CYCLOPENTENONE FROM FURAN: AN UNUSUAL MARCKWALD REACTION

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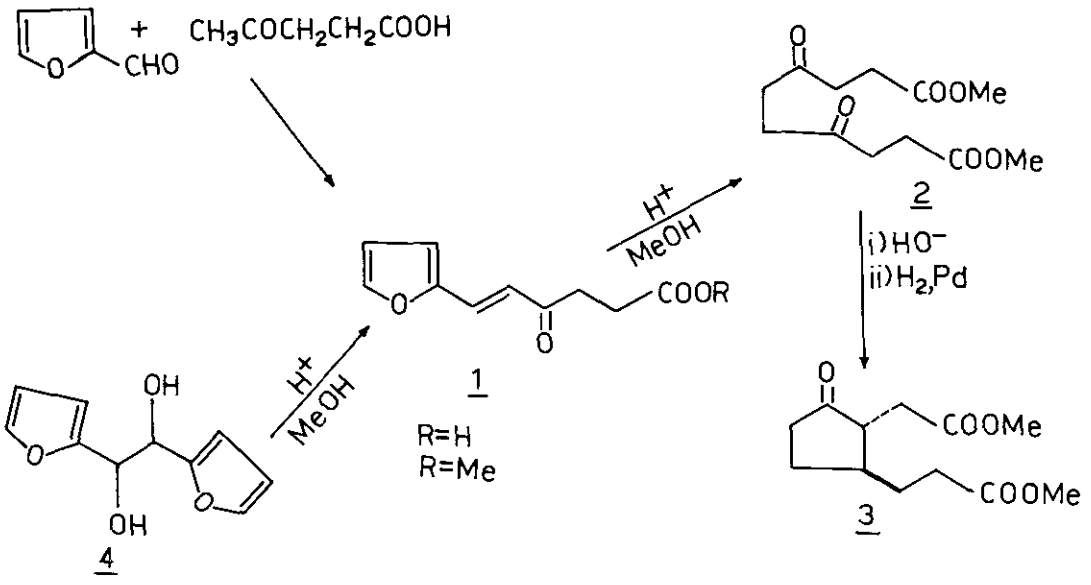
Abstract - A "one pot" conversion of methyl furfurylidenepyruvate 5 directly to the cyclopentenone 8, by means of the Marckwald reaction, is described.

Furans represent a condensed form of 1,4-diketones and are commonly prepared from the latter[1]. The acid-catalyzed hydrolysis of furans to diones in reasonable yields, coupled with the ease of metalation of the positions 2 and 5, has prompted several cyclopentenone syntheses using these versatile intermediates[2]. The most popular method involves a ring cleavage of the furan systems directly to the γ-diketones. The same key intermediates could be obtained by a route involving 2,5-dialkoxy-2,5-dihydrofurans, which on hydrogenation and acid hydrolysis give the desired 1,4-dicarbonyl compounds[3]. Another classic method implies an acid fission of either 2-vinyl furans or 2-furyl carbinols, giving substituted γ-keto esters (the so-called Marckwald reaction): these rearrangements are multi-step reactions, in which the formation of the levulate ester derivatives is the most favoured process[4]. A recent development[5], controlling the solvents and the solution acidity, by using zinc ions instead of protons, avoided the Marckwald reaction and allowed the intermediates to cyclize directly to cyclopentenone derivatives. This last reaction has a high synthetic value and has been successfully developed into a manufacturing process[6]. A recent report by Fetizon and co-workers[7] describes a new, simple synthesis of (±)-11-deoxyprostaglandins $F_{2\alpha}$, carried out from furfural and levulinic acid. 5-Furfurylidenelevulinic acid 1 was converted into the symmetrical key intermediate, dimethyl 4,7-dioxodecanedioate 2, by treatment with acid (the Marckwald reaction); the cyclization of the γ-diketone under basic conditions and the following reduction gave the trans-cyclopentanone 3 (Scheme 1).

We have been studying the elaboration of furans as a synthetic tool in the field of natural products since 1976 and several applications have been reported[8]. We focused our attention on this interesting synthetic sequence and we found that the commercially available α-furoin could be considered a good starting material. In fact, the reduction of the carbonyl group with $NaBH_4$ rapidly furnished the known dihydroxy derivative 4, in quantitative yield. 4 had a suitable structure to undergo the ring opening in acidic medium, first to 1 and then to 2.

The treatment of 4 in methanol with amberlyst H-15 ion exchange resin gave 1 (~ 80%), from which the compound 2 could be obtained by the method described by Yoda[9] (~ 80%); this procedure cleanly

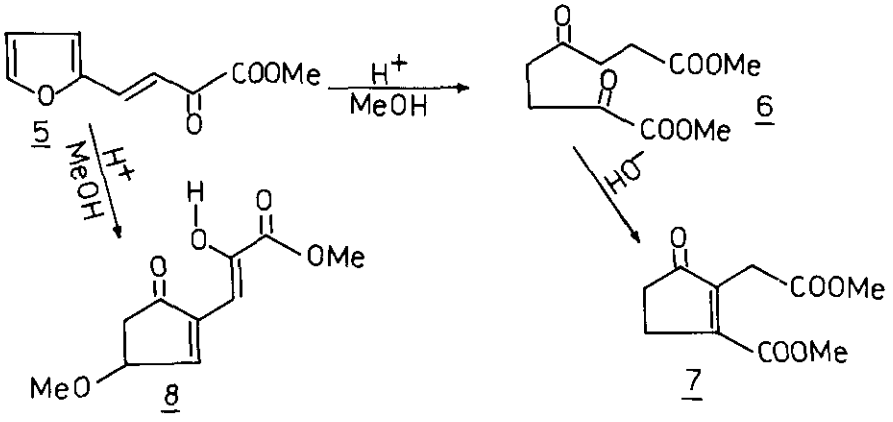
Scheme 1



improved the overall yield of 2[10].

To simplify the synthetic scheme leading to (±)-11-deoxyprostaglandins $F_{2\alpha}$, we thought of utilizing as a starting material methyl furfurylidenepyruvate 5, never tested in this type of reaction. In our mind, the acidic fission of 5 would give dimethyl 2,5-dioxo-octanedioate 6, from which the ring closure in basic medium would lead to the cyclopentenone 7 (Scheme 2).

Scheme 2

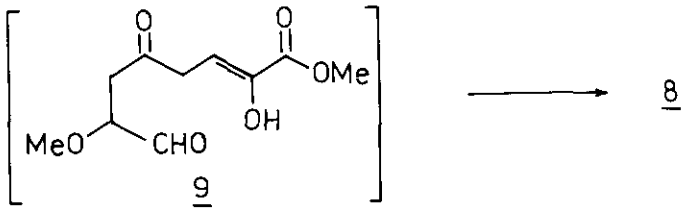


5 showed to be very unstable, even under mild experimental conditions; it can easily give black resins, rapidly by acids, but slowly by storage at room temperature.

Nevertheless, we were able to find efficient conditions, which allowed to achieve the "one pot"

conversion of 5 into a single compound, the cyclopentenone 8. The reaction was performed by treatment of 5 with a methanol-water mixture and hydrochloric acid as catalyst; the formation of 8, monitored by tlc, proceeded smoothly at reflux temperature, but we were able both to detect and to isolate neither the expected open intermediate 6 nor any different compound. The analytical and spectroscopic data are in agreement with the proposed structure (see experimental section); on the ground of ^{1}H-NMR data, 8 showed to be completely in enolic form (the enolic proton at 9.20 δ).

To our knowledge, this result could be considered the first report of an aldolic cyclization during the Marckwald reaction. In our opinion and in agreement with the proposed mechanism[4], the key-step could have been the formation of an open intermediate 9, which rapidly cyclized by means of the favourable steric situation, preventing the subsequent formation of other linear compounds, like 6, from occurring.



9 → 8

These results further broaden the utility of furans in this field and show that these compounds are highly versatile building blocks for cyclopentenone synthesis.

ESPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 257 Infracord; ^{1}H-NMR spectra with a Perkin-Elmer apparatus (90 MHz) in $CDCl_3$ using TMS as an internal standard; mass spectra of the reaction products were recorded with an AEI MS 12 apparatus. For TLC Kieselgel from Merck was used.

5-furfurylidenelevulinic acid methyl ester 1. To a stirred solution of 1,2-dihydroxy-1,2-difurylethane 4 (3 g) in methanol (50 ml) was added amberlyst H-15 ion exchange resin (5 g). The mixture was refluxed for 15 h; then it was cooled to 20°C and filtered. The filtrate was poured into water and extracted with diethyl ether. The combined ethereal extracts were washed with brine three times. After the solvent evaporation, the brown crude product was chromatographed on SiO_2; elution with n-hexane-diethyl ether (9:1, v/v) yielded the pure 1 (2.4 g). IR (CCl_4, 1%, ν_{max} cm^{-1}): 1742, 1692 and 1631, 1615, 880; ^{1}H-NMR (δ): 7.30 (s,1H), 7.15 (d, 1H, J=13 Hz), 6.50 (d, 1H, J=13 Hz), 6.45 (m, 1H), 6.28 (m, 1H), 3.53(s, 3H), 2.67 (broad m, 4H); MS, m/e: 208 (M^+).
Dimethyl 4,7-dioxodecanedioate 2 was prepared by the Yoda procedure[9].

Methyl 2-hydroxy-3-(5-methoxy-3-oxocyclopenten-2-yl)propenoate 8. To a solution of 5 (1 g)[11] in

methanol (30 ml) was rapidly added a mixture of 6N hydrochloric acid (12 ml) and methanol (8 ml). The mixture was stirred at 65°C for 9 h and then poured into water and the precipitate was extracted several times with diethyl ether. The organic layer was washed with brine and then dried on anhydrous Na_2SO_4. After evaporation of the solvent, the yellow crude product was chromatographed on SiO_2; elution with n-hexane-ether (95:5, v/v) gave the pure 8 (700 mg); mp 126-128°C (from n-hexane). IR (CCl_4, 1%, ν_{max},cm^{-1}): 3480, 3300 (broad), 1725-1700 (broad), 1645, 1600; ^{1}H-NMR (δ): 9.18 (s, 1H, -OH), 7.72 (d, 1H, 1-H, J=3 Hz), 6.28 (s, 1H, 3-H), 4.63 (complex m, 1H, 5-H), 3.90 (s, 3H, $-COOCH_3$), 3.47 (s, 3H, $-OCH_3$), 2.90 (dd, 1H, 4-H, J_1=18 Hz, J_2=6 Hz), 2.42 (dd, 1H, 4-H, J_1=18 Hz, J_2=3 Hz); MS, m/e: 212 (M^+).

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