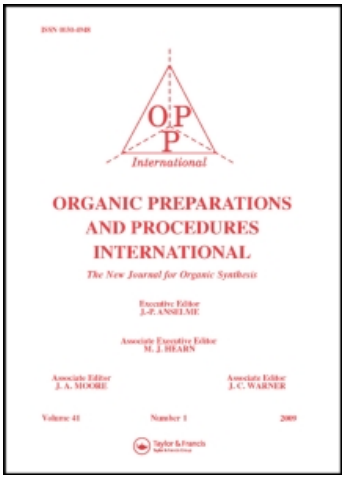

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PREPARATIVE PROCEDURES FOR ALDEHYDES FROM DIHYDRO-1,3-OXAZINES.[1]

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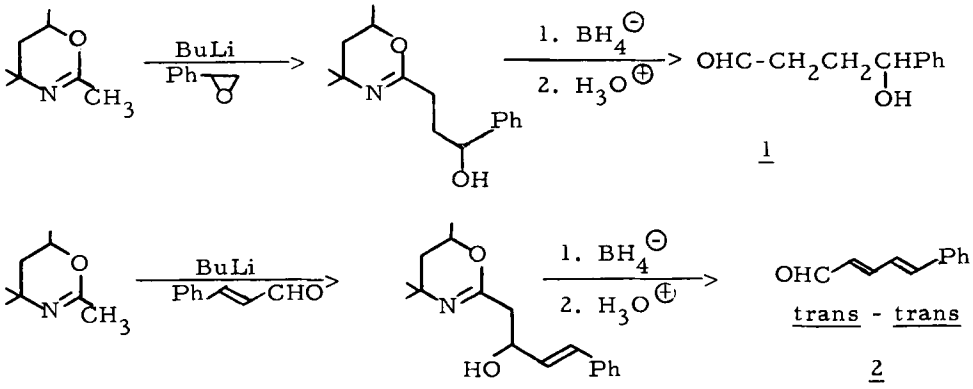
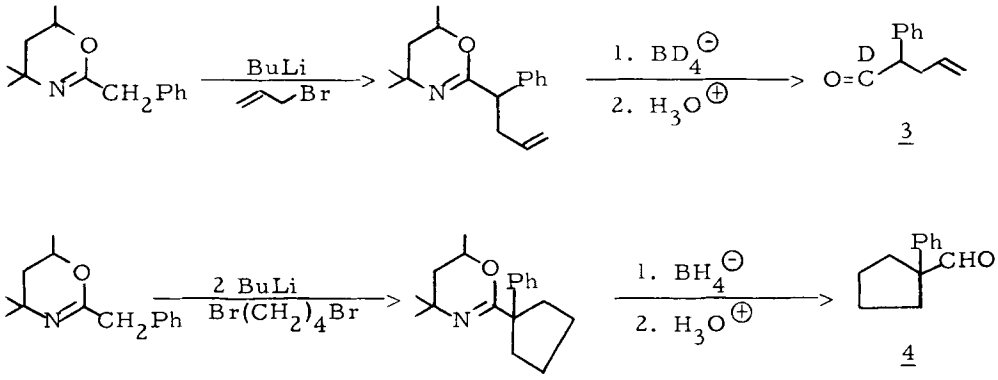
The formation of aldehydes and their C-1 deuterated derivatives from the readily available dihydro-1,3-oxazines has been briefly described.[2,3] We now report detailed procedures for utilizing this method and offer four typical examples (1-4) which adequately illustrate this technique. The procedures for 1-3 are virtually identical, whereas the method for obtaining 4 typifies the formation of cycloalkane carboxaldehydes. For this reason, a general procedure is given for the compounds reported and the individual properties of each compound are outlined at the end.





GENERAL PROCEDURE (1-3)

Preparation of Anion of 2-Methyl (or 2-Benzyl) dihydro-1,3-oxazine. - A 500-ml three-necked flask equipped with a magnetic stirring bar, a 75 ml addition funnel topped with a rubber septum, and a nitrogen inlet tube is successively evacuated and flushed with nitrogen. Anhydrous THF (100 ml) and 14.1 g (0.10 mole) of 2,4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine are added from a syringe through the rubber septum. The stirred solution is cooled to -78° (Dry Ice-acetone bath) and 69.0 ml (0.11 mole, 1.6 M) of n-butyllithium in hexane is injected into the addition funnel. The n-butyllithium is added dropwise over a period of 1 hour. Approximately 1 hour[4] after the addition is complete a yellow precipitate forms. This is indicative of complete anion formation. The anion may not precipitate if more than the above quantity of solvent is employed.

Alkylation of Anion. - The electrophile [(0.11 mole), halide, epoxide, ketone, etc.] in 25 ml of anhydrous THF is injected into the addition funnel and is slowly added to the mixture over a period of ~30 minutes. The reaction mixture is allowed to slowly warm to room temperature by

which time the yellow precipitate disappears. The mixture is then poured into ~100 ml of ice water and acidified (pH 2-3) with 9 N hydrochloric acid. The acidic solution is extracted with three 75 ml portions of pentane and made basic by the careful addition of 40% sodium hydroxide solution. Ice is added to keep the mixture cool during the neutralization. The resulting oil is extracted with three 75 ml portions of ether and the ether extracts are dried over anhydrous potassium carbonate. The ether is removed by rotary evaporation to give the crude alkylated dihydro-1,3-oxazine (90-98%).

Reduction of the Dihydro-1,3-oxazine. - To a 600-ml beaker is added 100 ml of THF, 100 ml of 95% ethyl alcohol, and the crude dihydrooxazine obtained in the preceding experiment. The mixture is cooled between -35 and -40° with an acetone bath to which Dry Ice is added as needed. Hydrochloric acid (9 N) is added to the magnetically stirred solution until an approximate pH of 7 is obtained. Sodium borohydride solution is prepared by dissolving 3.78 g (0.10 mole) in a minimum amount of water (~4-5 ml) to which 1 drop of 40% sodium hydroxide is added. The sodium borohydride solution and the 9N hydrochloric acid solution are added[5] to the stirred solution alternately so that pH 6-8 is maintained. The pH is monitored by periodic checks with pH paper. During the addition care is taken to maintain a temperature between -35 and -45°. After addition of this borohydride solution is complete, the solution is stirred with cooling for an additional hour (pH 7 is maintained by the occasional addition of hydrochloric acid solution).

The contents are then poured into ~100 ml of water and made basic by the addition of 40% sodium hydroxide solution. The layers are separated and the aqueous solution is extracted with three 75 ml portions of diethyl ether. The combined organic extracts are washed with 100 ml of saturated sodium chloride solution and dried over anhydrous potassium

carbonate. The ether is removed by rotary evaporation to give the crude tetrahydrooxazine (90-99%).

Cleavage of the Tetrahydrooxazine to the Aldehyde. A) Steam Distillation. To a 250 ml flask equipped with a distillation head and an addition funnel with a nitrogen tube, is added 50.4 g (0.40 mole) of hydrated oxalic acid and ~150 ml of water. Steam is introduced into the solution and the tetrahydrooxazine (~0.1 mole) is added dropwise over a period of 20 minutes. The addition funnel is then washed down with 5 ml of 1 M oxalic solution. The steam distillation is continued until the distillate is free of organic material. The distillate is extracted with three 50 ml portions of pentane or ether. The extracts are dried over anhydrous sodium sulfate and the solvent removed to give the pure aldehyde. In some instances distillation of the product may be necessary.

B) Hydrolysis.-[6] In cases where the aldehyde is water soluble or is insufficiently volatile to make steam distillation practical, the following procedure is used.[6] The crude tetrahydro-1,3-oxazine (0.1 mole) is added to the oxalic acid solution prepared above and heated to reflux for 2 hours. The cloudy solution is extracted with ether, pentane, or dichloromethane (depending on the nature of the aldehyde) and the extracts washed with 5% sodium bicarbonate solution, and dried (Na_2SO_4). Concentration of the solution is followed by either distillation or recrystallization.

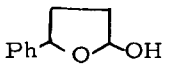
Preparation of Cycloalkane Carboxaldehydes (4).- To a 500-ml three-necked, round-bottom flask equipped with a nitrogen inlet tube, a rubber septum and a magnetic stirrer, is added 250 ml THF and 10.9 g (0.05 mole) of 2-benzyl-4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine. The mixture is cooled to -78° and 32.0 ml (0.06 mole, 1.6 M) n-butyllithium in

hexane is slowly added. After 1 hour of stirring, 11.5 g (0.05 mole) of 1,4-dibromobutane is added and allowed to react for 0.5 hour. n-Butyllithium (0.06 mole) is added and the mixture is allowed to slowly warm to -50° and maintained at that temperature for 2 hours. The mixture is then poured into 150 ml of water and crushed ice, acidified to pH 2-3, and is extracted with ether. The ether extract is discarded. The aqueous solution is basified with 40% sodium hydroxide and extracted with ether. The ether extract is dried over potassium carbonate and the solvent removed by rotary evaporation (90-97%).

When the 2-methyloxazine is employed, the cyclization step is carried out using two equivalents of butyllithium since yields are found to be generally lower when only one equivalent is employed.

The reduction and cleavage of the oxazine to the cycloalkane carboxaldehydes is performed using the procedures given above.

4-Hydroxy-4-phenylbutanal (1) was prepared using 35.5 g (0.25 mole) of the 2-methyloxazine, 164 ml (0.26 mole) n-butyllithium, and 31.3 g (0.26 mole) styrene oxide. There was obtained 26.6 g (65%) of 1 after hydrolysis and extraction from the oxalic acid solution. The sample may be further purified by elution through neutral alumina using pentane. Ir (neat) 3400 cm^{-1} (OH); nmr (CCl_4) δ 7.0-7.4 (m, 5H, aromatic), 4.8-5.8 (m, 2H, C-1, C-4), 4.5 (s, 1H, OH), 1.0-2.5 (m, 4H, CH_2CH_2). The absence of the aldehydic proton in the nmr spectrum and the absence of the carbonyl band in the ir spectrum confirm the cyclic nature of the product in its hemi-acetal form:



The product was also observed (tlc, nmr) to be a mixture of cis-trans isomers. A 2,4-dinitrophenylhydrazone derivative was readily prepared,

mp 106-107°. The product decomposed extensively on distillation (~50%), bp 142° (5 mm).[7]

5-Phenyl-2,4-pentadienal (2) was prepared using 35.5 g (0.25 mole) of the 2-methyloxazine, 170 ml (0.26 mole) n-butyllithium and 36.3 g (0.27 mole) cinnamaldehyde. The product was isolated by extraction (dichloromethane) of the oxalic acid solution after 1.5 hours reflux. The crude yield was 38.8 g (71%) of a tan solid. Recrystallization from pentane gave an analytically pure sample, mp 41° (lit.[8], mp 41°). The amount of loss during recrystallization varied drastically with the time of heating since the product is sensitive to heat.[9] The air sensitivity was also noted when a few pure crystals darkened and melted after 2 hours on a watch glass. The product is kept intact by storage in the freezer under nitrogen. Ir (KBr) 1610 cm^{-1}; nmr ($CDCl_3$) δ 6.0-7.70 (m, 9H, $C_6H_5CH=CH-CH=CH-$), 9.55 (d, J=8, C<u>H</u>O).

1-Deutero-2-phenyl-4-pentenal (3) was prepared using 21.7 g (0.10 mole) of 2-benzyl-4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine, 48 ml (0.11 mole) n-butyllithium, and 12.1 g (0.10 mole) allyl bromide. A 21.0 g (0.08 mole) sample of the oxazine thus produced was reduced with 3.7 g (0.09 mole) of sodium borodeuteride. The product, 3, was obtained in 70% overall yield by cleavage of the tetrahydro-1,3-oxazine derivative in oxalic acid solution (2 hours reflux). A fractionally distilled product weighed 8.5 g, bp 64-65° (0.3 mm), ir (neat) 2080 (C-D), 1705 (C=O), 1640 (C=C); nmr (CCl_4) δ 7.0-7.5 (m, 5H, phenyl), 3.3-6.0 (m, 1H, -C<u>H</u>=CH_2), 4.8-5.1 (m, 2H, CH=C<u>H</u>$_2$), 3.5 (t, J=7, 1H, PhCH), 2.1-3.1 (m, 2H, CH_2=CH-C<u>H</u>$_2$-); 2,4-dinitrophenylhydrazone, mp 100-103°.

<u>Anal</u>. Calcd. for $C_{11}H_{11}DO$: C, 81.95; H, 8.12.
Found: C, 81.91; H, 7.95.

1-Phenylcyclopentane Carboxaldehyde (4) was obtained in 60% overall yield by steam distillation from oxalic acid solution as a semi-solid; ir (neat) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 9.3 (s, 1H, CHO), 7.2 (s, 5H, phenyl), 1.5-2.7 (m, 8H, $-(CH_2)_4-$), 2,4-dinitrophenylhydrazone, mp 166-168° (lit.[10] 167-168°).

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3. The 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine and 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine are commercially available materials from Columbia Organic Chemicals, 912 Drake Street, Columbia, South Carolina. We wish to gratefully acknowledge a generous gift of sodium borodeuteride from Merck Frosst Laboratories, Montreal.

4. The use of t-butyllithium in place of n-butyllithium will generate the anion in a few minutes thus shortening the procedure by several hours.

5. It is convenient to introduce the acid and hydride solutions from two 50 ml burets placed above the beaker.

6. It has been found that this procedure for isolationg all the aldehydes prepared by this method is quite satisfactory since steam distillation, in many instances, required prolonged heating that consumed considerable time. However, certain acid sensitive aldehydes (i.e., cyclopropane, phenylcyclopropane carboxaldehydes) are best isolated by steam distillation since their contact time in the acid medium is minimized.

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