Cyclisation of Acetylenecarboxylic Acids; a Novel Route to γ-Methylenebutyrolactones

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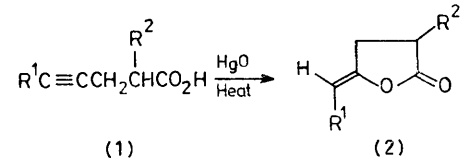
Summary Various γ-methylenebutyrolactones have been synthesized in good yield by the cyclisation of acetylenecarboxylic acids in the presence of a catalytic amount of mercury(II) oxide.

COMPOUNDS which have an unsaturated γ- or δ-lactone ring are reported to have carcinogenic[1] and antitumour[2] activity, as well as other biological properties.[3]

However, in contrast to the synthesis of other unsaturated butyrolactones, few syntheses of γ-methylenebutyrolactones have been reported.[4] A novel, high-yield synthesis of γ-methylenebutyrolactones by the cyclisation of acetylenecarboxylic acids in the presence of a catalytic amount of mercury(II) oxide is now reported.

Pent-4-ynoic acid (**1a**), which was prepared from diethyl malonate and prop-2-ynyl bromide followed by hydrolysis and decarboxylation, was heated at 60 °C for 30 min in the presence of yellow mercury(II) oxide [molar ratio of (**1a**): HgO 100:4—6) without solvent, and γ-methylenebutyrolactone (**2a**)[4a] was obtained in quantitative yield.† This cyclisation proceeded equally well in solvents such as chloroform, acetone, benzene, or dioxan.‡ No α- or β-angelica lactone, or 3,4-dihydro-2-pyrone was formed and the lactone (**2a**) was the sole product. Under similar conditions the acid (**1b**) gave the lactone (**2b**) in quantitative

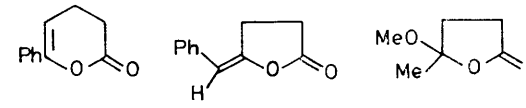


(1) (2)

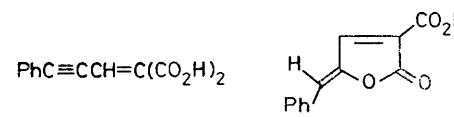
a; $R^1 = R^2 = H$

b; $R^1 = H$, $R^2 =$ 

c; $R^1 = Ph$, $R^2 = H$



(3) (4) (5)



(6) (7)

† All compounds gave satisfactory spectral data and elemental analyses, *e.g.* (**2a**): (*cf.* ref. 4a); i.r. (liq. film) 1815 (νC=O), 1670 (νC=C), and 890 cm^{-1} (=CH_2); δ (CCl_4) 2·52—3·04 (m, 4H), 4·25 (m, 1H), and 4·66 (m, 1H); *m/e* 98 (M^+), 70, and 56.

‡ When (**1a**) was heated at 100 °C for 3—6 h without mercury(II) oxide, (**2a**) was not obtained and (**1a**) was recovered almost quantitatively.

yield, and the methylenedioxy protecting group was not decomposed.

In contrast to these results, the acids (**1c**) and (**1d**) did not cyclise in 5—7 h below 80 °C in the presence of mercury(II) oxide with or without solvent. However, when (**1c**) was heated at 110 °C in the presence of mercury(II) oxide without solvent for 3 h, compounds (**2c**) (37%) and [(**3**) + (**4**)] (41%) were obtained. Treatment of (**1c**) in refluxing dimethylformamide with mercury(II) oxide for 2 h gave the γ-methylene lactone (**2c**) (83%), m.p. 85—87 °C, accompanied by a mixture of (**3**) and (**4**) (9%). The *exo*-methylene proton signal appeared at δ 5·4 and 6·5 in the n.m.r. spectra of (**2c**) and (**4**), respectively. The *syn*-proton (adjacent to the oxygen) signal would appear at lower field than the *anti*-proton,[4a] so (**2c**) was shown to be the isomer having the *anti*-proton arrangement. From its i.r. and n.m.r. spectra§ compound (**3**) was assigned the six-membered enol-lactone structure.

When the diacid (**6**) was heated under reflux in dimethylformamide for 1 h in the presence of HgO, (**7**) (88%) was formed, m.p. 220—222 °C (decomp.) (lit.,[5] 218 °C, decomp).

The acid (**1a**) also cyclised under similar conditions in methanol to give the saturated lactone (**5**) (68%). The saturated lactone (**5**) was also formed by treatment of (**2a**) with mercury(II) oxide in refluxing methanol, but (**5**) was not formed by treatment of (**2a**) with toluene-*p*-sulphonic acid in refluxing methanol.

Treatment of the lactone (**2a**) with hydrochloric acid in refluxing methanol afforded methyl 4-oxopentanoate in quantitative yield.

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§ Spectral data for (**3**) (crude): i.r. (KBr) 1760, 1670, and 695 cm^{-1}. (*cf.* K. Yamada, Y. Togawa, T. Kato, and Y. Hirata, *Tetrahedron*, 1971, **27**, 5445.); δ ($CDCl_3$) 2·42—2·80 (m, 4H), 5·76 (t, 1H), and 7·20—7·64 (m, 5H).

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