had ceased, the excess cyclohexanone was distilled, bp 25–35 °C (3–4 Torr).

Distillation of the residue produced fraction A, bp 45–105 °C (0.05–0.1 Torr), and fraction B, bp 105–125 °C (0.05–0.01 Torr). Redistillation of fraction A with a short-path still resulted in 7.36 g (0.04 mol, 57% yield) of ethyl (cyclohexen-1-oxy)ethanoate (**1**): bp 60–65 °C (0.05–0.1 Torr) [lit.[1] bp 103.5–104.5 (6 Torr)]; single peak by VPC analysis on QF-1 at 210 °C. NMR, τ 8.73 (3 H, t, J = 7 Hz), 5.80 (2 H, q, J = 7 Hz), 5.76 (2 H, s), 8.15–8.60 (4 H, m), 7.50–8.60 (4 H, m), 5.32–5.58 (1 H, m); IR 2990 (m), 2939 (s), 2860 (m), 2850 (m), 1752 (s), 1725 (s), 1660 (m) cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75; mol wt 184. Found: C, 65.14; H, 8.68; mol wt 184 (MS, 70 eV, 140 °C).

A sample of the compound was hydrolyzed with an excess of a 2% (w/v) solution of HCl in 90% ethanol for 1.5 h at reflux. Removal of excess ethanol followed by distillation of the residue and treatment of successive portions of the distillate with 2,4-dinitrophenylhydrazine and *p*-nitrobenzoyl chloride produced the corresponding derivatives of cyclohexanone and ethyl glycolate, respectively. The NMR spectrum of the distillate confirmed the presence of a mixture of cyclohexanone and ethyl glycolate.

2-Methylcyclohexanone Reaction. The reaction was carried out in the same manner as with cyclohexanone to give as the lower boiling product(s) (short-path distillation unit) a clear liquid, bp 55–60 °C (0.05–0.10 Torr), identified as a mixture of ethyl (6-methyl-1-cyclohexen-1-oxy)ethanoate (**2**) (60% yield) and ethyl (2-methyl-1-cyclohexen-1-oxy)ethanoate (**3**) (5% yield). The NMR spectrum showed peaks (areas only approximate) at τ 8.82 (3 H, t, J = 7 Hz), 8.64 (3 H, d, J = 7 Hz), 7.2–9.1 (7 H, broad envelope), 5.76 (2 H, q, J = 7 Hz), 5.70 (2 H, s), 5.36–5.59 (1 H, m); with addition of $Pr(fod)_3$, the lower field portion of the spectrum showed peaks at τ 6.34 (1 H, t, J = 4 Hz, C=CH), 6.90 (0.17 H, s, OCH_2CO of minor isomer), 723 (2 H, q, J = 7 Hz, CH_2OCO), 7.55 (2 H, s, OCH_2CO of major isomer); IR (neat) 2980 (m), 2920 (s), 2850 (m), 1745 (s), 1720 (s), 1650 (m) cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; mol wt 198. Found: C, 66.68; H, 9.14; mol wt 198 (MS, 70 eV, 48 °C).

3-Methyl-2-butanone Reaction. The reaction was carried out in the same manner as with cyclohexanone to give as the lower boiling product a clear liquid, bp 35–40 °C (15–20 Torr), identified as ethyl (3-methyl-1-buten-2-oxy)ethanoate (**4**). The NMR spectrum showed absorptions at τ 8.90 (6 H, d, J = 7 Hz), 8.73 (3 H, t, J = 7 Hz), 7.62 (1 H, sept, J = 7 Hz), 6.19 (2 H, doublet of doublets, J = 13, and 3 Hz), 5.77 (2 H, q, J = 7 Hz), 5.68 (2 H, s); IR (neat), 2970 (s), 2930 (m), 2870 (m), 1750 (s), 1725 (s), 1644 (m), 1600 (m) cm^{-1}.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36; mol wt 172. Found: C, 62.76; H, 9.58; mol wt 172 (MS, 70 eV, 60 °C). As much as 1% of the isomeric enol ether might have been present but could not be definitely identified.

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Registry No.—**1**, 64825-54-3; **2**, 64825-55-4; **3**, 64825-56-5; **4**, 64825-57-6; cyclohexanone, 108-94-1; ethyl diazoacetate, 623-73-4; 2-methylcyclohexanone, 583-60-8; 3-methyl-2-butenone, 563-80-4.

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Formyl-*d* Aromatic Aldehydes

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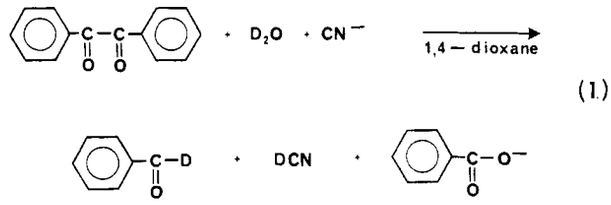
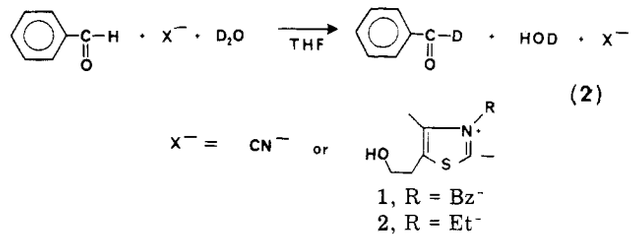
Aldehydes labeled with deuterium at the formyl carbon are useful precursors for a variety of labeled compounds containing deuterium at a specified position.[2] Although several procedures are available which provide such compounds by deuteration of an acyl anion equivalent[3] or by degradation of labeled precursors,[4,5] simple exchange reactions cannot be used to prepare these compounds.[9] Currently the simplest procedure for preparation of benzaldehyde and other aromatic aldehydes deuterated at the formyl position is that described by Schowen and co-workers in which benzil is cleaved by stoichiometric amounts of cyanide ion in deuterium oxide (eq 1).[5] We wish to report that a simple exchange reaction can be



(1)

successfully accomplished with several aromatic aldehyes, a catalytic or stoichiometric amount of either potassium cyanide or a thiazolium salt, a weak Lewis base, and deuterium oxide as the deuterium source. This reaction (eq 2) can be evaluated



(2)

1, R = Bz^-
2, R = Et^-

easily with small amounts of substrate by NMR and is a straightforward, simple method for incorporation of deuterium into some aldehydes without the isolation of any intermediates.

Since the proton transfer reactions in the benzoin condensation are known to occur faster than carbon–carbon bond formation,[6] we reasoned that a reaction like eq 2 would be synthetically useful as an exchange procedure leading to labeled aldehydes. In fact, when benzaldehyde was allowed to react with a catalytic amount of potassium cyanide in ethanol/deuterium oxide (benzoin reaction conditions), about 50% deuterium incorporation occurred as measured by NMR before significant amounts of benzoin product began to form. By using excess potassium cyanide and a phase isolation procedure (vide infra), the deuterium incorporation could be raised to 96% without appreciable amounts of benzoin product forming. Similar experiments shown in Table I establish that this procedure is applicable to other aromatic aldehydes in addition to benzaldehyde.

A phase isolation technique was used to slow the rates of condensation reactions relative to those for proton exchange, thus minimizing competing side reactions. In this procedure, an organic solvent containing the aldehyde is stirred vigorously with a solution of potassium cyanide in deuterium oxide. We presume that under these conditions aldehyde in the deuterium oxide phase exchanges its formyl proton via the cyanohydrin anion and that the condensation reaction is suppressed because the concentration of free aldehyde in the deuterium oxide phase is low. This phase isolation technique has other applications.[7]

Like the benzoin condensation, the exchange reaction we have described apparently involves transient formation of an acyl anion equivalent. We have found that both cyanide anion and alkyl or aryl thiazolium salts in the presence of mild bases like triethylamine or sodium acetate can be used for these reactions.[8] With different catalysts the rates of deuterium

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Table I. Formyl-*d* Aldehydes by Exchange with Deuterium Oxide

Aldehyde	Registry no.	Catalyst (equiv)	Organic phase	Time, h	Formyl-*d*,[a] %	Registry no.	Isolated yield, %
Benzaldehyde	100-52-7	KCN (1)	Et_2O	72	96	3592-47-0	62
		KCN (2)	Ph-H	72	>90		*b*
		1, NaOAc (1)[c]	THF	170	>90		*b*
		2, Et_3N (1)[c]	THF	18	>90		*b*
1-Naphthaldehyde	66-77-3	KCN (2)	Et_2O	98	~50	42007-09-0	*b*
		1, Et_3N (1)[c]	THF	2	>90		50
2-Chlorobenzaldehyde	89-98-5	KCN (2)	Et_2O	27	>98	64852-98-8	75
4-Chlorobenzaldehyde	104-88-1	KCN (2)	Et_2O	67	96	1517-47-1	76
3,4-Dimethoxybenzaldehyde	120-14-9	KCN (2)	Et_2O	119	81	27167-79-9	75
9-Anthraldehyde	642-31-9	**1**, Et_3N (1)[c]	THF	18	82	64852-99-9	70
Heptanal	111-71-7	**1**, Et_3N (1)[c]	THF	120	~60	64853-00-5	*d*
		2, Et_3N (1)[c]	THF	48	30		~50[e]

[a] Determined by NMR on isolated product where applicable. [b] The product was not isolated in this case. [c] Equimolar mixtures of the thiazolium salt and base were used. [d] The aldehyde product was purified by preparative gas chromatography. Gas chromatographic yields in similar reactions were less than 30%. [e] Yield determined by gas chromatography.

incorporation and condensation appear to be altered, but no systematic study has been carried out to measure these effects. In general, the thiazolium salts worked well with unsubstituted aromatic aldehydes and potassium cyanide worked best with substituted aromatic aldehydes. Extension of these reactions to aliphatic aldehydes was unsuccessful. For example, heptanal slowly exchanged its formyl proton for deuterium under our reaction conditions, but we were only able to isolate low yields of incompletely deuterated product (see Table I). Although NMR spectra of reaction mixtures containing stoichiometric amounts of heptanal, **2** (eq 2), and triethylamine showed that the aldehydic formyl proton had disappeared after two days, workup and isolation of the heptanal showed only ca. 30% deuterium incorporation (ca. 50% recovery of starting aldehyde by GLPC). Although we have not continued these studies, we believe that 1,2 addition or reversible condensation occurs under these conditions, making this reaction impractical for the synthesis of formyl-*d* aliphatic aldehydes. Some aromatic aldehydes also failed in these reactions. For example, *p*-nitrobenzaldehyde failed to incorporate deuterium using either potassium cyanide or thiazolium salts as catalysts. In this case, side reactions appeared to consume the starting aldehyde rapidly.

The thiazolium salt or potassium cyanide catalyzed exchange of aromatic aldehyde formyl protons for deuterium described above appears to be an efficacious procedure for the synthesis of some deuterated aldehydes. Advantages include its experimental simplicity, its ease of evaluation by NMR, and the absence of isolated synthetic intermediates. Disadvantages include its lack of complete generality, especially for aliphatic aldehydes, and the excessive reaction times needed in some cases.

Experimental Section

Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were determined on a Varian T-60 spectrometer. Aldehydes used in these experiments were purchased from commercial sources in reagent quality and tested for purity by NMR prior to use. Other organic reagents were used as supplied. Deuterium oxide was purchased from either Aldrich Chemical Co. or Merck Sharp & Dohme Canada Ltd. and was 99.8% *d*. Gas chromatographic analyses of aldehydes were carried out using a Varian Model 2440 gas chromatograph and a 3% SE-30 on 80–100 Chromosorb G column at 100–150 °C.

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (1) was prepared according to a literature procedure[7] in 72% yield and had mp 138.5–140.5 °C (lit.[7] mp 140–140.5 °C).

3-Ethyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide (2) was prepared according to a literature procedure[7] in 67% yield from 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole and ethyl bromide and had mp 81–80 °C (lit.[7] mp 85–86.5 °C); NMR (Me_2SO-d_6) δ 1.5 (t, 3 H), 2.5 (s, 3 H), 3.1 (t, 2 H), 3.6 (m, 2 H), 4.5 (m, 2 H), 10 (s, 1 H).

General Experimental Procedure. A solution of aldehyde in an organic solvent (1–2 M) and a solution of catalyst (1 or 2 equiv of either thiazolium salt **1** or **2** with an equal amount of base or potassium cyanide) in an equal volume of deuterium oxide were mixed and stirred vigorously at room temperature with a magnetic stirrer. Throughout all reactions two distinct phases were present. The reaction could be monitored periodically by stopping the stirring and examining the organic layer by NMR to determine the amount of deuterium incorporation at the formyl position of the aldehyde. After the exchange had gone to completion, the deuterated aldehyde was isolated by an extractive procedure followed by distillation or column chromatography, or, in the case of heptanal, preparative gas chromatography. Deuterium incorporation in the purified product was measured by NMR, and the product's purity was established by comparison with literature spectra, thin-layer or gas chromatography, melting point, and by conversion of liquid products to an established solid derivative using standard procedures. All of the reactions reported with isolated yields in Table I were run on 10–50 mmol of aldehyde.

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Registry No.—Deuterium-oxide, 7789-20-0; **1**, 16311-68-5; **2**, 54016-70-5.

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