crystallize. The crystalline acid was filtered and dried in a vacuum oven overnight. Yield, 3.0 g (83%); NMR ($CDCl_3$ + DMSO-d_6) τ 8.02 (s, 3 H, CH_3), 5.4 (s, 2 H, $PhOCH_2$), 5.33 (bs, 1 H, C_4–H), 4.65 (d, J = 5.0, 1 H, C_6–H), 4.36 (q, J = 5 and 9, 1 H, C_7–H), 3.14–2.52 (m, 5 aromatic H), and 2.1 (d, J = 9.0 Hz, NH). Anal. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04; O, 22.96; S, 9.20. Found: C, 54.82; H, 4.74; N, 7.72; O, 22.79; S, 8.98.

C. 7-Phenoxyacetamido-3-methylenecepham-4-carboxylic Acid 1-Oxide. *p*-Nitrobenzyl 7-phenoxyacetamido-3-methylenecepham-4-carboxylate 1-oxide,[6] 1.5 g (3 mM) was dissolved in 36 mL of dimethylformamide and 20 mL of water and cooled in an ice–water bath for addition of sodium sulfide, 1.1 g (4.5 mM), in 10 mL of water. The reaction mixture was stirred in the cold for 30 min. The mixture was poured into a mixture of 5% HCl and ethyl acetate. The organic layer was separated and washed with 5% HCl and then water. The ethyl acetate solution was slurried with water; the pH was adjusted to 7. The aqueous layer was separated and slurried with ethyl acetate and the pH was readjusted to 2.5. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to dryness in vacuo. The amorphous residue weighed 600 mg and was made to crystallize by trituration with ether. Yield of pure product; 500 mg (46%); NMR ($CDCl_3$ + DMSO-d_6) τ 6.19 (s, 2 H, C2-H_2), 5.45 (s, 2 H, α-CH_2), 4.97–4.87 (d and s, 3 H, C4-H and C6-H), 4.60 and 4.30 (2s, 2 H, C3-CH_2), 4.09 (q, 1 H, C7-H), 3.14–2.52 (m, 5 H, aromatic H), and 0.21 (d, 1 H, amide-NH); IR (Nujol mull) 1668, 1735 and 1758 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.72; H, 4.54; N, 7.91.

D. 7-Amino-3-methyl-2-cephem-4-carboxylic Acid. A suspension of 798 mg (2 mmol) of *p*-nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate in 10 mL of THF and 8 mL of water was cooled in an ice bath and a solution of 480 mg (2 mmol) of $Na_2S \cdot 9H_2O$ in 4.0 mL of water was added. The mixture was stirred at 0–5 °C for 35 min, then 2.0 mL of 1 N HCl was added, and THF was evaporated in vacuo. The resulting aqueous solution (pH 8.5) was extracted with 20 mL of ethyl acetate, and the extract was discarded. The pH of the aqueous solution was adjusted to 3.9 with 1 N HCl while being cooled in an ice bath. After approximately 3 min, the precipitate began to form. After 30 min the solid was filtered and dried in a vacuum oven overnight. Yield of 6 h, 320 mg (75%); *m/e* 214. Anal. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08; O, 22.40; S, 14.97. Found: C, 44.90; H, 4.70; N, 13.94; O, 22.14; S, 15.17.

Registry No.—**3g,** 27487-21-4; **4g,** 61-33-6; **5h,** 29124-83-2; **5v,** 28974-31-4; **6h,** 56487-68-4; **6v,** 10209-07-1; **7v,** 63427-57-6; **8v,** 64811-71-8.

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Regiospecificity of Enol Ether Formation in the Catalyzed Decomposition of Ethyl Diazoacetate in the Presence of Unsymmetrical Ketones

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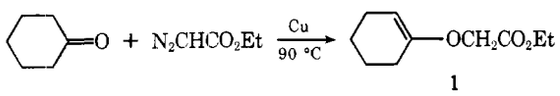
In 1953, Kharasch and co-workers[1] reported (among other products) the formation of ethyl (cyclohexen-1-oxy)ethanoate (1) in 43% yield from the reaction of excess cyclohexanone with ethyl diazoacetate in the presence of copper at 90 °C. We have found that the use of copper(I) chloride in place of copper gives similar results.



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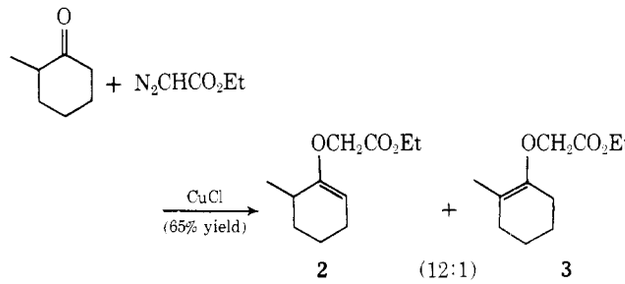
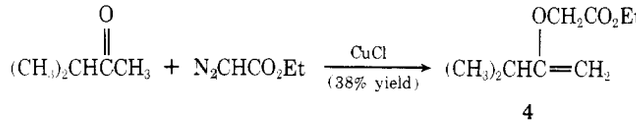
As part of an investigation of the reactions of carbenes and carbenoids with enolizable ketones, we report two examples of the decomposition of ethyl diazoacetate in the presence of copper(I) chloride and an excess of an unsymmetrical ketone which resulted in modest yields of the simple enol ether in which the least-substituted isomer dominated. For example, the use of 2-methylcyclohexanone results in a 65% yield of an isomer mixture in which approximately 92% is enol ether **2.**[2]



2 (12:1) 3

When the same reaction was carried out with 3-methyl-2-butanone, the only low-boiling product observed was enol ether **4.** The observed dominance of the least-substituted enol ether is consistent with simple steric and electronic considerations for the intramolecular proton abstraction required to get from the presumed intermediate carbonyl ylide **5** to the product.



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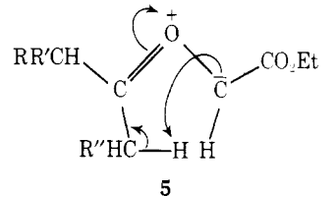

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Products which had a boiling point substantially higher than that of the simple enol ethers already described were not investigated for the reaction of 3-methyl-2-butanone and have been described previously by Kharasch[1] for the reaction with cyclohexanone.

Experimental Section

Elemental analyses were done by the Department of Medicinal Chemistry at the University of Kansas. Mass spectra were obtained on a Varian CH-5 mass spectrometer. Infrared spectra were obtained on a Beckman IR-8 (sodium chloride optics). Varian A-60 and T-60 spectrometers were used for determining NMR spectra of samples as solutions in chloroform-*d* containing an internal tetramethylsilane standard. An F&M Model 700 chromatograph (thermal-conductivity detector) was used for VPC analyses with the following columns: 10% QF-1 (a fluorosilicone; Dow Corning) on 80–100 mesh Gas Chrom Q (10 ft × 0.25 in. copper column) and 10% Hi-EEF 8 AP (a polycyclohexane–dicarbinol adipate; Applied Science Laboratory) on 60–80 mesh Gas Chrom Q (8 ft × 0.25 in. copper column).

Copper(I) chloride was prepared from copper(II) sulfate[4] and purified by washing several times each with glacial acetic acid, absolute ethanol, and anhydrous diethyl ether. Ethyl diazoacetate was prepared by the method of Searle.[5] All ketones were distilled prior to each reaction.

Cyclohexanone Reaction. A solution of ethyl diazoacetate (8.0 g, 0.0701 mol) and cyclohexanone (16 g, 0.163 mol) was added slowly (1.5–2.0 h) with stirring to a mixture of copper(I) chloride (0.10 g) and cyclohexanone (32.0 g, 0.326 mol) maintained at 90–95 °C (N_2 atmosphere). When the addition was complete and nitrogen evolution

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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.

Acknowledgments. The authors are grateful for support from the University of Kansas General Research Fund.

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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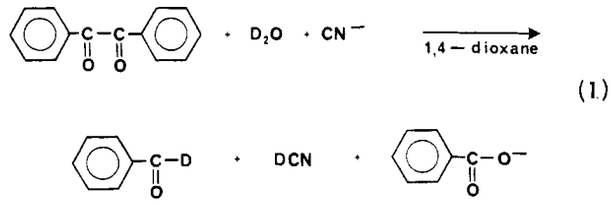
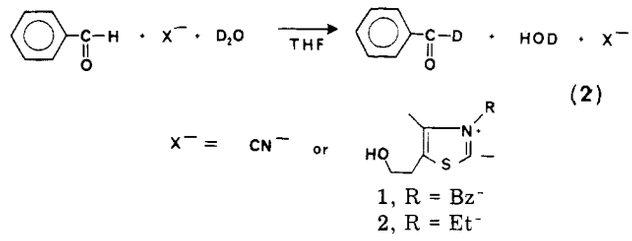
Aldehydes labeled with deuterium at the formyl carbon are useful precursors for a variety of labeled compounds containing deuterium at a specified position.[2] Although several procedures are available which provide such compounds by deuteration of an acyl anion equivalent[3] or by degradation of labeled 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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