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STUDIES ON REACTIVITY OF FUMARALDEHYDE: A FACILE SYNTHESIS OF FUNCTIONALISED FURANS

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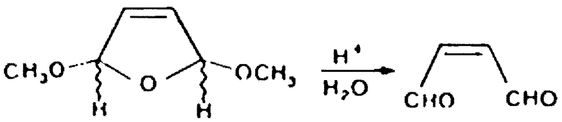
Abstract—The first results on reactivity of fumaraldehyde in cyclisation reactions are described, functionalised furans and polyunsaturated molecules 9 were obtained by intermolecular condensation of fumaraldehyde with active methylene compounds in acidic media. The mechanism of the reaction is discussed and the formation of a new iron carbonyl complex is described as well.

2, 5-Dihydro-2, 5-dimethoxy-furan 1 (DHDMF) is a precursor of malealdehyde 2; 1 is stable under both alkaline and neutral conditions, but in acidic media the ring is opened and the dialdehyde 2 is formed. This compound is particularly labile: until now there are no other data on its synthesis, isolation and purification. As a rule, the 1, 4-dicarbonyl compound is not isolated, but the aqueous solution containing 2 is directly used for further syntheses, consisting of intramolecular or intermolecular condensations.[1]

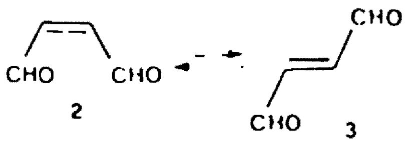
In acidic media 2 can be partly isomerised to fumaric aldehyde, yielding a *cis-trans* equilibrium, in which the *trans*-dialdehyde 3 is nearly 27%, as reported by Hufford, *et al.*[2]

In this paper we wish to describe a novel cyclisation reaction which affords functionalised furans by a simple procedure, by reaction of 3 with active methylene compounds in aqueous media.

Efficient methods for preparing 3 have not been found in the literature; a very few patented syntheses are reported, based on the same procedure: the acid-catalysed isomerisation of 2 (obtained by hydrolysis of DHDMF) to 3, and is following laborious isolation.[2]



1 2



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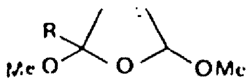
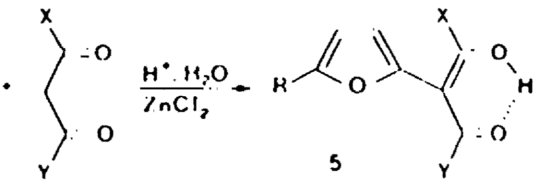


1

R = H; CH$_3$



4 5

X = CH$_3$; OEt; CH$_3$ ...
Y = CH$_3$; OEt; OEt ...

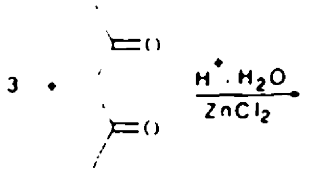
The reaction of 1 with active methylene compounds of type 4 in acidic media allowed the synthesis of a new class of furan derivatives 5 in high yields.[3] These compounds have shown to be efficient and versatile precursors of the cyclopentenones.[4] Up till now, the reactions observed have been attributed to the *cis*-dialdehyde; the reactivity of the *trans*-dialdehyde 3 is unknown.

We have found it more convenient and cheaper to prepare 3 *in situ* and use it without further purification. The addition of an active methylene compound (e.g. acetylacetone) to an aqueous solution of 3 (prepared by hydrolysis of 1 in acidic media for 24 hr at room temperature) furnished a new compound 6, whose structure was completely in agreement with the analytical and spectroscopic data. In particular, the double bond was *trans*-IR: 957 cm^{-1}; ^{1}H-

NMR: 6.75 δ (d, 1 H, J = 17 Hz), 6.14 δ (d, 1 H, J = 17 Hz). **6** clearly comes from the *trans*-aldehyde **3**, by intermolecular condensation with two molecules of acetylacetone and subsequent, acid-catalysed cyclisation. Both aldehydes were present in the acidic media, the observed high reaction rate with **4**, preventing a possible, slow interconversion,[2] led to the compound **5** ($R=H$; $X=Y=CH_3$), besides **6**, in the ratio 2.5–3:1. Furthermore, we can exclude an acid-catalysed *cis-trans* isomerisation after the condensation of **2** with **4**, because the pure *cis*-aldehyde gave only **5**, also long reaction time for'

The reaction mechanism was explained by the initial formation of the triene **7**; its ring closure to furan **6** was attributed to the formation of an extensively delocalised carbonium ion **8**, which could be intercepted in a geometrically favorable manner by the oxygen of the proximate ketone group (Scheme 1).

In this case we never isolated the triene **7**; on the contrary the employment of both β-keto esters and β-diesters allowed to obtain only the triene **9**. The *trans*-stereochemistry of the trienes **9** was deduced only from IR data (950 cm⁻¹).



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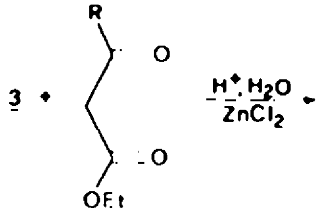
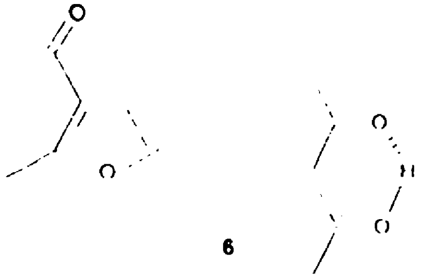
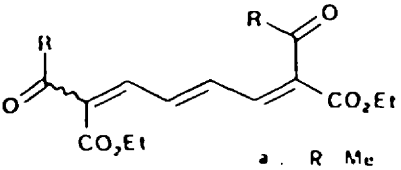


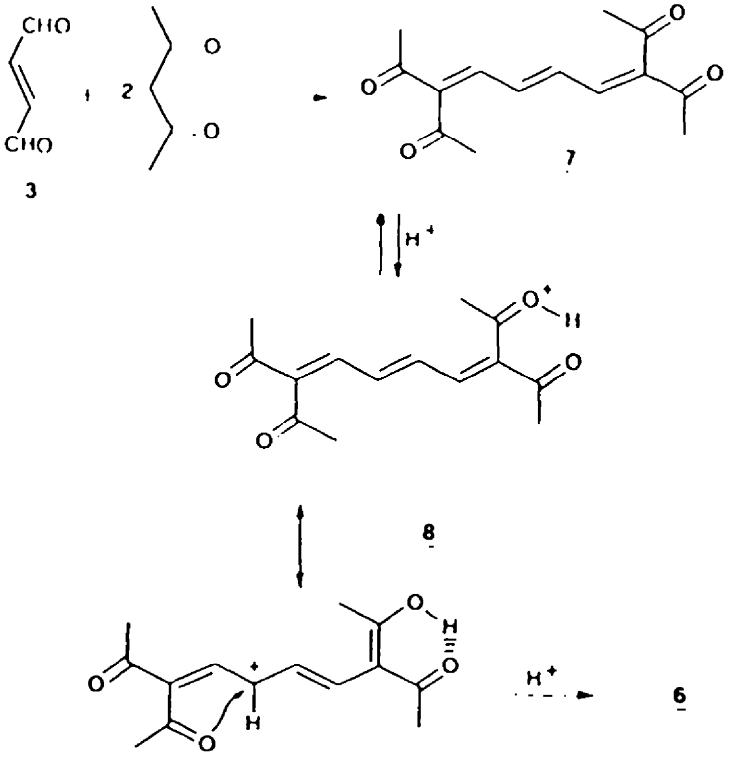


6

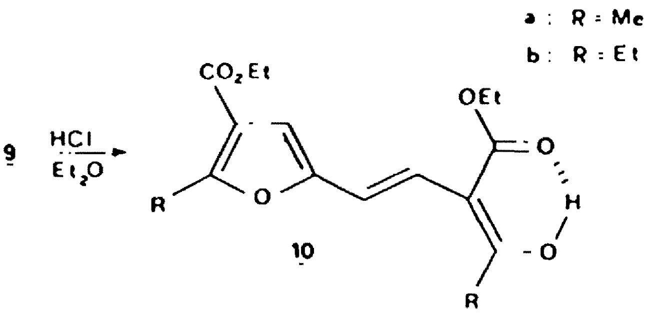


9

a: R = Me
b: R = Et
c: R = OEt



Scheme 1

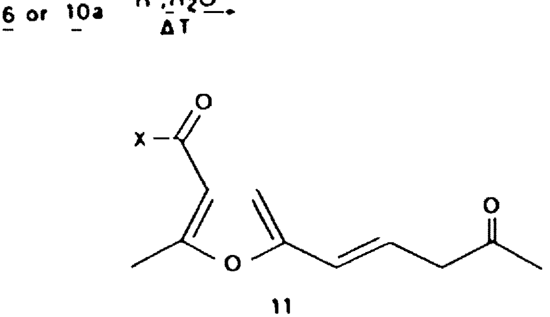


9a and **9b**, in more drastic conditions by treatment with an ethereal solution of HCl, immediately and quantitatively were cyclised to furans **10**, in agreement with the above proposed mechanism. **6**, **10a** and **10b** are completely enolised (enolic protons respectively at 17.05, 14.20 and 13.40 δ), on the ground of ^{1}H-NMR data.

The triene **9c** did not undergo ring closure, even under more drastic conditions. This result can be attributed to the lower nucleophilic character of an ester group in comparison with a keto group, hindering both the protonation and the following cyclisation (Scheme 1).

The yields of **6** and **9a–c**, based upon the DHDMF, were between 20–30%.

It is noteworthy that these compounds can undergo easily an acid-catalysed β-diketonic fission, directly to **11** in high yields



11

a : X = CH_3
b : X = OEt

9c showed the interesting capability to form an iron carbonyl complex. In fact, by reaction with $Fe_2(CO)_9$, it gave almost quantitatively a mononuclear complex; from the spectral evidence, this seemed to have the structure **12**. There are three bands in the region ν_{max} 2000 cm^{-1} [$Fe(CO)_3$], while the NMR spectra showed "inner and outer" protons, according with the proposed structure: 7.1 δ (m, 1 H), 6.2–5.75 δ (b. m, 2 h), 0.98 δ (m, 1 H). The isomerisation of the olefinic double bonds in polyunsaturated compounds has been described.[5]

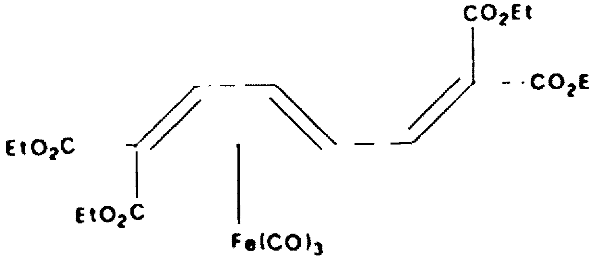
12 was stable under acidic condition (ethereal hydrochloric acid, room temp for 48 h), while it gave back the starting material **9c** for treatment with trimethylamine N-oxide. We are studying now the synthetic applications of this complex.

EXPERIMENTAL

^{1}H-NMR spectra were taken with a Perkin–Elmer R-32 spectrometer, with TMS as internal standard. IR spectra were taken with a Perkin–Elmer 257 Infracord spectrometer. Mass spectra were obtained with an AEI MS–12 spectrometer at 70 eV, by using direct insertion at source temperature of 150°. Commercial Merck Silica gel was used for column chromatography. Carlo Erba precoated Silica gel plates were used in TLC. The chromatograms were detected by spraying with 5 N H_2SO_4 and heating at 110° for 10 min. 1,3-Dicarbonyl compounds, all commercially available, were utilised directly without purification. DHDMF (prepared through the procedure by Hufford *et al.*[3]) was employed without purification.

Typical general procedure.

A solution of DHDMF (650 mg, 5 mmol) in AcOH (13 ml), 1,2-dimethoxyethane (15 ml) and H_2O (4 ml) was stirred for 24 h at room temperature. Then the solution was treated with $ZnCl_2$ (3 g, 22 mmol) and 1,3-dicarbonyl compound (20 mmol). After 24 h the mixture was poured into water and extracted several times with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$, water and dried over anhyd Na_2SO_4. The solvent was removed in vacuo. The crude product was chromatographed on SiO_2 and eluted with benzene-Et_2O 9:1 to give **6** and **9a–c**.-furan **6**, 24%, needles from hexane, m.p. 79–81°. ^{1}H-NMR ($CDCl_3$, δ) 17.05 (s, 1 H), 6.76 (d, 1 H, J = 17 Hz), 6.14 (d, 1 H, J = 17 Hz), 6.48 (s, 1 H), 2.63 (s, 3 H), 2.38 (s, 3 H), 2.22 (s, 6 H). IR (1%, $CHCl_3$, ν_{max}) 1680, 1585, 1400, 1378, 1170, 1095, 957 cm^{-1}. MS m/e 248 (M^+). Calc for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50, found C, 67.81, H 6.45%. **9a**. Yield 24%. Needles from Et_2O, m.p. 143–145°; ^{1}H-NMR (CD_3COCD_3; δ) 7.28 (m, 4H), 4.31 (q, 4 H), 2.33 (s, 6 H), 1.33 (t, 6 H). IR (1%, CCl_4, ν_{max}) 1720, 1680, 1608, 1593, 1378, 1360, 1290, 1440, 980 cm^{-1}. MS m/e 308 (M^+). Calc for $C_{16}H_{20}O_6$: C 62.33; H 6.54, found C, 62.50; H 6.64%. **9b**. Yield



12

30%. Needles from hexane, m.p. 101–102°C. ^{1}H-NMR (CCl_4, δ) 7.23 (m, 4H), 4.39 (q, 4 H), 2.68 (q, 4 H), 1.42 (t, 6 H), 1.12 (t, 6 H); IR (1%, CCl_4, ν_{max}) 1720, 1680, 1195, 1120, 978 cm^{-1}. MS *m/e* 336 (M^+); Calc for $C_{18}H_{24}O_6$: C, 64.27, H, 7.19; found C, 64.21; H, 7.08%. **9c** Yield 30%. Needles from hexane, m.p. 81–82°. ^{1}H-NMR (CCl_4, δ) 7.15 (m, 4 H), 4.26 (q, 4 H) 4.22 (q, 4 H), 1.34 (t, 6 H), 1.31 (t, 6 H); IR (1%, CCl_4, ν_{max}) 1720, 1680, 1627, 1392, 1380, 1305, 1150, 1065, 1030, 995 cm^{-1}; MS *m/e* 368 (M^+); Calc for $C_{18}H_{24}O_8$: C, 58.69, H, 6.57; found C, 58.65; H 6.39%.

General cyclisation procedure

The trienes **9a–b** were dissolved into HCl-saturated Et_2O. After 1–2 min the solvent was removed in vacuo. The pure furans **10a–b** were obtained (yield 100%). **10a** Needles from hexane, m.p. 51–53°. ^{1}H-NMR (CD_3COCD_3, δ) 14.20 (s, 1 H), 6.55 (d, 1 H, J = 17 Hz), 6.50 (d, 1 H, J = 17 Hz), 6.54 (s, 1 H), 4.33 (q, 2 H), 4.24 (q, 2 H), 2.55 (s, 3 H) 2.20 (s, 3 H), 1.30 (m, 6 H); IR (1%, CCl_4, ν_{max}) 1740, 1670, 1630, 1260, 1245, 1100, 978 cm^{-1}; MS *m/e* 308 (M^+; Calc for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54; found C, 62.50; H 6.61%. **10b** Oil. ^{1}H-NMR (CCl_4, δ) 13.40 (s, 1 H), 6.40 (d, 1 H, J = 14 Hz), 6.32 (d, 1 H, J = 14 Hz), 6.34 (s, 1 H), 4.25 (q, 2 H), 4.21 (q, 2 H), 3.03 (q, 2 H), 2.57 (q, 2 H), 1.30 (m, 12 H). IR (1%, CCl_4, ν_{max}) 1715, 1641, 1598, 1220, 965 cm^{-1}. MS *m/e* 336 (M^+). Calc for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19; found C, 64.12; H, 7.27%. **11b** Concentrated H_2SO_4 (1.8 ml) was added to a stirred solution of **10a** (155 mg, 0.5 mmol) in 15 ml of (4:1) acetone–water. The mixture was stirred at 70° for 24 h and then poured into water and extracted several times with Et_2O. The combined extracts were washed with water until neutrality and dried over Na_2SO_4. After the removal of the solvent *in vacuo*, the crude product was chromatographed on SiO_2. The elution with benzene–Et_2O 9:1 gave 90 mg of pure **11b** as oil (yield 76%). ^{1}H-NMR (CCl_4, δ) 6.33 (s, 1 H), 6.12 (m, 2 H), 4.21 (q, 2 H), 3.18 (m, 2 H), 2.54 (s, 3 H), 2.10 (s, 3 H), 1.32 (t, 3 H); IR (1%, CCl_4, ν_{max}) 1725 (broad), 1610, 1410, 1300, 1228, 1085, 965 cm^{-1}. MS *m/e* 236 (M^+); Calc for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83, found C, 66.21; H 6.97%. **11a** was prepared under the same conditions as **11b**, from **6** (yield 81%). ^{1}H-NMR (CCl_4, δ) 6.33 (s, 1 H), 6.14 (m, 2 H), 3.19 (m, 2 H), 2.54 (s, 3 H), 2.27 (s, 3 H), 2.11 (s, 3 H), IR (1%, CCl_4, ν_{max}) 1730, 1680, 1582, 1550, 1405, 1360, 1220, 1158, 955 cm^{-1}; MS *m/e* 206 (M^+); Calc for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84; found C, 69.81, H 6.69%.

Triene complex preparation

$Fe_2(CO)_9$ (750 mg, 2 mmol) was added, under nitrogen, to a solution of **9c** (600 mg, 1.63 mmol) in benzene (25 ml), previously treated with nitrogen. The suspension was stirred for 36 h at room temperature. The solvent was removed *in vacuo* and the oil crude product was chromatographed on Florisil and eluted with benzene–Et_2O 1:1, treated with nitrogen. The purification afforded to 790 mg of yellow oil complex **12** (yield 95.4%). ^{1}H-NMR ($CDCl_3$, δ) 7.1 (m, 1 H), 6.2–5.75 (b.m, 2 H), 0.98 (m, 1 H), 4.15 (2q, 8 H), 1.25 (2t, 12 H); IR (1%, $CHCl_3$, ν_{max}) 2950, 2050, 1970, 1705 cm^{-1}; MS *m/e* 508 (M^+); Calc for $C_{21}H_{24}O_{11}Fe$: C, 49.60, H, 4.72; found C, 49.69; H 4.78%.

Stability of the complex **12**

1 M Hydrochloric acid (1 ml) was added to a solution of the complex **12** (50 mg) in Et_2O (10 ml). The mixture was stirred for 48 h at room temperature. the complex was completely recovered after the working up.

Decomplexation

Trimethylamine N-oxide (300 mg) was added to a solution of the triene complex **12** (50 mg) in benzene (10 ml) and the mixture was refluxed for 1.5 h. The usual work up afforded quantitatively the starting triene **9c**.

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