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NEW ROUTES TO γ-KETOESTERS, β-HYDROXY-δ-KETOESTERS, α,β-UNSATURATED γ-KETOALDEHYDES, AND ACETALS. SYNTHESIS OF CYCLOPENTENONES

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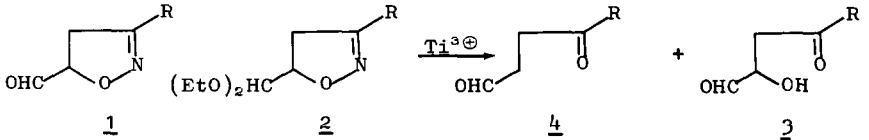
Abstract - New methodology, based on the chemistry of silyl nitronates, nitrile oxides (hydroxamic acid chlorides), and derived 2-isoxazolines, is developed for the preparation of the title compounds.

In an earlier paper the addition of nitrile oxides to acrolein and acrolein diethyl acetal was investigated.[1] It was found that the 5-formylisoxazoline was unstable and was formed in poor yield, but the acetal 2 was well characterized and could be synthesized in reasonably good yield. The reduction of 2 with titanous ions to the expected 2-hydroxy-4-oxoaldehyde 3 was unsuccessful; cleavage of the C^5-O bond occurred and the 4-ketoaldehyde 4 was isolated in 20-30 % yield. In view of the general synthetic value of compounds of type 3, *e.g.* for synthesis of heterocycles and cyclopentenones, we investigated the behaviour of 2 towards selective reduction. Catalytic hydrogenation over Raney-Ni in ethanol[2] cleaved the N-O bond smoothly and selectively and 5 was formed nearly quantitatively (Scheme 1).



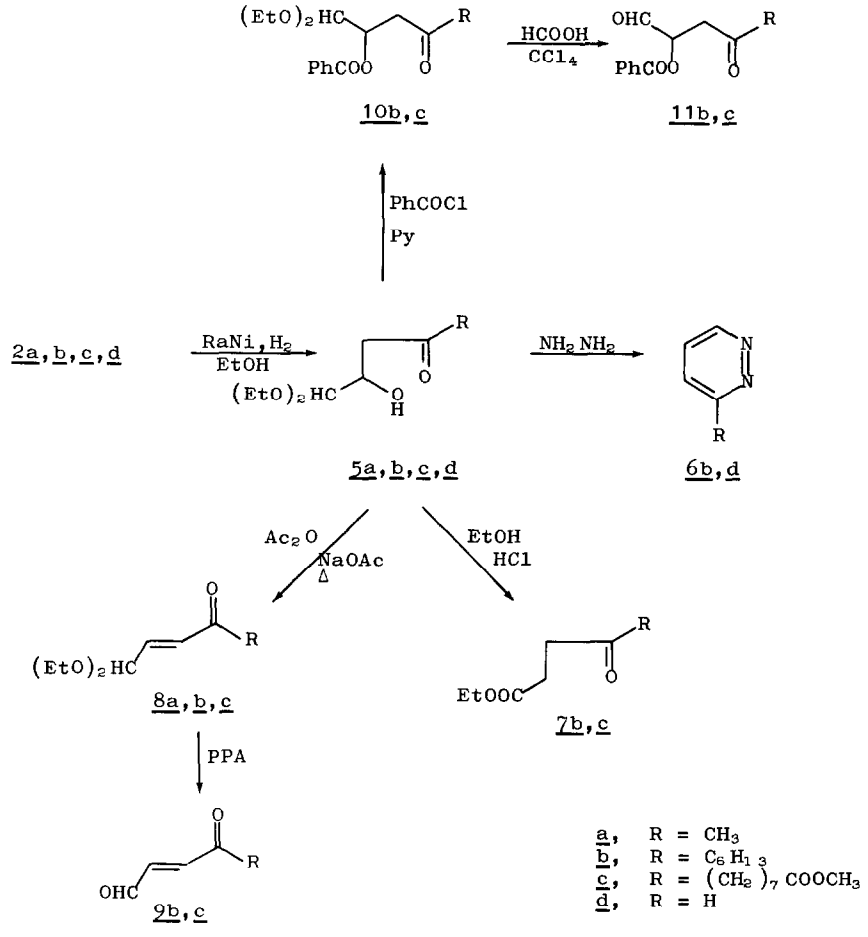
1 2 4 3 (traces)

The acetal 2d was obtained by reacting acrolein diethyl acetal with nitromethane, trimethylchlorosilane, and triethylamine for 6 days in acetonitrile/benzene. Catalytic reduction gave 5d, the half acetal of malic dialdehyde, a compound synthesized earlier in a different way for the synthesis of tropinone.[3] The structure of 5d was proved by its conversion into pyridazine 6d with hydrazine sulfate. Reaction of 5b with hydrazine sulfate gave 3-hexylpyridazine 6b.

When 5b,c were treated with catalytic amounts of dry hydrogen chloride in ethanol, generated by addition of acetyl chloride, they rearranged practically quantitatively to the γ-ketoesters 7b,c. The ease of the rearrangement is rather surprising because it is usually not observed in carbohydrate chemistry, where glycosides contain the same structural entity. The unsaturated γ-ketoacetals 8b,c are not on the reaction path, since they do not give 7b,c under the same experimental conditions. This constitutes a novel synthesis of γ-ketoesters which are valuable synth-

etic intermediates.[4]

Compounds 5a,b,c were converted into α,β-unsaturated γ-ketoacetals 8a,b,c by heating with acetic anhydride and sodium acetate. The corresponding α,β-unsaturated γ-ketoaldehydes 9b,c were obtained from 8b,c by treatment with PPA in aqueous acetone.

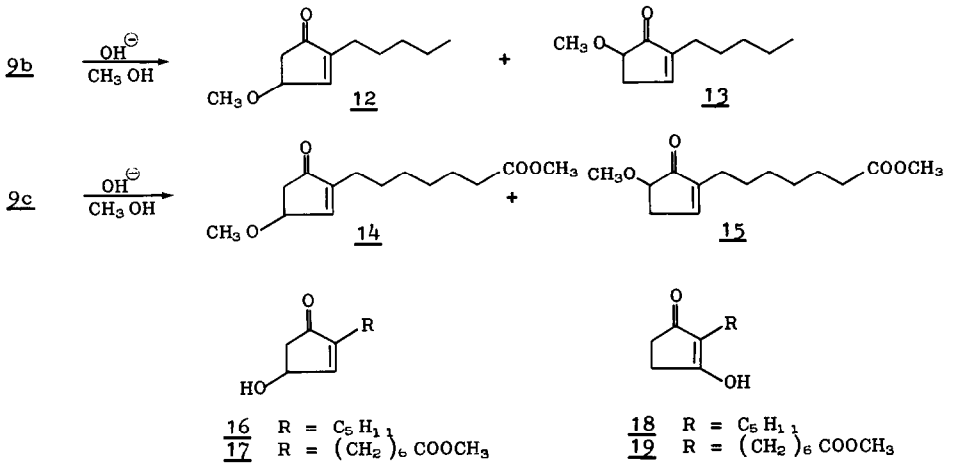


SCHEME 1

Compounds 5b,c gave the benzoates 10b,c on treatment with benzoyl chloride in pyridine which were transformed into the α-benzoyloxy-γ-ketoaldehydes 11b,c with formic acid in carbon tetrachloride. Thus, by changing the reaction conditions slightly it is possible to obtain a number of useful synthetic intermediates from 5.

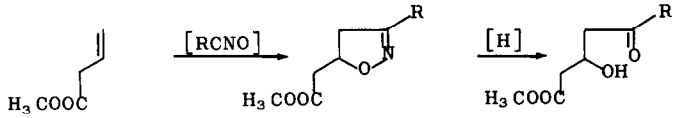
Having access to compounds of the general structures 5 or 11, an attempt was made to convert them into cyclopentenones. According to the literature[5-9] and our experience[1,10] the conditions for base-catalyzed cyclizatio.. of the 4-ketoaldehydes 3 are much more critical than those for 1,4-diketones. Derivatives of type 9 have been cyclized in methanol to the corresponding methoxycyclopentenones.[9] When 9b was cyclized according to this method, the ^{1}H NMR spectrum of the product indicated the formation of a mixture of 12 and 13. Compound 9c gave likewise a mixture of 14 and 15. This route was therefore abandoned. Attempts to prepare 16 and 17 by controlled acid-catalyzed hydrolysis of the acetals 5b,c to the corresponding aldehydes in aqueous acetone at 25 °C and subsequent treatment of the crude product with

base were unsuccessful. Compound 16 was isolated in a low yield (ca.20 %) by treatment of 11b with 4 M sodium hydroxide in a water:ether two-phase system, but surprisingly 17 could not be detected in the reaction mixture when 11c was reacted with base under the same conditions. We therefore investigated the acid catalyzed cyclization of 5 and 11 and these efforts proved somewhat more successful. A 3:1



mixture of 18:16 (ca. 40 %) was obtained by heating 5b with PPA in acetone:water at 50 °C for 20 hours. The yield was slightly improved (50-55 %) by heating 11b under the same conditions for 22 hours. Compound 18 was converted quantitatively into 16 by treatment with Al_2O_3.[6] Unfortunately the carbomethoxy-functionalized derivates 5c and 11c did not behave according to expectations. Only a trace of the desired prostaglandin intermediate 17 was detected. Very recently[11] it has been reported that a mixed acid-base ion exchanger[12] could effect the cyclization of 5b to the cyclopentenone derivative. The methyl acetal corresponding to 5c was also converted into a prostanoid by a slightly different route.

In conclusion, isoxazolines of type 2 and their reduction products are useful intermediates for the preparation of γ-ketoesters and a variety of functionalized aldehydes. Furthermore, it is possible to convert them into 2-substituted 4-hydroxycyclopentenones under carefully controlled conditions.



20a R = C_6H_{13}
20b R = COOEt

21a

Condensation of nitrile oxides with methyl 3-butenoate gives methyl isoxazoline-5-acetates 20a,b, substituted in the 3-position. These give rise to β-hydroxy-δ-ketoesters, *e.g.* 21a, on reduction which are possible precursors for 2-pyrones and phenols by controlled cyclization.

EXPERIMENTAL

Methyl 9-hydroximinononanoate was obtained by stirring methyl 9-oxononanoate[13] with hydroxylamine hydrochloride (1.1 eq.) and sodium bicarbonate (1.3 eq.) in an aqueous two-phase system for 24 h. The oxime precipitated as white oily crystals which were filtered and dried, mp. 47-49 °C (from petrol ether), yield 70 %. The oxime was sufficiently pure for the further reactions. The preparation of 2a,b,d is described earlier.[1] 3-(ω-Methoxycarbonylheptyl)-5-diethoxymethyl-2-isoxazoline 2c was synthesized from methyl 9-hydroximinononanoate according to the same method, $bp._{0.2}$ 170 °C, yield 46 %. ^1H NMR ($CDCl_3$): δ 1.0-1.9 (10H,m), 1.18 (3H,t,J 8 Hz), 1.21 (3H,

t,J 7 Hz), 2.30 (4H,br.t), 2.95 (2H,d,J 7 Hz), 3.4-3.9 (4H,m), 3.63 (3H,s), 4.3-4.7 (2H,m). MS: 298 (M^+-OC_2H_5).

Catalytic reduction of 2a-d to 5a-d was carried out at room temperature in 95 % ethanol over Ra-Ni (commercial, active, in H_2O) at atmospheric pressure. One mole of hydrogen was absorbed after ca. 3-4 hrs. The reduction of 2d was rapid, and complete in half an hour. Filtration of the catalyst and evaporation of the solvent gave 5a-d in practically quantitative yield. The crude product was used directly for the further conversions. ^{1}H NMR ($CDCl_3$): 5a: δ 1.21 (6H,t,J 7 Hz), 2.19 (3H,s), 2.69 (2H,d,J 5 Hz), 3.3-4.3 (5H,m), 4.36 (1H,d,J 4.7 Hz). 5b: δ 0.88 (3H,br.t), 1.0-2.0 (8H,m), 1.20 (6H,t,J 7 Hz), 2.45 (2H,t,J 7 Hz), 2.66 (2H,d,J 5 Hz), 3.3-4.3 (5H,m), 4.39 (1H,d,J 5 Hz). MS: 215 (M^+-OC_2H_5). 5c: δ 1.20 (6H,t,J 7 Hz), 1.0-2.0 (10H,m), 2.1-2.5 (4H,m), 2.64 (2H,d,J 5.5 Hz), 3.61 (3H,s), 3.4-4.3 (5H,m), 4.34 (1H,d,J 5 Hz).

3-Hexylpyridazine (6b) was obtained as an oil in 85 % yield by heating crude 5b with hydrazine sulfate in aqueous methanol at 45 °C for 24 hrs.[10] ^{1}H NMR ($CDCl_3$): δ 0.87 (3H,br.t.), 1.0-2.0 (8H,m), 2.97 (2H,t,J 7.2 Hz), 7.35 (2H,m), 8.98 (1H,t, J 3.6 Hz).

Pyridazine (6d) was obtained in 80 % yield by heating crude 5d with hydrazine sulfate in aqueous methanol at 50 °C for 18 hrs. The solvent was evaporated in vacuo and the residue was purified by preparative TLC (SiO_2, $CHCl_3$).

Ethyl 4-oxodecanoate (7b). The acetal 5b (80 mg) in abs.alcohol (2 ml) was treated with acetyl chloride (40 mg) at 25 °C for 4 hrs. Chloroform was added and the solution was washed with aqueous sodium bicarbonate. Evaporation of solvent and purification of the remainder by TLC (silica, $CHCl_3$) gave 30 mg of pure 7b, 47 % yield, and a second, slightly impure fraction of 7b (30 mg). ^{1}H NMR ($CDCl_3$): δ 0.89 (3H, br.t), 1.0-1.9 (11H,m), 2.46 (2H,t,J 7 Hz), 2.65 (4H,m), 4.13 (2H,q,J 7 Hz). MS: 215 (M^+-OC_2H_5). IR (film): 1725(s), 1750(s) cm^{-1}.

Diethyl 4-oxo-1,12-dodecanedioate was obtained in 76 % yield by heating 5c for 2 hrs at 70 °C in abs.alcohol with a small amount of acetyl chloride added. Transesterification to the diethyl ester occurred at 70 °C. If the rearrangement was carried out for 60 hrs at 25 °C, the methylethyl ester 7c was obtained. ^{1}H NMR ($CDCl_3$, diethyl ester) :δ 1.24 (6H,t,J 7 Hz), 1.0-1.9 (10H,m), 2.1-2.5 (4H,m), 2.64 (4H,m), 4.09 (4H,q,J 7 Hz). MS: 301 (M^+ + 1), 255 (M^+-OC_2H_5).

Synthesis of the acetals 8a,b,c. 0.5 mmol of 5a,b or c, sodium acetate (60 mg) and 1.5 mmol of acetic anhydride were heated at 100 °C for 1¼ h. Chloroform was added and the mixture was washed with aqueous sodium bicarbonate, dried over Na_2SO_4, and evaporated in vacuo. The product, 8a,b,c, was purified by TLC (silica, $CHCl_3$, 5 % ethyl acetate). The yield was 50-70 %. ^{1}H NMR ($CDCl_3$), 8a: δ 1.23 (6H,t,J 7 Hz), 2.27 (3H,s), 3.57 (2H,q,J 7 Hz), 3.60 (2H,q,J 7 Hz), 5.03 (1H,d,J 3.6 Hz), 6.30 (1 H,d, J 16.2 Hz), 6.57 (1H,dd,J 16.2 and 3.6 Hz). MS: 127 (M^+-OC_2H_5), bp.$_{10}$ 106 °C. 8b: 0.89 (3H,br.t), 1.0-1.9 (14H,m), 2.57 (2H,t,J 7 Hz), 3.54 (2H,t,J 7 Hz), 3.60 (2H,t,J 7 Hz), 5.00 (1H,d,J 3.4 Hz), 6.28 (1H,d,J 16.6 Hz), 6.56 (1H dd,J 16.6 and 3.4 Hz). MS: 243 (M^++1), 197 (M^+-OC_2H_5), bp.$_1$ 122 °C. 8c: 1.22 (6H,t,J 7 Hz), 1.1-1.9 (10H,m), 2.30 (2H,t,J 7 Hz), 2.58 (2H,t,J 7 Hz), 3.56 (2H,q,J 7 Hz), 3.60 (2H, q,J 7 Hz), 3.63 (3H,s), 5.01 (1H,d,J 3.4 Hz), 6.31 (1H,d,J 16.2 Hz), 6.54 (1H,dd, J 16.2 and 3.4 Hz).

Compounds 9b,c were prepared by heating 8b,c (5 mmol) in acetone:water, 2:1 (22 ml) with polyphosphoric acid (120 mg) at 50 °C for 23 hrs. Evaporation of most of the acetone in vacuo and extraction with methylene chloride gave 9b,c, liquids. They were purified by TLC (silica, $CHCl_3$). The yield of 9b was 48 % and of 9c 68 %. ^{1}H NMR: 9b: δ 0.88 (3H,br.t), 1.0-1.9 (8H,m), 2.69 (2H,t,J 7 Hz), 6.77 (2H,m), 9.74 (1H,dd,J 5.2 and 2.2 Hz). 9c: 1.0-1.9 (10H,m), 2.34 (2H,t,J 7 Hz), 2.71 (2H,t,J 7 Hz), 3.67 (3H,s), 6.80 (2H,m), 9.75 (1H,dd,J 5.2 and 2.5 Hz).

Benzoylation of 5b,c. To 10 mmol of 5b or c in dry pyridine (12 ml) 18 mmol of benzoyl chloride were added slowly with stirring and cooling with ice-water. The mixture was stirred for 50 hrs at 25 °C. Carbon tetrachloride (20 ml) was added and the mixture was extracted twice with water and then with 4 M hydrochloric acid until the pH of the aqueous phase is slightly acid. Drying over sodium sulfate and evaporation of the solvent gave the benzoates 10b og 10c which were purified by chromatography on silica ($CHCl_3$:CCl_4, 2:3). The yield was 70-80 % of light yellow, viscous liquids. ^{1}H NMR (CCl_4): 10b: δ 0.86 (3H,br.t), 1.16 (6H,t,J 7 Hz), 0.9-1.6 (8H,m), 2.35 (2H,t,J 7 Hz), 2.77 (2H,d,J 6 Hz), 3.2-3.6 (4H,m), 4.57 (1H,d,J 4 Hz), 5.31 (1H,dt,J 4 and 6 Hz), 7.3 (3H,m), 7.8 (2H.m). 10c: δ 1.15 (6H,t,J 7 Hz), 1.0-1.9 (10H,m), 2.0-2.6 (4H,m), 2.75 (2H,d,J 6 Hz), 3.3-3.8 (4H,m), 3.53 (3H,s), 4.56 (1H, d,J 4 Hz), 5.32 (1H,dt,J 4 and 6 Hz), 7.3 (3H,m), 7.9 (2H,m).

The aldehydes 11b and 11c. 2 mmol of the benzoate 10b or 10c was vigorously stirred in a mixture of 6 ml carbon tetrachloride and 2 ml of formic acid for 35 min at 25 °C. Water (1 ml) was added and the organic phase was separated, washed with 2 ml of saturated sodium bicarbonate solution, and dried over sodium sulfate. Evaporation of the solvent gave 11b and 11c, respectively, sufficiently pure for

further reactions. The yield was ca. 80 %. The aldehydes 11b,c could be purified by TLC (SiO_2, $CHCl_3$: CCl_4, 3:2). ^1H NMR ($CHCl_3$): 11b: δ 0.87 (3H,br.t), 1.0-2.0 (8H, m), 2.47 (2H,t,J 7 Hz), 3.15 (2H,d,J 5 Hz), 5.48 (1H,t,J 5 Hz), 7.4 (3H,m), 8.0 (2H, m). 11c (CCl_4): δ 1.0-1.9 (10H,m), 2.0-2.6 (4H,m), 3.02 (2H,d,J 5 Hz), 3.57 (3H,s), 5.32 (1H,t,J 5 Hz), 7.3 (3H,m), 7.9 (2H,m).

Cyclization of 11b to 16. The aldehyde 11b (140 mg) was vigorously stirred in a two-phase system of ether (5 ml) and aqueous sodium hydroxide (2 ml, 10 %) under nitrogen for 15 min. The aqueous phase was separated and extracted with ether (5 ml). The combined ether phases were dried over sodium sulfate, evaporated, and chromatographed (TLC, silica, $CHCl_3$, 10 % ethyl acetate). 15 mg of 16 (liquid) was isolated from a band ca. 2 cm from the starting line. ^1H NMR (CCl_4): δ 0.89 (3H,br.t), 1.0-1.8 (6H,m), 2.09 (2H,br.t), 2.16 (1H,dd,J 18 and Hz), 2.58 (1H,dd,J 18 and Hz), 3.3 (OH,br. s), 4.74 (1H,m), 6.99 (1H,br.s).

Cyclization of 10b to 16 and 18. The acetal 10b (500 mg) was heated at 55-60 °C for 22 hrs in acetone (11 ml), water (4 ml) containing 1.4 g of polyphosphoric acid. Part of the acetone was evaporated and the remainder was extracted with methylene chloride, which was dried and evaporated. The crude product, which contained small amounts of 9b and traces of 7b, was chromatographed as above. A 3:1 mixture of 18:16 was isolated in a yield of 55 %. The ketone 18 was rearranged into 16 by absorption on basic alumina, Brockmann, grade III for 16 hrs.[8] Extraction with methanolic chloroform gave pure 16, the ^1H NMR spectrum of which was identical with that above. ^1H NMR (CCl_4): 18: δ 0.90 (3H,br.t), 1.0-1.7 (8H,m), 2.5 (1H,m), ca. 4.2 (1H,br.s), 4.50 (1H,br.s), 5.99 (1H,d,J 6 Hz), 7.37 (1H,dd,J 6 and 2 Hz).

The ketones 16 and 18 were obtained as a 1:2 mixture when 5b was heated with PPA at 50 °C for 20 hrs in aqueous acetone as above. The total yield was ca. 40 %. We were not able to isolate 17 or 19 from the reaction mixture, when 5c or 11c was treated with PPA under the same conditions.

The 2-isoxazoline (20a) was prepared from methyl 3-butenoate and heptanehydroaxamic chloride; $bp._{0,15}$ 130-132 °C. Yield: 37 %. ^1H NMR $CDCl_3$): δ 0.89 (3H,br.t), 1.0-1.9 (8H,m), 2.34 (2H,br.t), 2.4-3.3 (4H,m), 3.69 (3H,s), 4.85 (1H,br.quint,J 7 Hz). MS: 228 (M^++1).

The compound 20b was prepared from methyl 3-butenoate and ethyl chlorooximinoacetate. The nitrile oxide was generated by slow addition of triethylamine, diluted in chloroform, over a period of ca. 2 hrs, at room temp. This procedure gives a pure product, yield 93 %. ^1H NMR ($CDCl_3$): δ 1.35 (3H,t,J 7 Hz), 2.3-3.6 (4H,m), 3.68 (3H,s), 4.32 (2H,q,J 7 Hz), 5.10 (1H,br.quint). MS: 216 (M^++1), 170, 142.

Methyl 3-hydroxy-5-oxoundecenoate (21a) was obtained by reduction of 16 with titanous ions for 3 days in aqueous acetic acid according to the usual procedure. The yield of purified product (silica, $CHCl_3$, 5 % ethyl acetate) is 52 %. ^1H NMR ($CDCl_3$) δ 0.88 (3H,br.t), 1.0-1.9 (8H,m), 2.3-2.7 (6H,m), 3.3 (1H,br.s), 3.67 (3H,s), 4.48 (1H,quint,J 6.3 Hz). MS: 231 (M^++1).

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