of less than 2.0 eq of the Grignard reagent resulted in partially recovered starting material. This suggests the initial formation of a strong complex between 1 and the Grignard prior to alkylation.[3] The reduction of crude 3 with aqueous sodium borohydride at -35°, as previously described[1] produced the tetrahydro derivative, 4, which was directly converted to the α,β-disubstituted propionaldehyde by hydrolysis in aqueous oxalic acid. The overall yields of the aldehydes were found to vary between 25-72% and since most of these reactions were performed only once on a 50-100 mmole scale, the conditions may not be optimum.[4] In cases where the overall yields were low, the technique still has considerable preparative value mainly because the hydrolysis of the crude tetrahydro derivative, 4, produces pure aldehyde by either extraction or steam distillation. Furthermore, the entire sequence can be carried out in approximately two days providing multigram quantities of the aldehydes.

The vinyl oxazine, 1, may be considered as "protected" acrolein which undergoes 1,4-addition of Grignard reagents followed by alkylation of the intermediate α-carbanion. This is of particular significance since acrolein undergoes almost exclusive 1,2-addition with organometallics[5] and thereby limits the Michael addition to alcohols, amines, and active methylene compounds. In the single instance investigated, the vinyl oxazine was found to behave as an excellent Michael acceptor and produced the di-ester oxazine, 5, when treated with sodio malonic ester.[6] The major advantage to this technique over utilizing acrolein is the fact that the corresponding C-1D aldehyde is thereby made available. The double alkylation procedure was also found to be useful for obtaining γ-hydroxyaldehydes, 6,[7] when styrene oxide was put in place of the alkyl halide (Table I). It is of interest that the vinyl group in 1 competes effectively with the epoxide under the reaction conditions for the Grignard reagent. This method of obtaining γ-oxo derivatives of aldehydes can be considered as complementary to that already reported involving a two carbon chain extension.[1d]

Further studies to increase the utility of this three-carbon chain extension are in progress.[8,9]

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REFERENCES

1. a) A.I. Meyers, A.Nabeya, H.W. Adickes, and I.R. Politzer, J. Am. Chem. Soc., 91, 763 (1969); b) A.I. Meyers, A. Nabeya, I.R. Politzer, H.W. Adickes, J.M. Fitzpatrick, and G.R. Malone, ibid., 764 (1969); c) A.I. Meyers, H.W. Adickes, I.R. Politzer, and W.N. Beverung., ibid., 766 (1969); d) H.W. Adickes, I.R. Politzer, and A.I. Meyers, ibid., 000 (1969), in press.

2. The yield of 3 in Table I includes 10-30% polymer which did not interfere with the subsequent steps nor the isolation of pure aldehyde. Polymerization of 1 was complete in the absence of alkyl halide at all temperatures examined (25 to -78°). If the alkyl halide was added immediately after the addition of the Grignard reagent to 1, little or no alkylation occurred.

3. E.C. Ashby, [Quart. Rev., 21, 259 (1967)] has discussed the interaction between amines and Grignard reagents. The exact nature of this complex and the role it plays will require further consideration. It should be noted here that all attempts to duplicate this alkylation of the vinyl oxazine using alkyl or aryllithium reagents failed to produce anything other than the oxazine polymer.

4. The use of sodium borodeuteride would have produced in comparable yields, the C-1 deuteriated derivatives of 2.

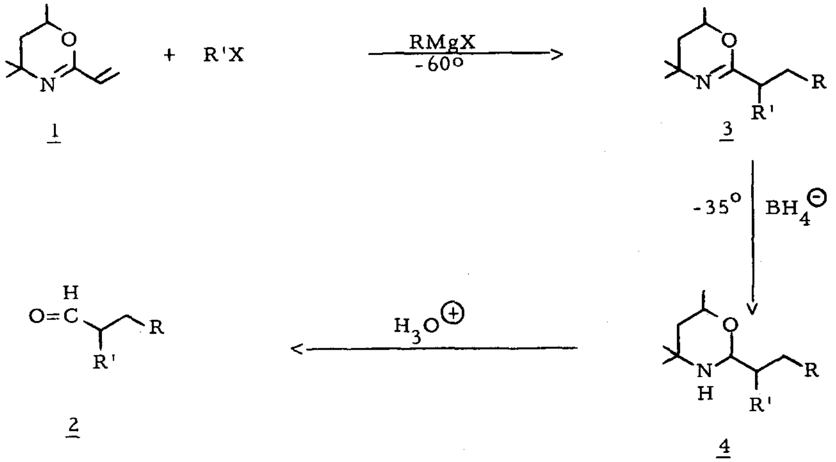
5. M.S. Kharasch and O. Reinmuth, "Grignard reactions of Nonmetallic Substances", Prentice-Hall, New York, 1954, pp. 196-199.

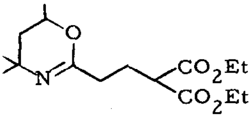
6. Obtained in 94% yield, ir (neat), 1740, 1665 cm^{-1}; nmr ($CDCl_3$)δ 4.2 (q, 4H), 4.1 (b, 1H), 3.4 (t, 1H), 2.2 (m, 4H), 1.0-1.8 (m, 17H); m/e (calcd. 313, Found 313).

7. Exists predominantly in the hemiacetal form. No carbonyl band or aldehyde proton was discernible in the ir or nmr spectra respectively.

8. For other three-carbon extensions leading to aldehydes, see J. Carnduff, Quart. Rev., 20, 169 (1966).

9. The vinyl oxazine, 1, can be prepared in 200 gram quantities using a modification of the procedure described by Ritter and Tillmanns [J. Org. Chem., 22, 839 (1957)]. The authors would be pleased to supply, upon request, complete experimental details concerning this compound and others described above.





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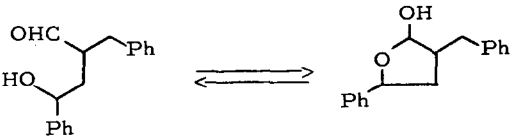

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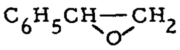
TABLE I

α, β-Disubstituted Propionaldehydes[a] from 2-Vinyloxazine, 1.

RMgBr	R X	% 3 (crude)	% 4 (crude)	%Aldehyde, 2 (overall)	2,4-DNP
C_6H_5	CH_3I	93	92	71	122-123[b]
C_6H_5	$C_6H_5CH_2Br$	89	98	60	165-166[d]
C_6H_5	$CH_2{=}CHCH_2Br$	87	90	43	125-126[d]
C_6H_5	 $C_6H_5CH\underset{O}{-}CH_2$	74	94	44	168-172[c]
C_6H_5	CH_3CH_2I	72	98	31	112-113[e]
CH_3	$C_6H_5CH_2Br$	84	95	26	114-115[e]
C_2H_5	$C_6H_5CH_2Br$	93	96	72	86-87 [d]
$CH_2{=}CHCH_2$	$C_6H_5CH_2Br$	72	98	31	76-77 [d]

a) All new compounds gave satisfactory analyses and were completely characterized by ir, nmr, and mass spectra.

b) Semicarbazone, R. Lucas and L. Labaune, Ann. Chim, 16, 293 (1931); mp 123-124°.

c) No attampt was made to separate the mixture of diastereoisomers.

d) New compounds.

e) Identical compounds, I. Scriabine, Bull. Soc. Chim, France, 1194 (1961); mp 114-115°.