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Synthesis of 3-Hydroxy-4,5-dimethyl-2(5H)-furanone and its Analogues; Utilisation of an Intramolecular Darzens Reaction

G. Fráter* and U. Müller

Givaudan-Roure Research Ltd, CH-8600 Dübendorf/Switzerland

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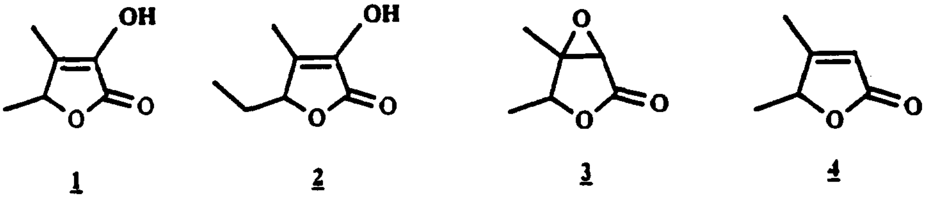
intramolecular Darzens reaction

Abstract: The intramolecular Darzens reaction of chloroacetates of hydroxy ketones leads to α, ß-epoxy-γ - and δ-lactones. Acid catalysed rearrangement of the latter furnished the α-keto lactones 1, 10, 16 and 20.

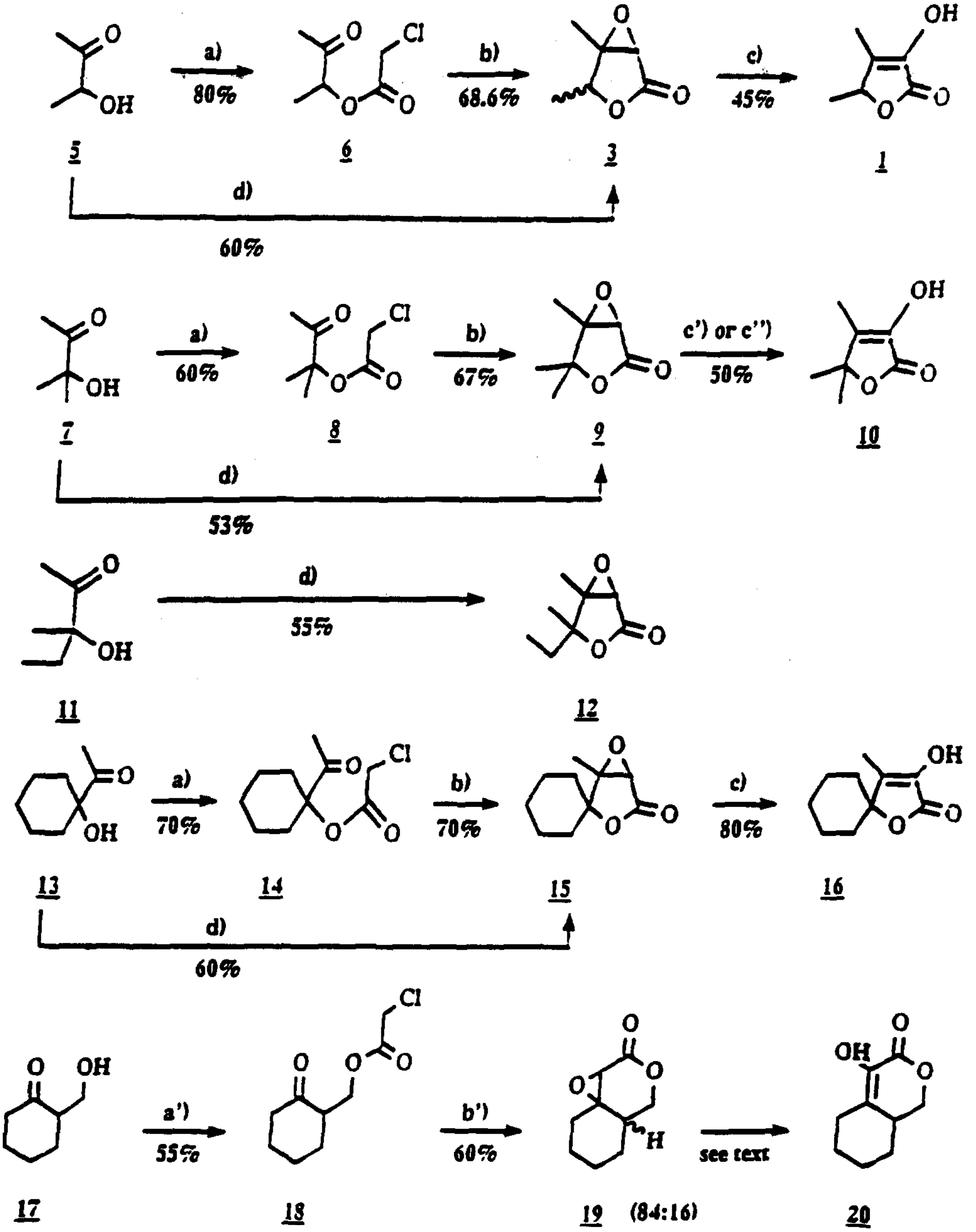
The title compound, 3-hydroxy-4,5-dimethyl-2(5H)-furanone[1] (1) is an extremely powerful and very important flavor ingredient. The 5-ethyl homologue 2 has first been found in hydrolysed vegetable protein[2]. The title compound 1 was isolated from aged sake,[3] from botrytised wine,[4] from roasted tobacco volatiles[5] and most importantly from raw sugar cane.[6] Its synthesis has been described several times long before its interesting flavor properties have been known. Most of the syntheses are based on the reaction of α-keto-butyric acid or its derivatives,[7] but other approaches were also used[8] e.g. for the synthesis of the enantiomers of 1.[9]

Scheme 1



It occurred to us that acid catalysed rearrangement of the epoxide 3 (Scheme 1) should also furnish the target molecule 1. Conventionally this route depends on the preparation of 4,5-dimethyl-2 (5H)-furanone (4) and on the epoxidation of the latter to 3. The epoxidation of furanones like 4 has been described as notoriously difficult[10] and only the specially developed protocol by Tishler et al.[11] (NaOCl, pyridine) works satisfactorily. On the other hand an intramolecular Darzens reaction of the α-chloro ester 6 (^{t}BuOK, THF) (Scheme 2) yielded a ca. 1:1 cis, trans-mixture 3 in 68%.[12] Under acidic conditions the epoxy butenolide 3 has been transformed into the desired 3-hydroxy-4,5-dimethyl-2 (5H)-furanone (1) in satisfactory yield (K-10, 1.1.2-trichloroethane, reflux (111° C) for 1 h; 45% 1).

Scheme 2

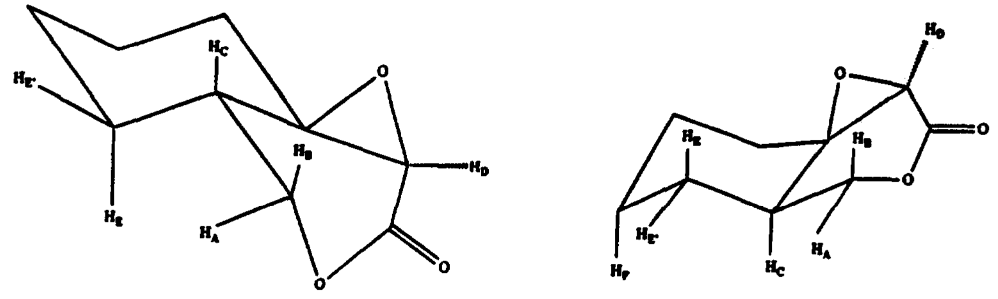


a) 1.1 eq. pyridine, 1 eq. $ClCH_2COCl$, ether, 0 - 5° C; a') crude 17,$(ClCH_2CO)_2O$, cat.DMAP, CH_2Cl_2, 1h, 40° C. b) THF, ^{t}BuOK, 10-20° C; b') THF, ^{t}BuOK, -18° C →0° C; c) K-10, 1,1,2-trichloroethane, reflux (108°); c') 2xg K-10, tetrachloroethylene (bp. 120 - 122° C), reflux, 2 h; c'') BF_3 in toluene, -30° →0° C →r.t., 6 h; d) ^{t}BuOK, $ClCH_2COOC_2H_5$, THF, -20° C.

In Scheme 2 a few more examples of the intramolecular Darzens reaction are depicted. It has been found, that the reaction can conveniently be carried out directly starting with the hydroxy-carbonyl compound like **5**, **11** or **13** with ethyl-chloroacetate in the presence of ^{t}BuOK without isolation of the chloroacetate intermediate; this one pot variant leads in a very efficient, fast, mild and experimentally simple manner to the epoxybutenolides **3**, **12** and **15**. In the case of the δ-lactone example **18** →**19a** + **19b** the main product was proven to be **19a** with cis-fused carbon ring system, which results from axial attack of the initially formed anion on the carbonyl group of the cyclohexanone[13], whereas the minor isomer has the structure **19b** (Scheme 3).

Treatment of **19a** + **19b** with dehydrated K-10 in tetrachloroethylene at 120° C for 1 h furnished a mixture of **19a** and **20**, i.e. only **19b** rearranged under this condition. However, in toluene in the presence of 1 equivalent of BF_3-etherate (exothermic reaction 20° →55° C) **19a** + **19b** gave the α-keto-δ-lactone **20** in 46% yield.[14]

Scheme 3



19a **19b**

The successful synthesis of epoxy butenolides by means of the intramolecular Darzens reaction[15] opens up a new access to α-keto-γ and δ-lactones. On the other hand the epoxy-butenolide moiety itself is found in a series of biologically active natural products like Lophotoxin,[16] Micromelin,[17] compound A[18] and Linderane.[19]

References and Notes

1. It is also named 2-hydroxy-3,4-dimethyl-butenolide, 2-hydroxy 3-methyl-2-penten-4-olide or Sotolon in the Japanese literature[6].
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12. **3**: 189.3 g (1.15 mol) **6** in 1150 ml THF were treated dropwise and under stirring with the solution of 141.9 g (1.26 mol) ^{t}BuOK in 300 ml THF. The strongly exothermic reaction is kept at 10 - 20° C with cooling with a dry ice-acetone bath. After the addition (~45 min) the reaction is stirred further for 15 min at ambient temperature, then most of the THF is evaporated and the reaction mixture is worked up with ethyl acetate and water. The product was distilled at 63 - 67° C and 0.06 Torr; yield: 88.4 g (68.6%); two isomers in the ratio of ca. 55 : 45 (glc, NMR); IR. (film): 1785 (broad); NMR. 4.615 and 4.46 (2xq; >CH-O of the isomers), 3.61 and 3.60 (2x s; >CH-CO-), 1.61 (s,CH_3-), 1.42 and 1.41 (2xd, $\underline{CH_3}$-CH=).
13. ^{1}H-NMR (400 MHz, $CDCl_3$); **19a**: 4.56 (dd,J (BA)=11.5, J (BC)~3.6; H_B), 3.9 (d,J (AB)=11.5, J (AC)~0; H_A), 3.35 (s,H_D), 2.15 (ddd,J (CE)~13, J (CB)~3.6,J (CE')~3.5,H_C); **19b**: 4.08 (dd,J (BA)~J (BC)~11,H_B), 3.98 (dd,J (AB)~11,J((AC)~3.6; H_A), 3.42 (s,H_D), 1.23 (dddd,J (EE')~J (EC)~J (EF)~13, J (EF')~3.5; H_E); IR.(film) for **19**:1738.
14. **20**: m.p. (crist. from ^{t}BuOCH_3-hexane): 68° C; IR. ($CHCl_3$): 1700cm^{-1}; NMR (200 MHz; $CDCl_3$): 5,63 (s,OH); 4.365 and 3.955 (ABX-system of -O-CH_2-; J(AB)=11Hz, J(AX)=6Hz, J(BX)=11Hz), 3.09 - 2.93 (m,1H), 2.76 - 2.55 (m,1H), 1.98 - 1.74 (m,4H), 1.50 - 1.20 (m,2H), 1.16 - 0.92 (m,1H).
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