

Facile Synthesis of Furan-3,4-diacetates

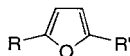
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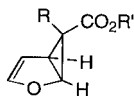
Dedicated to the memory of Professor *Paolo Ceccherelli*

A procedure for bis-cyclopropanation of furans with ethyl diazoacetate or methyl α -diazopropionate under dirhodium-tetraacetate catalysis is presented. Treatment of the products with ethanolic HCl furnished furan-3,4-diacetates.

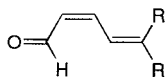
Introduction. – In an exhaustive study of the reaction of furan (**1a**) with ethyl diazoacetate (in furan as solvent), catalyzed by dirhodium tetraacetate, it was discovered that, in 66% overall yield, the reaction had furnished cyclopropa-furancarboxylate **2a** and furan-unravelled 6-oxohexadienoate **3a** as major products and substances **3b** and **4** as minor compounds of the product mixture [1]. This observation and the one showing iodine-induced product isomerization without prior product separation affording solely one compound in high yield (*e.g.*, **1** \rightarrow **3a**) [1] has led to a broad investigation of this two-step, ‘one-pot’ procedure for the preparation of (1*E*,3*E*)-1,4-diacylbuta-1,3-dienes [1–4].



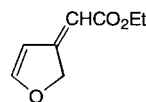
- 1a** R = R' = H
b R = Me, R' = H
c R = R' = Me
d R = CH₂CO₂Et, R' = H
e R = CH₂OAc, R' = H



- 2a** R = H, R' = Et
b R = R' = Me



- 3a** R = CO₂Et, R' = H
b R = H, R' = CO₂Et

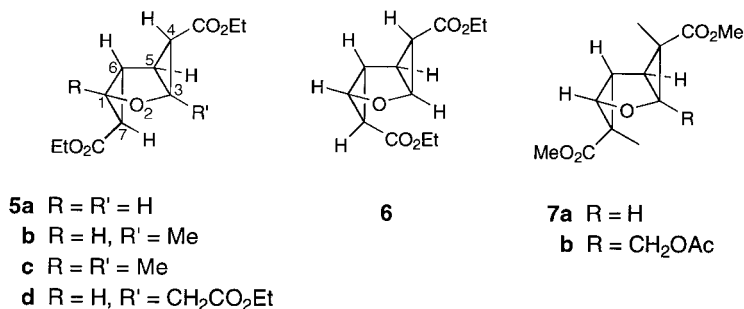


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Results and Discussion. – It now became of interest to pursue reactions of furans with α -diazocarbonyl compounds without furan-ring opening, *i.e.*, preparation of materials of type **2**, or preferably, bis-cyclopropanated substances. This required the use of excess of diazo compound and, hence, a solvent other than the furans. CH₂Cl₂ was chosen for all the cyclopropanations, and the study was initiated with ethyl cyclopropana-

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furancarboxylate **2a**. $[\text{Rh}_2(\text{OAc})_4]$ -Catalyzed interaction of the latter in CH_2Cl_2 with ethyl diazoacetate afforded diester **5a** (76%). When the same reaction was carried out on furan (**1a**), diesters **5a** (35%) and **6** (14%) were obtained.



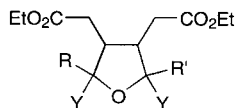
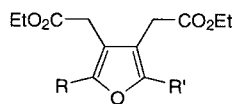
Introduction of Me groups on the furans or the diazo compounds had no ill effect on the reactions. Thus, for example, the involvement of furan (**1a**) with methyl α -diazopropionate [5] yielded diester **7a** (69%)²⁾, and the interactions of 2-methylfuran (**1b**) as well as 2,5-dimethylfuran (**1c**) with ethyl diazoacetate gave diesters **5b** (28%) (and its isomer(s), 24%) and **5c** (80%), respectively³⁾.

With dicyclopropana-furans **5–7** in hand, the time had arrived for an examination of the ease of their ring opening. To avoid the production of (1*E*,3*E*)-1,4-diacylbuta-1,3-diene equivalents (*cf.* **3**) [1], reaction conditions had to be found which would mask intermediates of the enol-ether type and, thus, prevent their participation in the unravelling process. After much experimentation, refluxing ethanolic HCl was chosen for the task. Treatment of diesters **5a**, **6**, **5b**, and **5c** in this manner furnished furan-diacetates **9a** (58%), **9a** (46%), **9b** (39%), and **9c** (37%), respectively (presumably *via* intermediates of the type **8**)⁴⁾⁵⁾.

2) The monocyclopropanated compound **2b** could be obtained (51%) from the non-polar portion of the products of a Rh-catalyzed decomposition of methyl α -diazopropionate in furan. Colorless, sweet-smelling oil. ¹H-NMR: 0.93 (*s*, Me); 2.84 (*dd*, *J* = 3, 6, H–C(4a)); 3.68 (*s*, MeO); 4.74 (*d*, *J* = 6, H–C(1a)); 5.26 (*t*, *J* = 2.6, H–C(4)); 6.45 (*d*, *J* = 2.4, H–C(3)). ¹³C-NMR: 5.0 (Me); 18.5 (C(6)); 36.9 (C(5)); 51.7 (MeO); 70.4 (C(1)); 102.1 (C(4)); 148.4 (C(3)); 174.8 (C=O).

3) Bis-cyclopropanations could be executed also on furans with side chains containing functional groups (*e.g.*, furan-2-acetate **1d** [6]): **1d** → **5d** (59%). Colorless oil. ¹H-NMR: 1.2–1.3 (*m*, 3 Me); 1.96 (*d*, *J* = 4, CHCOOEt); 2.29 (*d*, *J* = 3, CHOOEt); 2.46 (*dd*, *J* = 3, 4, H–C(5), H–C(6)); 2.80 (*d*, *J* = 17, 1 H, CH_2OOEt); 2.92 (*d*, *J* = 17, 1 H, CH_2OOEt); 3.84 (*d*, *J* = 6, H–C(1)); 4.0–4.2 (*m*, 3 CH_3CH_2). ¹³C-NMR: 13.8 (Me); 13.9 (2 Me); 26.4 (CH_2COOEt); 31.4 (CHCOOEt); 31.6 (CHCOOEt); 32.4 (C(5) or C(6)); 32.6 (C(5) or C(6)); 60.3 (MeCH_2); 60.5 (MeCH_2); 60.6 (MeCH_2); 62.8 (C(1)); 70.2 (C(3)); 169.7 (CH_2COOEt); 170.0 (CO); 170.1 (CO). Similarly, **1e** → **7b**. Colorless oil. ¹H-NMR: 1.41 (*s*, Me); 1.54 (*s*, Me); 2.04 (*s*, MeCO); 2.28 (*d*, *J* = 6, H–C(5)); 2.54 (*s*, H–C(5) or H–C(6)); 3.66 (*s*, MeO); 3.69 (*s*, MeO); 3.84 (*d*, *J* = 6, H–C(1)); 4.45 (*s*, CH_2). ¹³C-NMR: 7.7 (Me); 8.9 (Me); 20.3 (MeCO); 27.2 (C(4) or C(7)); 30.6 (C(4) or C(7)); 31.2 (C(5) or C(6)); 32.6 (C(5) or C(6)); 52.0 (MeO); 52.2 (MeO); 62.9 (CH_2); 68.2 (C(1)); 74.7 (C(3)); 170.1 (CO); 171.6 (CO); 172.3 (CO).

4) Ring opening of **5d** ($\text{CF}_3\text{CO}_2\text{H}/120^\circ/2$ h) afforded triester **9d** (57%). Colorless liquid. ¹H-NMR: 1.2–1.3 (*m*, 3 Me); 3.42 (*s*, CH_2 –C(3) or CH_2 –C(4)); 3.45 (*s*, CH_2 –C(4) or CH_2 –C(3)); 3.66 (*s*, CH_2 –C(2)); 4.1–4.3 (*m*, 3 CH_2O); 7.34 (*br. s.*, H–C(5)).

**8** Y = Cl or OEt

- 9a** R = R' = H
b R = Me, R' = H
c R = R' = Me
d R = CH₂CO₂Et, R' = H

Conclusion. – A simple, two step procedure for the synthesis of furan-3,4-diacetates **9** from 3,4-unsubstituted furans has been presented.

Experimental Part

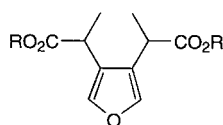
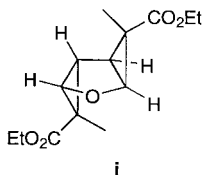
General. Typical reaction workup: Aq. soln. extracted with Et₂O, CH₂Cl₂, AcOEt, the org. extract washed successively with H₂O and brine, dried (Na₂SO₄ or MgSO₄), and solvent evaporated under vacuum. TLC: *EM Laboratories* precoated silica gel 60F-25 on 0.2 mm plates; column: *EM Laboratories* 60–200 mesh silica gel or *Florisil* or alumina (elution with AcOEt/hexane mixtures). MPLC: *Merck Laboratory* (A, B, C) silica-gel columns, *Fluid metering Inc.* pump. M.p.: *Reichert* micro hotstage; uncorrected. IR Spectra [cm⁻¹]: *IBM 9000* spectrophotometer. ¹H- and ¹³C-NMR Spectra (CDCl₃ solns.): *General Electric QE-300* spectrometer. MS: *Hewlett-Packard 5890* GC/MS spectrometers.

Diethyl (1α,3β,5β,6α)-2-Oxatricyclo[4.1.0.0^{3,5}]heptane-4α,7β-dicarboxylate (5a). A soln. of N₂CHCO₂Et (570 mg, 5.0 mmol) in dry CH₂Cl₂ (5 ml) was added dropwise to a stirring mixture of **2a** (462 mg, 3.0 mmol) and [Rh₂(OAc)₄] catalyst (3 mg) in dry CH₂Cl₂ (20 ml) over 3 h under Ar at r.t. Stirring was continued for 0.5 h and the mixture concentrated. The concentrate, as Et₂O suspension, was filtered through a short *Florisil* column and the filtrate was evaporated. Silica-gel chromatography hexane/AcOEt 19:1 afforded 550 mg (76%) of **5a**. Colorless, sweet-smelling liquid. IR (neat): 1722 (C=O). ¹H-NMR: 1.25 (t, J = 7, 2 Me); 1.84 (d, J = 2, H–C(4), H–C(7)); 2.40 (dd, J = 4, 5, H–C(5), H–C(6)); 3.88 (d, J = 5, H–C(1), H–C(3)); 4.10 (q, J = 7, 2 CH₂O). ¹³C-NMR: 14.0 (2 Me); 27.5 (C(4), C(7)); 29.8 (C(5), C(6)); 60.6 (2 CH₂O); 63.5 (C(1), C(3)); 170.2 (2 CO). HR-MS: 240.0983 (C₁₂H₁₆O₅; calc. 240.0998).

General Cyclopropanation Procedure. A soln. of the α-diazo ester (25 mmol) in CH₂Cl₂ (10 ml) was added dropwise to a stirring mixture of [Rh₂(OAc)₄] (10 mg) and the furan starting material (10 mmol) in CH₂Cl₂ (30 ml) over a 3-h period at ambient temp. The mixture was concentrated under vacuum, filtered through a short *Florisil* column, and evaporated.

Diethyl (1α,3β,5β,6α)-2-Oxatricyclo[4.1.0.0^{3,5}]heptane-4α,7α-dicarboxylate (6). A reaction of ethyl diazoacetate (5.70 g, 50 mmol) and **1a** (1.36 g, 20 mmol) under conditions of the *General Procedure* yielded a pale-

- ⁵⁾ Solvolysis of diester **7a** (refluxing HCl/EtOH/3 h) was very slow, leading to transesterification product **i** (colorless liquid; ¹H-NMR: 1.24 (t, J = 7, 2 MeCH₂); 1.46 (s, 2 Me); 2.20 (d, J = 5, H–C(5), H–C(6)); 3.81 (d, J = 5, H–C(1), H–C(3)); 4.11 (q, J = 7, 2 CH₂). ¹³C-NMR: 7.7 (2 Me); 14.0 (2 MeCH₂); 26.9 (C(4), C(3)); 30.2 (C(5), C(6)); 60.8 (2 CH₂); 68.1 (C(1), C(3)); 172.4 (2 CO)), ring-opened diester **ii** (colorless liquid; ¹H-NMR: 1.37 (d, J = 7, 2 Me); 3.51 (dq, J = 7, 2, 2 CHCO); 3.69 (s, 2 MeO); 7.50 (d, J = 2, H–C(2), H–C(5))), and transesterified, ring-opened diester **iii** (colorless liquid; ¹H-NMR: 1.24 (t, J = 7, 2 MeCH₂); 1.46 (d, J = 7, 2 Me); 3.62 (dq, J = 7, 2, 2 CHCO); 4.14 (q, J = 7, 2 CH₂); 7.34 (d, J = 2, H–C(2), H–C(5)). ¹³C-NMR: 14.1 (2 MeCH₂); 18.5 (2 Me); 35.4 (2 CH); 60.8 (2 CH₂O); 123.8 (C(3), C(4)); 140.1 (C(2), C(5)); 174.2 (2 CO)).



- ii** R = Me
iii R = Et

yellow oil, whose MPLC (hexane/AcOEt 19:1) gave diethyl fumarate and diethyl maleate (in the earliest eluates), 1.67 g (35%) of **5a** (spectrally identical with the above sample), and 0.68 g (14%) of colorless, liquid **6**. ¹H-NMR: 1.24 (*t*, *J* = 7, Me of *exo*-ester); 1.30 (*t*, *J* = 7, Me of *endo*-ester); 1.55 (*dd*, *J* = 6, 9, H–C(7)); 1.81 (*dd*, *J* = 1, 4, H–C(4)); 2.28 (*dd*, *J* = 6, 9, H–C(6)); 2.38 (*dd*, *J* = 4, 6, H–C(5)); 3.87 (*t*, *J* = 6, H–C(3)); 4.05 (br. *d*, *J* = 6, H–C(1)), 4.10 (*q*, *J* = 7, *exo*-CH₂O); 4.20 (*q*, *J* = 7, *endo*-CH₂O). ¹³C-NMR: 14.2 (2 Me); 24.7 (C(7)); 26.8 (C(4)); 28.2 (C(6)); 28.9 (C(5)); 60.5 (*endo*-CH₂O); 60.9 (*exo*-CH₂O); 67.0 (C(1), C(3)); 168.3 (*endo*-CO); 170.6 (*exo*-CO). HR-MS: 240.0999 (C₁₂H₁₆O₅; calc. 240.0998).

Diethyl (1α,3β,5β,6α)-3,6-Dimethyl-2-oxatricyclo[4.10.0.0^{3,5}]heptane-4α,7β-dicarboxylate (7a). Following the *General Cyclopropanation Procedure*, the combination of methyl *α*-diazopropionate (3.98 g, 35 mmol) and **1a** (1.03 g, 15 mmol) furnished 2.51 g (69%) of colorless, crystalline **7a**. M.p. 98°. ¹H-NMR: 1.46 (*s*, 2 Me); 2.21 (*d*, *J* = 6, H–C(5), H–C(6)); 3.65 (*s*, 2 MeO); 3.82 (*d*, *J* = 6, H–C(3), H–C(1)). ¹³C-NMR: 7.7 (2 Me); 26.9 (C(4), C(7)); 30.2 (C(5), C(6)); 51.8 (2 MeO); 68.1 (C(3), C(1)); 172.6 (2 CO). HR-MS: 240.0992 (C₁₂H₁₆O₅; calc. 240.0998).

Diethyl (1α,3β,5β,6α)-3-Methyl-2-oxatricyclo[4.10.0.0^{3,5}]heptane-4α,7β-dicarboxylate (5b). A reaction of ethyl diazoacetate (7.12 g, 62 mmol) and 2-methylfuran (**1b**) (2.05 g, 25 mmol) as above yielded an oil, whose MPLC (hexane/AcOEt 19:1) afforded diethyl fumarate, diethyl maleate, and 1.78 g (28%) of colorless, liquid **5b**. IR (neat): 1754 (C=O), 1775. ¹H-NMR: 1.24 (*t*, *J* = 7, MeCH₂); 1.26 (*t*, *J* = 7, MeCH₂); 1.46 (*s*, Me–C(3)); 1.74 (*d*, *J* = 4, H–C(7)); 1.86 (*d*, *J* = 4, H–C(4)); 2.26 (*d*, *J* = 4, H–C(5)); 2.43 (*dd*, *J* = 4, 6, H–C(6)); 3.83 (*d*, *J* = 6, H–C(1)); 4.10 (*q*, *J* = 7, CH₂O); 4.12 (*q*, *J* = 7, CH₂O). ¹³C-NMR: 13.9 (3 Me); 27.9 (C(7)); 31.6 (C(6)); 32.2 (C(4)); 32.8 (C(5)); 60.3 (2 CH₂O); 62.6 (C(1)); 70.2 (C(3)); 169.9 (2 CO). HR-MS: 254.1149 (C₁₃H₁₈O₅; calc. 254.1154).

A subsequent eluate led to 1.52 g (24%) of liquid isomer(s) of **5b**. HR-MS: 254.1157 (C₁₃H₁₈O₅; calc. 254.1154)⁶.

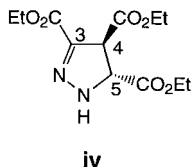
Diethyl (1α,3β,5β,6α)-1,3-Dimethyl-2-oxatricyclo[4.1.0.0^{3,5}]heptane-4α,7β-dicarboxylate (5c). Ethyl diazoacetate (2.85 g, 25 mmol) interacted with 2,5-dimethylfuran (**1c**) (0.96 g, 10 mmol) according to the above method, and MPLC of the crude product (hexane/AcOEt 19:1) furnished 2.15 g (80%) of colorless, liquid **5c**. ¹H-NMR: 1.26 (*t*, *J* = 7, 2 MeCH₂); 1.47 (*s*, 2 Me); 1.77 (*d*, *J* = 4, H–C(4), H–C(7)); 2.31 (*d*, *J* = 4, H–C(5), H–C(6)); 4.13 (*q*, *J* = 7, 2CH₂O). ¹³C-NMR: 13.9 (2 MeCH₂ or 2 Me); 14.1 (2 Me or 2 MeCH₂); 32.7 (C(4), C(7)); 34.7 (C(5), C(6)); 60.4 (2 CH₂O); 69.6 (C(3), C(1)); 170.1 (2 CO). HR-MS: 268.1268 (C₁₄H₂₀O₅; calc. 268.1310).

General Cyclopropane Ring-Opening Procedure. A soln. of the bis-cyclopropane diester (1.0 mmol) in a conc. HCl/EtOH mixture 1:1 (*v/v*) (4 ml) was refluxed for 2 h and then cooled to r.t. The mixture was diluted with H₂O (5 ml) and extracted three times with Et₂O (20 ml each). The combined extracts were dried and then evaporated. Silica-gel chromatography and elution with hexane/AcOEt 19:1 afforded oily furan-3,4-diacetate.

Diethyl Furan-3,4-diacetate (9a). Application of the above procedure to 300 mg of ester **5a** or **6** gave each 130 mg (43%) or colorless, liquid **9a**. ¹H-NMR: 1.27 (*t*, *J* = 7, 2 Me); 3.46 (*s*, 2 CH₂); 4.16 (*q*, *J* = 7, 2 CH₂O); 7.34 (*s*, H–C(2), H–C(5)). ¹³C-NMR: 13.9 (2 Me); 29.3 (2 CH₂); 60.9 (2 CH₂O); 117.5 (C(3), C(4)); 141.1 (C(2), C(5)); 170.8 (2 CO). MS: 240, 194, 167, 166, 149, 121, 111, 95. HR-MS (CI): 241.1053 (C₁₂H₁₆O₅ + H; calc. 241.1075).

Refluxing 5a (280 mg) in CF₃COOH (0.5 ml) for 2.5 h led to 160 mg (58%) of **9a**. When **6** (117 mg) and TsOH (65 mg) in CCl₄ (5 ml) were refluxed for 6 h, 53 mg (46%) of **9a** were obtained.

- ⁶) In view of the presence of trace amounts of a substance derivable from solely diazoacetate in the product mixture of the bis-cyclopropanations, a reaction was executed under the conditions of the *General Cyclopropanation Procedure* but in the absence of any furan. This led to the usual fumarate and maleate esters, and 12% of the ubiquitous compounds **iv** [7] as a pale-yellow semi-solid: ¹H-NMR: 1.29 (*t*, *J* = 7, Me); 1.31 (*t*, *J* = 7, Me); 1.35 (*t*, *J* = 7, Me); 4.23 (*q*, *J* = 7, CH₂); 4.25 (*q*, *J* = 7, CH₂); 4.32 (*q*, *J* = 7, CH₂); 4.40 (*d*, *J* = 6, H–C(4)); 4.77 (*d*, *J* = 6, H–C(5)); 6.99 (br. *s*, NH). ¹³C-NMR: 13.8, 13.9, 14.0 (3 Me); 52.2 (C(4)); 61.3, 62.0, 62.3 (3 CH₂); 66.1 (C(5)); 139.6 (C=N); 161.1 (conjugated CO); 168.9, 169.6 (2 C=O).



Diethyl 2-Methylfuran-3,4-diacetate (9b). Following the *General Procedure* for cyclopropane opening on 56 mg of **5b** led to 22 mg (39%) of colorless, liquid **9b**. ¹H-NMR: 1.27 (*m*, 2 MeCH₂); 2.24 (*s*, Me); 3.36 (*s*, C(3)–CH₂); 3.43 (*s*, C(4)–CH₂); 4.16 (*m*, 2 CH₂O); 7.24 (*br. s.*, H–C(5)). MS: 254, 208, 181, 180, 163, 135, 125, 109.

Diethyl 2,5-Dimethylfuran-3,4-diacetate (9c). The same reaction on 200 mg of **5c** resulted in the formation of 79 mg (37%) of colorless, liquid **9c**. ¹H-NMR: 1.26 (*t*, *J* = 7, 2 MeCH₂); 2.19 (*s*, 2 Me); 3.34 (*s*, 2 CH₂); 4.12 (*q*, *J* = 7, 2 CH₂O). ¹³C-NMR: 11.4 (2 Me); 14.0 (2 MeCH₂); 29.7 (2 CH₂); 60.6 (2 CH₂O); 112.4 (C(3), C(4)); 146.8 (C(2), C(5)); 171.3 (2 CO). MS: 268, 222, 195, 194, 177, 149, 139, 123.

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