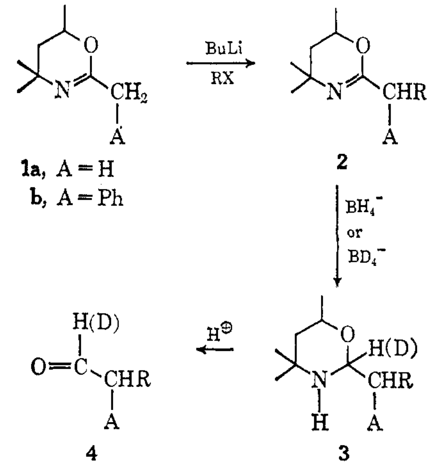
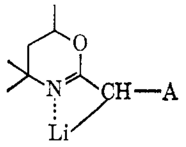
Aldehydes from Dihydro-1,3-oxazines. I. A New Synthesis of Aliphatic Aldehydes and Their C-1 Deuterated Derivatives

Sir:

We describe in this and the subsequent reports an aldehyde synthesis which originates from the readily available heterocyclic systems **1a,b**.[1] Although the latter have been known for many years,[2] little is known regarding the chemistry of the 2-alkyl group.[3] We have found that, after examining a wide variety of bases and solvents, **1a** is quantitatively converted into the lithio salt **5** (A = H) at −78° by addition of phenyl-, *n*-butyl-, or *t*-butyllithium in tetrahydrofuran.[4]





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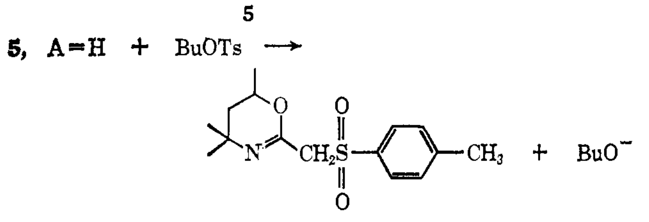

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The anion is alkylated immediately upon the addition of a variety of alkyl halides (Table I) producing high yields of the oxazines **2a**.[5] The benzyloxazine **1b** was found to behave in a similar manner, forming the anion **5** (A = Ph) and producing the alkylated products **2b** in excellent yields.[6] In many instances, the alkylated oxazines were isolated and characterized in pure state, but it was found that this delay of the sequence was unnecessary and the crude products were reduced in consistently high yields with sodium borohydride (or deuteride) to the tetrahydro-1,3-oxazines **3** in THF–EtOH–H_2O solution.[7] The final operation in the aldehyde synthesis simply involved hydrolysis of the crude tetrahydro-1,3-oxazines in dilute oxalic acid and isolation of the product by steam distillation or extraction from the acidic solution. *All the reactions were performed on a preparative scale (20–100 mmol) and yields of aldehyde represent product in hand.*[8]

Since alkyl bromides and iodides were found to be suitable for reaction with the anion **5** (A = H), the reaction was examined with respect to chloride and tosylate as the leaving group. *n*-Butyl chloride proved to be very slow in alkylating the anion, and a considerable quantity of starting material **1a** was recovered. However, *n*-butyl tosylate, under usual alkylation conditions, resulted in the formation of the sulfone **6** which must have arisen from nucleophilic displacement on sulfur. The yield of **6** was low (~10%) and the remainder of the tosylate and the oxazine was recovered unchanged. This aldehyde synthesis bears a relationship to that described by Stork[9] which utilizes the magnesium salt of an enamine. However, there are several advantages (as well as differences) to the present method which should be emphasized. The fact that the starting material is commercially available or readily prepared[10] offers an advantage over the unstable Schiff bases previously employed. The reduction of **2** to **3**, the major difference in the two methods, which produces quantitative yields, allows the introduction of deuterium or tritium into the molecule. This step, in our opinion, represents the most versatile method for preparing C-1 labeled aldehydes yet reported.[11] In addition, the deuteride reduction of **1a** and **1b** themselves followed by cleavage provides a convenient source of C-1 deuterated acetaldehyde and phenylacetaldehyde,

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(1) 2,4,4,6-Tetramethyl-5,6-dihydro-1,3(4H)-oxazine (**1a**) and 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine (**1b**) were obtained from Columbia Organic Chemicals, Columbia, S. C.

(2) Z. Eckstein and T. Urbanski, *Advan. Heterocyclic Chem.*, **4**, 311 (1963).

(3) W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellmann, *Angew. Chem. Intern. Ed. Engl.*, **5**, 875 (1966).

(4) Anion formation is incomplete using 1 equiv of butyllithium above −50° but is complete after 30 min below this temperature (checked by deuteration of **5**. The anion is stable for several days below −50°; however, proton abstraction from THF is noted above −30°[H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 1165 (1957)]. For convenience, all the anions were generated and subsequent alkylations were performed at −78°, using *n*-butyllithium as the base.

(5) The oxazine anion **5** is only partially soluble in the THF–hexane solvent under the conditions we have employed, thus providing visual monitoring of the process. The yellow suspension which initially appears disappears almost as quickly as the alkyl halide is introduced. Even though the anion is ambident, no trace of alkylation on nitrogen was observed.

(6) The sodio salt of **1b** was also generated in excellent yield using $Na^+ {}^-CH_2SOCH_3$ [E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962)], but this base failed to generate **5** (A = H). The difficulties encountered in freeing the aldehyde from DMSO precluded its use in this synthesis. In contrast to **5** (A = H), the anion derived from the benzyloxazine **5** (A = Ph) was stable indefinitely at room temperature and could be deuterated quantitatively to its monodeuterated derivative.

(7) An alternate, but less versatile, procedure for obtaining deuterated aldehydes is based upon converting a nitrile into its dihydro-1,3-oxazine derivative and then reducing the C=N link. This represents a complementary technique to that described here in that it allows the transformation RCN → RCDO [A. I. Meyers and A. Nabeya, *Chem. Commun.*, 1163 (1967)].

(8) The yields of aldehyde in Table I are not necessarily optimum since each run was performed only once. Small-scale (20 mmol) reactions invariably resulted in lower over-all yields than those carried out on a larger scale (100 mmol).

(9) G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

(10) J. J. Ritter and E. J. Tillmans, *J. Org. Chem.*, **22**, 839 (1957); A. I. Meyers, *ibid.*, **25**, 145 (1960). Approximately 200 g of **1a** or **1b** can be prepared in a single experiment and stored for months at room temperature, under a nitrogen or argon atmosphere.

(11) Other useful but more limited labeled aldehyde syntheses have been reported [D. Seebach, B. Erickson, and G. B. Singh, *ibid.*, **31**, 4303 (1966); J. C. Craig, *ibid.*, **33**, 871 (1968); R. A. Olafson and D. M. Zimmerman, *J. Am. Chem. Soc.*, **89**, 5058 (1967); D. J. Bennett, *Chem. Commun.*, 218 (1967); ref 7 above].

respectively. This method (as well as the extensions described in the subsequent articles) complements the synthesis described by Corey and Seebach[12] which adds one carbon in the conversion of alkyl halides to their corresponding aldehydes.[13] Further nucleophilic reactions of the anion **5** (A = H, Ph) are currently being examined with other substrates. Reactions, in high yield, have been observed using epoxides, esters, nitriles, and acid chlorides which provide a wide variety of alkylated oxazines **2** and in turn significantly increase the scope of this aldehyde synthesis.[14]

Table I. Formation of Aldehydes from Dihydro-1,3-oxazines[a]

RX	% **2**[b]	% **3**[b]	% **4** (over-all)	2,4-DNP mp, °C (lit.)
		A = H		
Methyl iodide	99	99	60	149–150 (142–148)[c]
n-Propyl iodide	98	90	65	102–104 (106)[c]
n-Butyl bromide	95	100	67	102–103 (104)[c]
Allyl bromide	90	90	53	116–118 (120)[c]
2-Bromoethyl ether	93	98	54	88–89 (88–89)[d]
Isopropyl iodide	99	90	47	121–122 (121–122)[c]
Benzyl bromide	88	100	54	153–154 (144–145)[c]
3-Bromocyclohexene	89	90	50	92–94 (97)[e]
		A = Ph		
Methyl iodide	91	96	70	137–138 (135)[f]
n-Propyl bromide	92	98	69	112–113 (115–116)[g]

[a] Deuterated aldehydes were obtained in comparable yields and were checked for isotopic purity using nmr. [b] Contained 95+% pure material. [c] I. Heilbron, "Dictionary of Organic Compounds," Oxford Press, New York, N. Y., 1965. [d] H. Adkins and G. Krsek, *J. Am. Chem. Soc.*, **71**, 3051 (1949). [e] C. W. Whitehead, *et al.*, *J. Org. Chem.*, **26**, 2814 (1961). [f] C. F. H. Allen and J. Van Allen, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955. [g] Semicarbazone derivative, Beilstein, "Handbuch der Organische Chemie," Vol. 7, Julius Springer, Berlin, 1925, p 329.

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(12) E. J. Corey and D. Seebach, *Angew. Chem. Intern. Ed. Engl.*, **4**, 1075, 1077 (1966).

(13) For recent reviews on other aldehyde syntheses see (a) J. Carnduff, *Quart. Rev.* (London), **20**, 169 (1966); (b) S. Patai, "Chemistry of the Carbonyl Group," John Wiley & Sons, Inc., New York, N. Y., 1966.

(14) The authors will provide complete experimental details to anyone requesting them.

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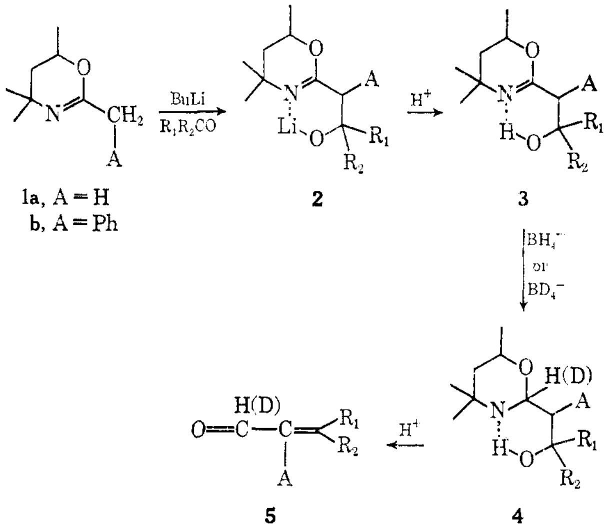
Aldehydes from Dihydro-1,3-oxazines. II. A New Synthesis of α,β-Unsaturated Aldehydes and Their C-1 Deuterated Derivatives

Sir:

It was previously shown[1] that the lithio salts of dihydro-1,3-oxazines (**1a,b**) are excellent nucleophiles and react efficiently with alkyl halides producing precursors to a variety of aliphatic aldehydes. We now wish to describe the reaction of these oxazine anions with a host of carbonyl compounds, giving rise to good yields of the adducts, **2**, which are useful precursors to conjugated aldehydes. Addition of aldehydes or ketones to the THF solution of the lithio salt of **1** (**a** or **b**) at −78° followed by hydrolytic work-up produces near quantitative yields of the oxazinyl alcohols, **3** (Table I). The crude adducts thus obtained are suitable for borohydride or borodeuteride reduction, as previously described,[1] leading to the tetrahydro-1,3-oxazines, **4**. Cleavage of **4** with aqueous oxalic acid gives 48–69% over-all yields of α,β-unsaturated aldehydes.[2] The complete scheme is therefore a three-step operation requiring no purification of intermediates



and can be accomplished, as in the case of aliphatic aldehydes,[1] in approximately 1.5 days from commercially available starting materials. In cases where the oxazinyl alcohols, **3**, were solids they could be readily purified by crystallization. However, if these products are liquids attempted purification by distillation results in reversal to the carbonyl compound and **1**.[3] The thermal instability of **3** is of no serious consequence in this synthesis since the "crude" material is formed in high yield and any impurities present do not interfere with the subsequent reduction step to **4**.

The alkylation of the anions **1** with ketones forming β,β-disubstituted acroleins is particularly valuable in this scheme since the aldehyde ylide reagents do not react with ketones.[4,5] Comparison of this method with that recently reported by Wittig indicates that the over-all yields[6] of unsaturated aldehydes appear to be comparable. The advantages of the present technique may be summarized as follows: (a) it permits labeling of the C-1 position with deuterium or tritium; (b) it starts with stable, commercially available materials;

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(1) A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Am. Chem. Soc.*, **91**, 763 (1969).

(2) The procedures mentioned in ref 1 are adaptable to the preparation of α,β-unsaturated aldehydes. Over-all yields are not necessarily optimum since many reactions were performed only once and on a 20–50-mmole scale.

(3) This behavior is not unexpected since aldol-type products are well known to reverse under the influence of heat and base. Note that **3** has a built-in basic site which obviously facilitates reversal to starting materials. The intramolecular hydrogen bonding in **3** and **4** was confirmed by infrared and nmr techniques.

(4) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 152, 205.