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Mixed Acylals; Synthesis of Alkylidene Carboxylate Formates

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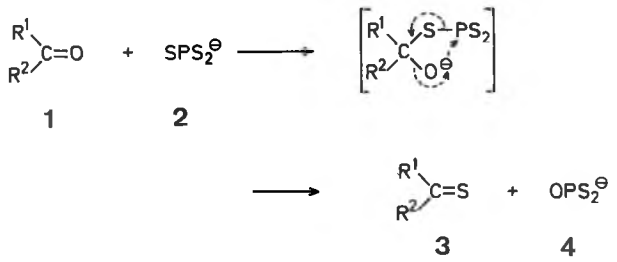
Sulfurization may be due to nucleophilic attack of these anions on the carbonyl C-atom followed by elimination of $O_2PS^{\ominus}$ or $OPS_2^{\ominus}$ (**4**), respectively, e.g.



1 **2**

3 **4**

If R^1 or R^2 is a good leaving group (as in acid chlorides), no thiono compound (**3**) is obtained[11], probably as a consequence of substitution of the leaving group. For aromatic ketones, the reaction rate is lower when R^1 or R^2 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 nitrile is not completely inert towards P_4S_{10}. During work-up under hydrolyzing conditions, thioacetamide 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 Carbonyl Compounds into Thiono Compounds; General Procedure:

All sulfurization reactions were performed by dissolving the carbonyl compound in a suitable solvent, adding the solution of P_4S_{10} 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 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 thioacetate 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 ^{1}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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Mixed Acylals; Synthesis of Alkylidene Carboxylate Formates

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Since excellent synthetic procedures for the preparation[1,2] 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.

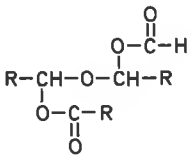
The relevant mixed anhydrides decompose readily at higher temperatures and in the presence of acids and bases. Thus, we performed our first experiments at 0° using iron(III) chloride[3] as a catalyst; formaldehyde was introduced into ethereal solutions of mixed anhydrides. However, the yields of mixed 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 ethylidene 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)*.

(1) $R-C(=O)-O-C(=O)-R + HCOOH \rightleftarrows R-C(=O)-O-C(=O)-H + R-COOH$

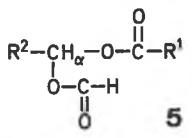
The best results were obtained when the anhydride and formic acid were used in excess (50% and 500%, respectively). If the molar ratio between aldehyde and anhydride is higher, α,α′-acyloxyethers, e.g.



are found as side products[5].

Among the several possible catalysts tested ($FeCl_3$, H_2SO_4, P_2O_5, 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_α-peak of



5

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

In view of the strong acylating and preferential formylating ability of the formic acid – acetic anhydride system[6] a tentative reaction scheme might be represented as follows.

(1) $R^2-CHO + R^1-COOH \rightleftarrows R^2-CH(OH)-O-C(=O)-R^1$

1 **2** **3**

(2) $R^2-CH(OH)-O-C(=O)-R^1 + H-C(=O)-O-C(=O)-R^1 \longrightarrow$

3 **4**

$R^2-CH(O-C(=O)-H)-O-C(=O)-R^1 + R^1-COOH$

5 **2**

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 (by ^{1}H-N.M.R. analysis) in the reaction mixture because the equilibrium lies far on the left side, and because compound **3** is used in Reaction *(3)*.

A similar scheme, combining Reactions *(2)*, *(4)*, and *(5)* but not involving Reaction *(3)*, could explain the formation of α,α′-diacyloxy ethers (**7**) when the aldehyde is used in excess.

(4) $R^2-CH(OH)-O-C(=O)-R^1 + R^2-CHO \rightleftarrows R^2-CH(OH)-O-CH(O-C(=O)-R^1)-R^2$

3 **1** **6**

(5) $R^2-CH(OH)-O-CH(O-C(=O)-R^1)-R^2 + R^1-C(=O)-O-C(=O)-H \longrightarrow$

6 **4**

$R^2-CH(O-C(=O)-H)-O-CH(O-C(=O)-R^1)-R^2 + R^1-COOH$

7 **2**

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 × 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.

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

R^1	R^2	Yield[a] (%)	b.p./torr	n_D^{20}
CH_3	n-C_3H_7	54	75°/10	1.4082
C_2H_5	CH_3	50	65°/12	1.4051
C_2H_5	C_2H_5	46	75°/12	1.4097
C_2H_5	n-C_3H_7	57	86°/11	1.4124
C_2H_5	i-C_3H_7	51	78°/12	1.4082
C_2H_5	t-C_4H_9	33	84°/12	1.4092
n-C_3H_7	CH_3	50	75°/13	1.4104
n-C_3H_7	C_2H_5	54	85°/10	1.4134
n-C_3H_7	n-C_3H_7	55	94°/13	1.4165
n-C_3H_7	i-C_3H_7	45	87°/12	1.4130
i-C_3H_7	CH_3	48	71°/10	1.4095
i-C_3H_7	C_2H_5	45	82°/12	1.4117
i-C_3H_7	i-C_3H_7	44	82°/12	1.4132

[a] The products showed no impurities in their N.M.R. spectra.

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A General Method for the Synthesis of Substituted Azetidines

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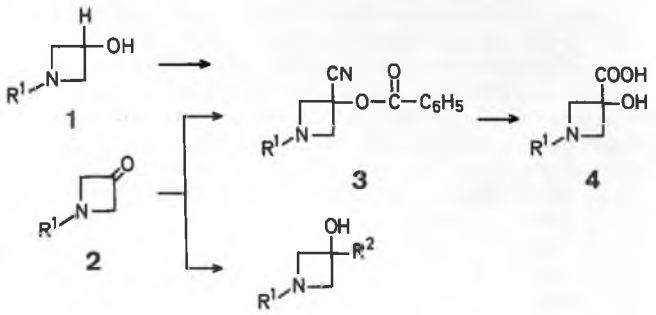
Despite current interest in the synthesis and chemistry of azetidines, there are only few reports on those derivatives which have functional groups directly attached to the ring[1] and there is only one example of an azetidin-3-one which is not fused to another ring[2]. Most of the methods available for the synthesis of substituted azetidines[3] 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[4], 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[5] 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 $C_{16}H_{15}NO$ [M^+, *m/e* 237, M-28 ($C_{15}H_{15}N$), M-70($C_{13}H_{11}$)]. The N.M.R. spectrum (in $CDCl_3$, TMS reference) showed a four-proton singlet at $\delta = 4.0$ ppm assignable to the ring methylene protons of **2a** and one proton singlet at $\delta = 4.6$ ppm assignable to the benzylic proton, 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, alkyllithium, or alkylmagnessium halides gave the corresponding 3-alkyl- and 3-arylazetidin-3-ols, respectively.



1-4 a $R^1 = -CH(C_6H_5)_2$ **5 c** $R^1 = -CH(C_6H_5)_2$, $R^2 = C_6H_5$
b $R^1 = c\text{-}C_6H_{11}$ **d** $R^1 = -CH(C_6H_5)_2$, $R^2 = CH_3$

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 acid 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 × 200 ml). The ether extract was dried with sodium sulfate. Evaporation of ether under reduced pressure 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°.

$C_{16}H_{15}NO$	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.)

$C_{19}H_{15}NO$	calc.	C 70.55	H 9.88	N 9.14
(273.3)	found	70.48	9.94	9.00

1-Benzhydryl-3-benzoyloxy-3-cyanoazetidine (3a):
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 recrystallized from benzene/hexane; yield 69%; m.p. 215°.

$C_{24}H_{20}N_2O_2$	calc.	C 78.24	H 5.47	N 7.61
(368.4)	found	78.11	5.49	7.48

I.R. (KBr): $\nu_{max} = 2240$ (w) and 1720 cm^{-1} (s).
^{1}H-N.M.R. ($CDCl_3$, TMS): $\delta = 4.1$–3.5 (m, 4H), 4.5 (s, 1H), 8.2–7.3 ppm (m, 15H).

1-Benzhydryl-3-carboxyazetidin-3-ol (4a):
A solution of 1-benzhydryl-3-cyano-3-benzoyloxyazetidine (3.7 g) was dissolved in 10% ethanolic sodium hydroxide (100 ml) and was stirred overnight at room temperature. Water (25 ml) was then added and the mixture refluxed for 2 hr on a water bath. Ethanol was removed under reduced pressure. The residue was diluted with water (100 ml) and the reaction mixture neutralized with 1*N* acetic acid (pH 7.5). The precipitated hydroxy-acid was isolated by filtration and washed with several portions of cold water. Recrystallization from benzene gave colorless needles; yield: 40%; m.p. 178° (dec.).

$C_{17}H_{17}NO_3$	calc.	C 72.08	H 6.00	N 4.95
(283.3)	found	71.86	5.99	N 5.14

1-Benzhydryl-3-phenylazetidin-3-ol (5c):
A solution of 1-benzhydrylazetidin-3-one (2.37 g) in anhydrous ether (50 ml) was added dropwise to a stirred and cooled (0°) solution of phenyllithium (2 g) in ether (200 ml). The reaction mixture was stirred in the cold for 2 hr and then left overnight at room temperature. The lithio compounds were then decomposed by the careful addition of water. The ether layer was separated and washed several times with water and then dried with sodium sulfate. Careful addition of 5% hydrogen chloride in isopropanol gave a colorless crystalline solid which could be recrystallised from isopropanol; yield 71%; m.p. 195°.

The free base was obtained as a viscous syrup by dissolving the hydrochloride in 1*N* sodium hydroxide and extracting the solution with ether.

$C_{22}H_{21}NO$	calc.	C 87.96	H 7.05	N 4.66
(315.4)	found	88.04	7.18	4.44

I.R. (KBr): $\nu_{max} = 3400$ (s) and 1585 (m).
^{1}H-N.M.R. ($CDCl_3$, TMS): $\delta = 2.7$ (broad hump, exchangeable with D by D_2O shake, OH), 3.8–3.5 (m, 4H); 4.5 (s, 1H), 7.8–7.2 ppm (m, 15H).

1-Benzhydryl-3-methylazetidin-3-ol (5d):
This compound was similary 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).
^{1}H-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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Amidoalkylierende Derivate des Ninhydrins

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Im Rahmen unserer Untersuchungen über reaktive Derivate von N-Acyl-Halbaminalen aktivierter Carbonyl-Verbindungen[1] haben wir als erstes Keton das unsubstituierte Indantrion in Form seines Hydrats (Ninhydrin, **1**) eingesetzt. Die Umsetzungen mit primären Carbonsäureamiden (**2a, b**) führten zu den kristallinen Addukten **3a, b**[2], die sich mit Thionylchlorid leicht in die umkristallisierbaren 2-Acylamino-2-chloro-1,3-dioxo-indane **4a, b** überführen ließen.

Im Vergleich zu den in Lit.[1] beschriebenen N-Acyl-α-chloro-glycin-Derivaten sind diese Chlor-Verbindungen unter Umgebungsbedingungen weitgehend stabil. Die elektronenziehenden Nachbargruppen verleihen dem C-2-Atom aber eine ausreichende Aktivität für Reaktionen mit nucleophilen Substanzen.