Mixed Acylals; Synthesis of Alkylidene Carboxylate Formates

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Sulfurization may be due to nucleophilic attack of these anions on the carbonyl C-atom followed by elimination of O₂PS₂²⁻ or OPS₂⁻³ (4), respectively, e.g.

\[ R^1\text{C}=O + \text{SPS}_2 \rightarrow \begin{array}{c}
\text{R}^1\text{S}^\text{=C} \text{O} \\
\text{R}^2\text{S}^\text{=C} \text{O}
\end{array} \]

If R¹ or R² is a good leaving group (as in acid chlorides), no thiono compound (3) is obtained⁵, probably as a consequence of substitution of the leaving group. For aromatic ketones, the reaction rate is lower when R¹ or R² is electronegative, suggesting that nucleophilic attack of the negative oxygen on phosphorus in the addition product is rate-determining.

In general, the reaction rates are higher in acetonitrile than in the other solvents used (see Table), but the nitrite is not completely inert towards PS₃₁₀. During work-up under hydrolyzing conditions, thiocacetamide is formed as a side product. With more reactive compounds such as carboxamides, even diethyl ether can be used as a solvent, although it does not give clear solutions with the sulfurizing agent. With esters, except formates, the best yields of thione derivatives are obtained when no solvent and only a catalytic amount of sodium sulfide or hydrogen-carbonate is used. We have no explanation for these observations.

**Conversion of Carboxyl Compounds into Thiono Compounds; General Procedure:**

All sulfurization reactions were performed by dissolving the carboxyl compound in a suitable solvent, adding the solution of PS₃₁₀ in the same solvent, and adding solid sodium-hydrogen carbonate to the mixture under stirring and at such a rate as allowed by the evolution of carbon dioxide. Stirring was then continued for several hours. Experimental details are given in the Table. Isolation of the products was performed using several, slightly different procedures:

**Isolation Procedure A:** The reaction mixture was poured into water. The solid product which was separated was isolated by filtration, washed several times with water, and dried at low pressure (0.5 torr) and ~ 50°.

**Isolation Procedure B:** Ether was added to the reaction mixture. The ethereal solution was washed several times with aqueous sodium-hydrogen carbonate (5%) and water, dried, and distilled at low pressure.

**Isolation Procedure C:** The reaction mixture was diluted with ether, filtered, and the filtrate distilled at low pressure.

**Isolation Procedure D:** Low-boiling reaction products were distilled from residual phosphorus compounds in the reaction mixture at low pressure and collected in a dry-ice trap. They were purified by redistillation.

Using these procedures, the products contained in some cases small amounts (up to 10%) of the starting compound. Pure samples (> 95%), however, could be obtained by redistillation or recrystallization. O-Ethyl thiocacetate contained some S-ethyl thioacetate, which could not be separated by distillation. To obtain a pure sample, the S-ethyl thioacetate was converted into ethyl dithioacetate via the sulfurization described. Separation of O-ethyl thioacetate and ethyl dithioacetate was possible by distillation. All products were identified and checked for purity by 'H-N.M.R. and in the case of aromatic ketones also by I.R. spectrometry. A comparison of the melting and boiling points found with values from the literature is given in the Table.

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Since excellent synthetic procedures for the preparation¹,² of pure mixed anhydrides of formic acid and other carboxylic acids are now available, it appeared worthwhile to investigate the reactivity of these anhydrides towards aldehydes, which might lead to a synthesis of the hitherto unknown mixed alkylidene dicarboxylates of formic acid and other carboxylic acids.
The relevant mixed anhydrides decompose readily at higher temperatures and in the presence of acids and bases. Thus, we performed our first experiments at 0°C using iron(III) chloride as a catalyst; formaldehyde was introduced into ethereal solutions of mixed anhydrides. However, the yields of mixed acylals obtained under these conditions were very low due to polymerization of the aldehyde and decomposition (evolution of gas) of the anhydride.

With acetaldehyde, the yields were better (up to 50%), but the reaction mixtures always contained substantial amounts of the ethyldiene dicarboxylate with identical acid residues. In some cases, complete separation of this side product from the desired alkylidene carboxylate formate was difficult or even impossible. Ethylene diformate was never found, probably due to its low stability.

Because the use of pure mixed anhydrides did not prevent the formation of acylals with identical acid residues, we modified the procedure, replacing the mixed anhydride by a formic acid-carboxylic acid mixture. It is known that such mixtures contain the mixed anhydride as a consequence of equilibrium (1).

\[
\text{(1): } R-CO-C-R + HCOOH \rightleftharpoons R-CO-O-C-H + R-COOH
\]

The best results were obtained when the anhydride and formic acid were used in excess (50% and 500%, respectively). If the molar ratio between aldehyde and anhydride is higher, \(a,a'-\text{acyloxyethers, e.g.}\)

\[
\text{(4): } R^2-\text{CH-O-CH}_2\text{-R} + R'-\text{COOH} \rightleftharpoons R^2-\text{CO-CH}_2\text{-R' + R-COOH}
\]

are found as side products.

Among the several possible catalysts tested (FeCl₃, H₂SO₄, P₂O₅, HCOONa, pyridine), phosphorus pentoxide appeared to be the most effective.

The alkylidene carboxylate formates (5) prepared by this procedure are listed in the Table. The compounds were identified and tested for purity by N.M.R. In all compounds, the \(H_a\)-peak of

\[
\text{(5): } R^2-\text{CH}_2\text{-O-C-R' + R-COOH} \rightleftharpoons R^2-\text{CH}_2\text{-O-C-R' + R-COOH}
\]

was found between \(\delta = 6.5\) and 6.9 ppm (TMS as internal reference).

In view of the strong acylating and preferential formylating ability of the formic acid – acetic anhydride system a tentative reaction scheme might be represented as follows.

\[
\text{(1): } R^2-\text{CHO} + R'^1-\text{COOH} \rightleftharpoons R^2-\text{CH}_2\text{-O-C-R' + R-COOH}
\]

In Reaction (2), the weaker acid will react more readily than formic acid, though not exclusively. Any alkylidene diformate resulting from the participation of formic acid in Reaction (2) will in any case decompose in the acidic medium; it was never found as side product. The hypothetical intermediate semi-acylal (3) could not be detected.

Preparation of Mixed Acylals; General Procedure:
The carboxylic anhydride is mixed with formic acid in a molar ratio of 1:5. After standing for 30 min at room temperature, an aldehyde (2/3 equivalents based on anhydride) and phosphorus pentoxide (0.5 g per mol of aldehyde) are added. The mixture becomes warm and a gas is evolved. After the mixture has been left for 3 hr at room temperature, formic acid is evaporated at reduced pressure (15 torr), ether is added, and the ethereal solution is extracted several times with aqueous sodium-hydrogen carbonate and finally with water. The solution is dried with sodium sulfate, ether is evaporated, and the residue is distilled using a Vigreux column (80 x 1.2 cm). Alkylidene acetate formates free from alkylidene diacetates can only be obtained by distillation of the crude products using a spinning-band column of at least 25 theoretical plates.
Communications 153

March 1973

Table. Alkylidene Carboxylate Formates (5) obtained according to Reactions (2) and (3).

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>b.p./torr</th>
<th>n²⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>n-C₃H₇</td>
<td>54</td>
<td>75°/10</td>
<td>1.4082</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>CH₃</td>
<td>50</td>
<td>65°/12</td>
<td>1.4051</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>C₂H₅</td>
<td>46</td>
<td>75°/12</td>
<td>1.4097</td>
</tr>
<tr>
<td>CH₃</td>
<td>n-C₃H₇</td>
<td>57</td>
<td>86°/11</td>
<td>1.4124</td>
</tr>
<tr>
<td>i-C₃H₇</td>
<td>i-C₃H₇</td>
<td>51</td>
<td>78°/12</td>
<td>1.4082</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>t-C₄H₉</td>
<td>33</td>
<td>84°/12</td>
<td>1.4092</td>
</tr>
<tr>
<td>n-C₅H₁₁</td>
<td>CH₃</td>
<td>50</td>
<td>75°/13</td>
<td>1.4104</td>
</tr>
<tr>
<td>n-C₅H₁₁</td>
<td>C₂H₅</td>
<td>54</td>
<td>85°/10</td>
<td>1.4134</td>
</tr>
<tr>
<td>n-C₅H₁₁</td>
<td>i-C₃H₇</td>
<td>45</td>
<td>87°/13</td>
<td>1.4165</td>
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<tr>
<td>i-C₅H₇</td>
<td>CH₃</td>
<td>48</td>
<td>71°/10</td>
<td>1.4093</td>
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<td>45</td>
<td>82°/12</td>
<td>1.4117</td>
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<tr>
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<td>i-C₃H₇</td>
<td>44</td>
<td>82°/12</td>
<td>1.4132</td>
</tr>
</tbody>
</table>

* The products showed no impurities in their N.M.R. spectra.

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5. At a molar ratio of aldehyde: anhydride = 2:1, acyloxy ethers are the main products; L. W. McTeer, U.S. Patent 3383374 (1968); C. A. 69, 26768 (1968).

A General Method for the Synthesis of Substituted Azetidines

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Despite current interest in the synthesis and chemistry of azetidines, there are only few reports on such derivatives which have functional groups directly attached to the ring; and there is only one example of an azetidin-3-one which is not fused to another ring. Most of the methods available for the synthesis of substituted azetidines seem to be limited by the availability of the starting materials and the methods themselves cannot claim wide applicability. However, recently an elegant method of preparing 1-alkylazetidin-3-ols was described, which makes these derivatives easily accessible. We now report a convenient method for the oxidation of these azetidinols to the corresponding ketones, and some reactions of 1-alkylazetidin-3-one, which provide easy entry to various functionally substituted azetidines.

1-Benzhydrylazetidin-3-ol was chosen for this study, as the benzhydryl group can easily be removed by catalytic hydrogenation and thus various alkyl and acyl substituents can be attached to position 1 of the ring. The oxidation of 1-alkylazetidin-3-ols (1) using various oxidising agents was investigated; in most of the cases, opening and fragmentation of the ring was observed. When milder oxidising agents were used no oxidation was observed and the starting material was recovered unchanged. However, using chromic acid in acetic acid under carefully controlled conditions it was possible to oxidise the azetidin-3-ols (1a and 1b) to the corresponding 3-ones (2a and 2b). Ketones 2 were unstable at room temperature; ketone 2a could be stored at 0–5° for several weeks without significant decomposition, whereas 2b could not be stored for more than 12 hours without less than 60% decomposition.

The assignment of structure 2a was supported by correct elemental analysis and by mass spectrometry which gave the molecular formula C₁₆H₁₅NO [M⁺, m/e 237, M-28 (C₁₃H₁₁N), M-70(C₂H₅)] The N.M.R. spectrum (in CDCl₃, TMS reference) showed a four-proton singlet at δ = 4.6 ppm assignable to the ring methylene protons of 2a and one proton singlet at δ = 6.4 ppm assignable to the benzyl protons, in addition to the signals expected for aromatic protons. Both ketones 2a and 2b showed an intense i.r. absorption at 1820 cm⁻¹ (strained cyclic ketones).

Ketones 2a and 2b were reduced with sodium borohydride in cold (5°) methanol to give the parent azetidin-3-ols (1a and 1b). Ketone 2a gave a cyanohydrin benzoate on treatment with potassium cyanide and benzoyl chloride. Nitrile 3a could be converted to the corresponding hydroxy acid by controlled hydrolysis. Treatment of ketones 3 with aryllithium, alkylmagnesium halides gave the corresponding 3-alkyl- and 3-arylazetidin-3-ols, respectively.

1. Benzhydrylazetidin-3-one (2a):
Cold (−5°) conc. sulfuric acid (20 g) was added gradually to a cooled (−5°) and stirred solution of 1-benzhydrylazetidin-3-ol (12 g), chromic anhydride (6 g), and acetic acid (20 ml) in 15% aqueous acetone (100 ml). The temperature during the addition and in all the following steps was never allowed to rise above 2°. The reaction mixture was stirred for a further 2 hr and was then made alkaline with aqueous ammonia (to pH 8.4). A large excess (~600 g) of sodium chloride was added to the mixture and then the slurry was extracted with ether (5 x 200 ml). The ether extract was dried with sodium sulfate. Evaporation of ether gave a syrupy mass, which was passed through a column of basic alumina. Elution with n-hexane/benzene (1:1) gave a white amorphous solid, which could be recrystallised from hexane; yield: 65%; m.p. 82°.

C₁₆H₁₅NO calc. C 80.98 H 6.37 N 5.90
(237.3) found 80.84 6.10 6.01

1-Cyclohexylazetidin-3-one (2b):
This compound was similarly prepared from 1-cyclohexylazetidin-3-ol; yield 40%, m.p. 67° (dec.)
A solution of benzoyl chloride (2.8 g) in benzene (20 ml) was gradually added to a stirred and cooled (0°) mixture of 1-benzhydrylazetidin-3-one (4 g), sodium cyanide (1 g), benzene (5 ml), and water (50 ml) during the course of 2 hr. The reaction mixture was stirred for a further 2 hr, after which the benzene layer was separated and washed with several portions of water and was dried with sodium sulfate. Evaporation of the solvent at reduced pressure at 35° gave a white crystalline solid which was recrystallised from benzene/hexane; yield 69%; m.p. 215°.

C_{24}H_{20}N_{2}O_{2} calc. C 78.24 H 5.47 N 7.61 found 78.11 5.49 7.48

I.R. (KBr): \nu_{max} = 2240 (w) and 1720 cm^{-1} (s).

1H-N.M.R. (CDCl_3, TMS): \delta = 4.1 - 3.5 (m, 4H), 4.5 (s, 1H), 8.2 - 7.3 ppm (m, 15H).

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This compound was similarly prepared from 1-benzhydrylazetidin-3-one and methyllithium. Alternatively, compound 5d could also be prepared by a similar procedure using methylmagnesium iodide instead of methyllithium. The product was recrystallised from hexane; yield 64%; m.p. 80° (dec.)

C_{17}H_{19}NO calc. C 80.60 H 7.56 N 5.53 (253.3) found 80.51 7.38 5.60

I.R. (KBr): \nu_{max} = 3400 (s) and 1585 (m).

1H-N.M.R. (CDCl_3, TMS): \delta = 2.2 (broad hump, exchangeable with D by D_2O shake, OH), 3.9 - 3.6 (m, 4H), 4.5 (s, 1H), 7.8 - 7.2 ppm (m, 10H).

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