Notes

The Stereochemical Course of the High-Pressure Reaction of 2,5-Dialkylfurans with Diethyl Mesoxalate

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A few years ago we have reported the high-pressure reaction of 2,5-dimethylfuran (**1**) with various carbonyl compounds **2** (Scheme I).[2,3] The reaction has led to highly functionalized compounds **3** of a potential synthetic value.[4]

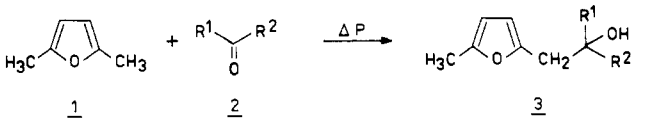
The controversial mechanism of this reaction[2] has prompted us to continue more detailed investigations. For these studies we selected a model reaction of **1** with diethyl mesoxalate (**2a**, $R^1 = R^2 = CO_2Et$). The reaction was carried out under 10 kbar of pressure at room temperature in methylene chloride during 20 h. The substrates were used in a 1:1 ratio. Under these conditions a single product **3a** ($R^1 = R^2 = CO_2Et$) was obtained in an 80% yield. No double substitution was observed.

The precisely performed reaction of **2a** with 2,5-di-[$^2H_3$]methylfuran in toluene under the same conditions did not exhibit any distribution of deuterium among positions 3 and 4 in the furan ring. 2-[$^2H_3$]Methyl-5-methylfuran treated with **2a** afforded products with preference (2.3:1) of substitution in the CH_3 group, thus pointing to a primary isotopic effect. Addition of deuterium oxide to the mixture containing **1** and **2a** caused incorporation of deuterium only into the hydroxy group of the high-pressure reaction product **3a**. These labeling experiments clearly testify to an acid-catalyzed electrophilic process.[5] Diethyl mesoxalate plays a double role as catalyst and substrate.

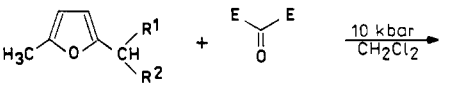
Studies shown below, carried out using model compounds **4**, **5**, and **6** (Scheme II), provided the further evidence for the mechanism and for the place of attack of acid catalyst. Substitution in substrates **4**, **5**, and **6** occurs predominantly in the ethyl (**7**), isopropyl (**9**), or benzyl group (**11**) as compared with that in the methyl group. This high regioselectivity can be useful in the synthesis of various furan derivatives.

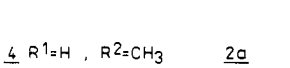
The only two reasonable pathways accounting for the formation of adduct **3a** are depicted in Scheme III. Path A proceeds via electrophilic attack of diethyl mesoxalate (**2a**) in position 3, followed by proton transfer from the methyl group at C-2, which is the rate-determining step (RDS), and finally by a (1,3)-sigmatropic rearrangement.

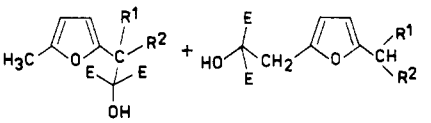
Scheme I



Scheme II







7 (90%)		**8** (10%)
9 (>97%)		**10** (<3%)
11 (57%)		**12** (43%)

On the other hand, path B involves electrophilic attack at C-2, proton transfer from the methyl group at C-5 (RDS), and a (1,5)-sigmatropic rearrangement. Bearing in mind the 1:1 ratio of substrates and high yield of the reaction products, we assumed a sigmatropic shift of the oxymalonate residue rather than an attack of a second molecule of **2a** in the last step of the reaction.

Taking into account the lack of 2,5-disubstitution and high regioselectivity observed for compounds **4**, **5**, and **6**, it seems that path B better explains the experimental results. Owing to the greater steric demands of the ethyl or isopropyl substituent as compared with the methyl group, the electrophilic attack of **2a** takes place in a position α to the latter group, and consequently substitution occurs in the ethyl or isopropyl group affording compounds **7** and **9**, respectively, as the major products. The attack of **2a** at C-2 or C-5 carbon atom of the furan ring well explains the lack of 2,5-disubstitution. The steric effect of the diethyl hydroxymalonate residue in compounds **3a** and **7**–**12** hinders the next attack of **2a** at the C-2 carbon atom, thus preventing substitution at the remaining alkyl group. Path A explains neither the preferred formation of regioisomers **7** and **9** nor the lack of double substitution.

Additional support of the path B involving (1,5)-sigmatropic rearrangement results from an analysis of the reaction of **1** with 2,3-*O*-isopropylidene-D-glyceraldehyde **13**[6] (Scheme IV). It is well known[7] that in the absence of chelating agents nucleophiles add to **13**, to yield predominantly the *S* configuration at the new formed chiral center.

Hence, it could be assumed that formation of the 2,3-*O*-isopropylidene-D-glyceraldehyde (**13**)–2,5-dimethylfuran

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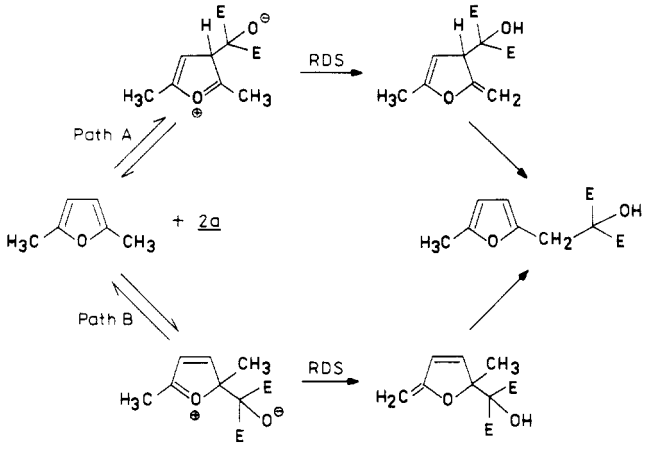
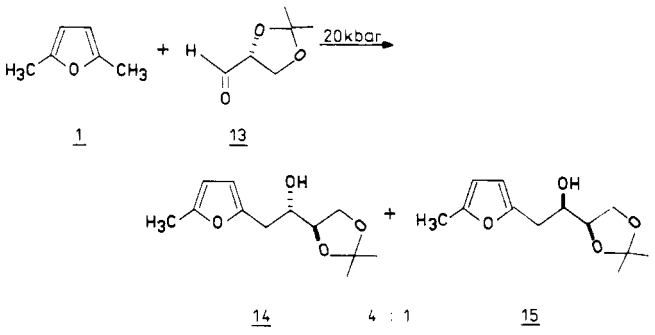
0022-3263/89/1954-4469$01.50/0

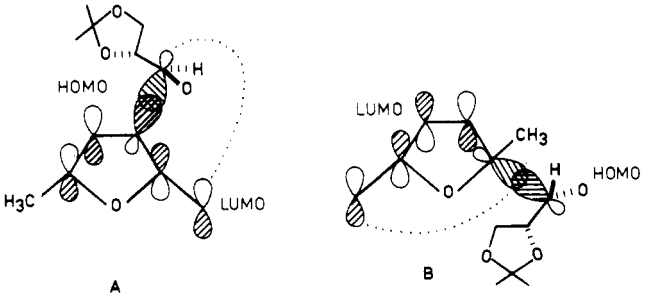
Scheme III



Scheme IV



Scheme V. (1,3)-Suprafacial Rearrangement with Inversion of Configuration (A) and (1,5)-Suprafacial Rearrangement with Retention of Configuration (B)



(1) complex should also lead to the *S* configuration (Scheme V). (1,3)-Suprafacial shift (path A) should cause inversion of configuration, affording mainly product **15**, whereas (1,5)-suprafacial shift (path B) should lead to retention of configuration, giving diastereoisomer **14** as the major product.[8]

The stereochemical course of the reaction between **1** and **13** is in agreement with the above considerations and is consistent with other findings, thus confirming the path B which involves (1,5)-suprafacial shift of the diethyl mesoxalate moiety.

Experimental Section

^{1}H NMR spectra were recorded at 100 MHz with a JEOL JNM-4H-100 spectrometer. ^{2}H NMR spectra were recorded at 38.4 MHz with a Bruker WM 250 spectrometer. Infrared spectra were recorded on a Beckman IR-4240 spectrophotometer.

Column chromatography was carried out with Merck Kieselgel 60 (230–400 mesh). All chromatographic separations were monitored by TLC analyses, performed on Merck DC Alufolien Kieselgel 60F-254.

High-pressure reactions were carried out in a piston–cylinder type apparatus with a working volume of about 10 mL. Construction details have been reported previously.[9] The pressure was measured with a manganin coil calibrated to ±0.1 kbar.

Commercially available 2,5-dimethylfuran (**1**) and diethyl mesoxalate (**2a**) were distilled before use. 2-[$^2H_3$]Methyl-5-methylfuran, 2,5-di[$^2H_3$]methylfuran, 2-methyl-5-ethylfuran (**4**), 2-methyl-5-isopropylfuran (**5**), and 2-methyl-5-benzylfuran (**6**) were prepared according to the Piancatelli's procedure.[10]

High-Pressure Reaction of 2,5-Dimethylfuran (1) with Diethyl Mesoxalate (2a). General Procedure. A solution of **1** (192 mg, 2 mmol) and **2a** (348 mg, 2 mmol) in methyl chloride (4 mL) was charged into a Teflon ampoule,[11] placed in a high-pressure vessel filled with pentane as a transmission medium, and compressed (10 kbar) at 20 °C for 20 h. After decompression, the reaction mixture was concentrated to dryness, and the residue was subjected to column chromatography (hexane–ethyl acetate, 7:3) to give 432.3 mg (80% yield) of the product **3a** ($R^1 = R^2 = CO_2Et$) as a colorless oil: IR (neat) ν 3500, 2980, 1740, 1560, 1440, 1230, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.91 (d, J = 3 Hz, 1 H), 5.76 (m, 1 H), 4.20 (q, J = 7 Hz, 4 H), 3.60 (br s, 1 H), 3.21 (s, 2 H), 2.19 (s, 3 H), 1.27 (t, 6 H). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.91; H, 6.85.

Mixture of products 7 and 8: colorless oil; IR (neat) ν 3480, 2980, 1740, 1560, 1450, 1220, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.90 (m, 1 H), 5.75 (m, 1 H), 4.20 (q, J = 7 Hz, 4 H), 3.76 (q, J = 6.5 Hz, 0.9 H), 3.60 (br s, 1 H), 3.28 (s, 0.2 H), 2.51 (q, J = 6.5 Hz, 0.2 H), 2.20 (s, 2.7 H), 1.50–1.00 (m, 9 H). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.39; H, 7.10.

Mixture of products 9 and 10: colorless oil; IR (neat) ν 3460, 2980, 1735, 1550, 1450, 1215, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.01 (d, J = 3 Hz, 1 H), 5.86 (m, 1 H), 4.25 (q, J = 7 Hz, 4 H), 3.88 (br s, 1 H), 3.36 (s, 0.05 H), 2.70 (m, 0.03 H), 2.22 (s, 2.9 H), 1.35–1.15 (m, 12 H). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.70; H, 7.29.

Mixture of products 11 and 12: colorless oil; IR (neat) ν 3460, 2980, 1735, 1600, 1550, 1450, 1210, 780, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50–7.00 (m, 5 H), 6.02 (m, 1 H), 5.85 (m, 0.43 H), 5.78 (m, 0.57 H), 5.00 (s, 0.57 H), 4.40–4.00 (m, 5 H), 3.87 (s, 0.86 H), 3.28 (s, 0.86 H), 2.20 (s, 1.71 H), 1.40–1.00 (m, 6 H). Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 66.00; H, 6.28.

Labeling Experiments. Products of the reactions of **2a** with 2,5-di[$^2H_3$]methylfuran and with 2-[$^2H_3$]methyl-5-methylfuran were characterized by the ^{1}H and ^{2}H NMR spectra. Distribution of deuterium was determined by integration of the CH_2 and CH_3 signals in the ^{1}H NMR spectra (δ 3.23 and 2.20, respectively) and of the C^2H_2 and C^2H_3 signals in the ^{2}H NMR spectra (δ 3.33 and 2.30, respectively).

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Registry No. **1**, 625-86-5; **2a**, 609-09-6; **3a**, 121571-86-6; **3a**-*O*-*d*, 121571-97-9; **4**, 1703-52-2; **5**, 10504-05-9; **6**, 34253-00-4; **7** (R^1 = H, R^2 = CH_3, E = (O_2Et), 121571-87-7; **8** (R^1 = H, R^2 = CH_3, E = CO_2Et), 121571-88-8; **9** ($R^1 = R^2$ = CH_3, E = CO_2Et), 121571-89-9; **10** ($R^1 = R^2$ = CH_3, E = CO_2Et), 121571-90-2; **11** (R^1 = H, R^2 = C_6H_5, E = CO_2Et), 121571-91-3; **12** (R^1 = H, R^2 = C_6H_5, E = CO_2Et), 121571-92-4; **13**, 15186-48-8; **14**, 93170-23-1; **15**, 93170-22-0; 2,5-di[$^2H_3$]methylfuran, 121571-93-5; 2-[$^2H_3$]-methyl-5-methylfuran, 111946-44-2; diethyl 2-[(5-[$^2H_3$]methylfuran-2-yl)[$^2H_2$]methyl]-2-hydroxy-1,3-propanedioate, 121571-94-6; diethyl 2-[(5-[$^2H_3$]methylfuran-2-yl)methyl]-2-hydroxy-1,3-propanedioate, 121571-95-7; diethyl 2-[(5-methylfuran-2-yl)[$^2H_2$]methyl]-2-hydroxy-1,3-propanedioate, 121571-96-8.

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