Pergamon

Tetrahedron Letters 40 (1999) 5439–5442

TETRAHEDRON LETTERS

The Effect of Substituents of α-Alkyl Sidechains on Furan-Diazoester Interactions

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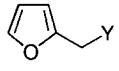
Received 4 February 1999; accepted 24 May 1999

Abstract: Reactions of various α-alkyl-substituted furans with ethyl diazoacetate or methyl diazopropionate in the presence of $Rh_2(OAc)_4$, followed by iodine-induced isomerization, yielded a variety of functionalized 1,3-diacyl-butadienes (furan ring-unravelled products). Though with furfural and 2-acetylfuran the reaction took place at the sidechain, with furfural acetal both the furan as well as acetal moities participated.

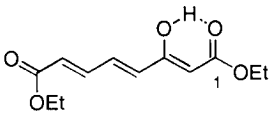
Keywords: Acetals; furans; carbenes and carbenoids; diazo compounds.

Whereas much work has been expended on the preparation of 1,4-diacyl-1*E*,3*E*-butadienes by way of $Rh_2(OAc)_4$-catalyzed reactions of α-diazocarbonyl compounds with furan and its alkylated derivatives (followed by iodine-induced isomerizations),[1] few examples of this high-yielding reaction sequence are known for cases of alkylfurans possessing sidechains with (possibly reactive) substituents thereon. The present communication addresses this problem.

Interaction of ethyl (α-furyl)acetate (**1a**)[2] with ethyl diazoacetate (EDA) under $Rh_2(OAc)_4$ catalysis furnished diester **2** (via β-ketoester **3**) in 73 % yield. Treatment of furfuryl acetate (**1b**) with methyl α-diazopropionate (MDP)[3] and the same catalyst produced ketodiester **4** (62 %) and cyclopropane **5** (7 %). The stereochemistry assignment of the quaternary center of cyclopropane **5** is based on the methyl hydrogen shifts (0.96 ppm) and those of the deacetoxymethyl equivalent (0.93)[3] as well as those of 6-methylbicyclo[3.1.0]hex-2-ene-6-carboxylic acid with *endo* 6-Me (1.01) and *exo* 6-Me (1.33).[4]



1a: Y = CO_2Et
b: Y = OAc
c: Y = CH(OAc)Bu
d: Y = Pr



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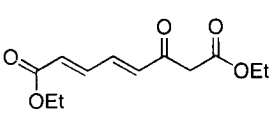

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Acetate **1c**, prepared by reaction of α-furyllithium[5a] with 1-hexene epoxide and subsequent acetylation, and EDA and the rhodium catalyst led to ketoester **6** (the ring unravelling having been followed by acetate β-

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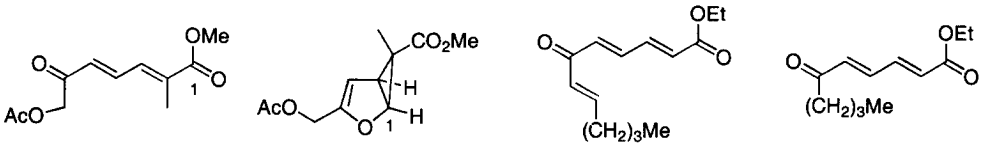
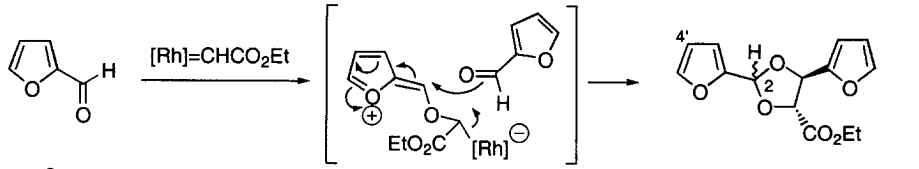
PII: S0040-4039(99)01062-X

elimination),[5b] but only in 15 % yield. The low yield could be attributed to preferred carbenoid attack at the carbonyl oxygen, as illustrated by the normal behavior of α-(*n*-butyl)furan (**1d**), affording ketoester **7** in 87 % yield.[6]



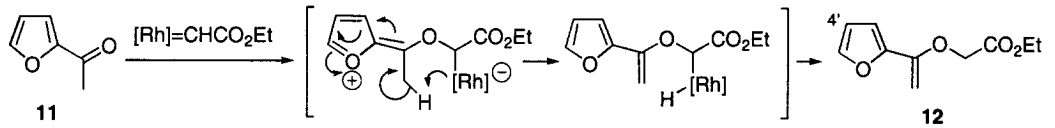
4 **5** **6** **7**

$Rh_2(OAc)_4$-induced reaction of furfural (**8**) with EDA affected only the sidechain, producing two stereoisomeric 2:1 adducts, **9** and **10**, in 68 % yield (**Scheme 1**).[7] A similar reaction of α-acylfuran (**11**) and EDA also led only to sidechain chemistry, furnishing enol ether **12** in unfortunately only low yield (16 %) (**Scheme 2**).[8]



8 **9** [α-H(2)] : **10** [β-H(2)] = 1:1

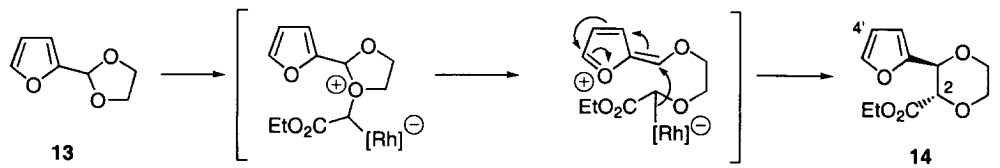
Scheme 1



11 **12**

Scheme 2

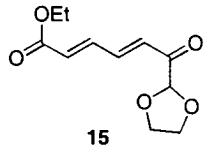
As a sequel of the aldehyde and ketone reactions, acetal **13**[9a] was made to react with EDA giving two products. The first product (17 % yield) was shown to be the acetal ring expansion product **14**[9b] (**Scheme 3**) and the second product (46 % yield) was derived from a furan ring-unravelling process.[10] Based on earlier experiments, ketone **15** was expected. But from NMR data[11] it was evident that the product was a *bis*-acetal. Comparison of the acetal chemical shifts [^{1}H and ^{13}C NMR (δ in ppm)] of **16**[12] [4.4-4.6 and 93-95.5] and **17**[12] [4.8-5.3 and 102.5-106.0] with the observed values [4.94 and 104.2, 106.8] revealed the structure to be the *bis*-



13 **14**

Scheme 3

acetal **18**. Even though acetal **13** was used in excess, it was not recovered from the black solution, presumably having acted as an acetalation transfer agent. In the same fashion, the reaction of acetal **13** with MDP produced 6 % of dioxane **19** and 48 % of *bis*-acetal **20** [^{1}H- and ^{13}C NMR (δ in ppm): 4.95 and 104.4, 107.1].[11]



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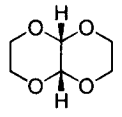

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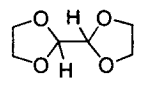

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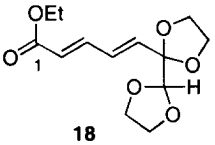

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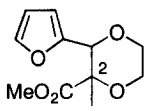

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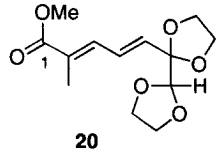

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References and Notes

[1] (a) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203. (b) Matlin, S. A.; Chan, L.; Catherwood, B. *J. Chem. Soc.,Perkin Trans. 1*, **1990**, 89. (c) Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112.

[2] Baciocchi, E.; Muraglia, E.; Sleiter, G. *J. Org. Chem.* **1992**, *57*, 6817.

[3] Wenkert, E.; Khatuya, H. *Helv. Chim. Acta* **1998**, *81*, 2370.

[4] Brook, P. R.; Duke, A. J.; Harrison, J. M.; Hunt, K. *J. Chem. Soc.,Perkin Trans. 1*, **1974**, 927.

[5] (a) Ng, J. S.; Behling, J. R.; Campbell, A. L.; Nguyen, D.; Lipshutz, B. *Tetrahedron Lett.* **1988**, *29*, 3045. (b) After iodine-isomerization, the crude material was treated with DMAP in EtOH at rt for 8 h.

[6] NMR (300 MHz, $CDCl_3$) data. **2**: IR (cm^{-1}) 1724, 1658, 1638, 1627; ^{1}H NMR δ 1.31 (*t*, 6, *J* = 7.1 Hz, 2 Me), 4.23 (*q*, 4, *J* = 7.1 Hz, CH_2s), 5.17 (br. *s*, 1, H-2), 6.11 (*d*, 1, *J* = 15.2 Hz, H-7), 6.22 (*d*, 1, *J* = 15.2 Hz, H-4), 7.10 (*dd*, 1, *J* = 11.6, 15.2 Hz, H-5), 7.33 (*dd*, 1, *J* = 11.6, 15.2 Hz, H-6), 11.79 (*d*, 1, *J* = 1.1 Hz, OH); ^{13}C NMR δ 14.2 (2 Me), 60.5 and 60.6 (CH_2s), 94.2 (C-2), 125.9 (C-7), 132.4 (C-5), 133.5 (C-4), 141.9 (C-6), 166.3 (C-1), 167.8 (C-8), 172.4 (C-3). **4**: IR (cm^{-1}) 1762, 1707, 1691; ^{1}H NMR δ 2.09 (*d*, 3, *J* = 0.9 Hz, 2-Me), 2.20 (*s*, 3, CH_3CO), 3.81 (*s*, 3, OMe), 4.86 (*s*, 2, CH_2), 6.49 (*d*, 1, *J* = 15.3 Hz, H-5), 7.22 (br. *d*, 1, *J* = 11.8 Hz, H-3), 7.58 (*dd*, 1, *J* = 11.8, 15.3 Hz, H-4); ^{13}C NMR δ 13.4 (2-Me), 20.4 (CH_3CO), 52.2 (OMe), 67.6 (CH_2), 129.2 (C-5), 134.6 (C-3), 137.1 (C-2), 137.4 (C-4), 167.6 (C-1), 170.1 (CH_3CO), 192.4 (C-6); Exact mass: calcd. for $C_{11}H_{14}O_5$: 226.0841; found: 226.0840. **5**: IR (cm^{-1}) 1745, 1720; ^{1}H NMR δ 0.96 (*s*, 3, 6-Me), 2.09 (*s*, 3, CH_3CO), 2.48 (*dd*, 1, *J* = 2.6, 5.8 Hz, H-5), 3.69 (*s*, 3, OMe), 4.64 (*s*, 2, CH_2), 4.78 (*d*, 1, *J* = 5.8 Hz, H-1), 5.31 (*d*, 1, *J* = 2.6 Hz, H-4); ^{13}C NMR δ 5.4 (6-Me), 18.1 (C-6), 20.6 (CH_3CO), 37.3 (C-5), 52.1 (OMe), 57.9 (CH_2), 70.8 (C-1), 102.7 (C-4), 155.9 (C-3), 175.0 (ester C=O), 170.3 (CH_3CO); Exact mass: calcd. for $C_{11}H_{14}O_5$: 226.0841; found: 226.0823. **6**: ^{1}H NMR δ 0.92 (*t*, 3, *J* = 7.2 Hz, H-12), 1.34 (*t*, 3, *J* = 7.2 Hz, CH_3CH_2O), 1.34 (*m*, 2, H-11), 1.48 (*m*, 2, H-10), 2.28 (*dq*, 2, *J* = 1.2, 7.0 Hz, H-9), 4.24 (*q*, 2, *J* = 7.1 Hz, CH_3CH_2O), 6.24 (*d*, 1, *J* = 14.4 Hz, H-2), 6.34 (*dd*, 1, *J* = 11.4, 15.4 Hz, H-7), 6.75 (*d*, 1, *J* = 14.4 Hz, H-5), 6.98 (*td*, 1, *J* = 7.0, 15.6 Hz, H-8), 7.22-7.41 (*m*, 2, H-3 and H-4); ^{13}C NMR δ 13.6 (C-12), 14.0 (CH_3CH_2O), 22.1 (C-11), 30.0 (C-10), 32.3 (C-9), 60.6 (CH_3CH_2O), 128.6 (C-2), 129.1 (C-5), 133.9 (C-7), 138.6 (C-4), 141.3 (C-3), 149.4 (C-8), 165.7 (C-1), 188.5 (C-6). **7**: IR (cm^{-1}) 1716, 1690; ^{1}H NMR δ 0.93 (*t*, 3, *J* = 7.2 Hz, H-10), 1.32 (*t*, 3, *J* = 7.2 Hz, CH_3CH_2O), 1.37 (*sext.*, 2, *J* = 7.2 Hz, H-9), 1.62 (*quint.*, 2, *J* = 7.2 Hz, H-8), 2.61 (*t*, 2, *J* = 7.5 Hz, H-7), 4.24 (*q*, 2, *J* = 7.2 Hz, CH_3CH_2O), 6.24 (*d*, 1, *J* = 15.0 Hz, H-2), 6.46 (*d*, 1, *J* = 15.0 Hz, H-5), 7.18 (*dd*, 1, *J* = 11.4, 15.0 Hz, H-

4), 7.32 (*dd*, 1, *J* = 11.4, 15.0 Hz, H-8); ^{13}C NMR δ 13.8 (C-10), 14.1 (CH_3CH_2O), 22.3 (C-9), 26.0 (C-8), 41.0 (C-7), 60.8 (CH_3CH_2O), 128.8 (C-2), 135.3 (C-5), 138.1 (C-4), 141.3 (C-3), 165.8 (C-1), 200.1 (C-6).

[7] (a) For similar 2:1 adducts with aryl aldehydes, see Alt, M.; Mass, G. *Tetrahedron* **1994**, *50*, 7435 and Doyle, M. P.; Forbes, D. C.; Protopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210. (b) The relative *trans*- stereochemistry of the 1,2-disubstituents also was supported by the following experiment: When the acetal mixture was treated with NaOEt in EtOH, the ratio remained unchanged.

[8] **Acetals 9 & 10**: IR (cm^{-1}) 1754; ^{1}H NMR δ 1.06 (*t*, 3, *J* = 7.1 Hz, Me), 1.27 (*t*, 3, *J* = 7.1 Hz, Me), 4.00 (*q*, 2, *J* = 7.1 Hz, CH_2), 4.26 (*q*, 2, *J* = 7.1 Hz, CH_2), 4.87 (*d*, 1, *J* = 6.2 Hz, H-5), 5.01 (*d*, 1, *J* = 7.0 Hz, H-5), 5.23 (*d*, 1, *J* = 6.2 Hz, H-4), 5.60 (*d*, 1, *J* = 7.0 Hz, H-4), 6.24 (br. *s*, 1, H-3), 6.34 (*m*, 4, H-3'), 6.50-6.58 (*m*, 4, H-4'), 6.56 (br. *s*, 1, H-3), 7.45-7.47 (*m*, 4, H-5'). ^{13}C NMR δ 13.9 (Me), 14.1 (Me), 61.4 (CH_2), 61.8 (CH_2), 73.9 (C-5), 75.2 (C-5), 77.0 (C-4), 77.3 (C-4), 99.0 (C-3), 99.4 (C-3), 109.7, 109.8, 110.0, 110.3, 110.4, 110.5, 110.56, 110.6 (C-3s & C-4s), 143.1, 143.6, 143.6, 143.7 (C-5s), 148.9, 148.9, 149.3, 150.1 (C-2s), 168.5 (C=O), 168.7 (C=O). Exact mass: calcd. for $C_{14}H_{14}O_6$: 278.0790; found: 278.0793. **Enol ether 12**: ^{1}H NMR δ 1.29 (*t*, 3, *J* = 7.2 Hz, Me), 4.14 (*d*, 1, *J* = 3.5 Hz, H-2'β), 4.26 (*q*, 2, *J* = 7.2 Hz, CH_3CH_2O), 4.50 (*s*, 2, CH_2CO), 4.79 (*d*, 1, *J* = 3.5 Hz, H-2'α), 6.39 (*dd*, 1, *J* = 1.6, 3.3 Hz, H-3), 6.58 (*d*, 1, *J* = 3.1 Hz, H-4), 7.36 (br. *d*, 1, *J* = 1.0 Hz, H-5). ^{13}C NMR δ 14.1 (Me), 61.2 (CH_3CH_2O), 64.9 (CH_2CO), 82.4 (C-2'), 107.2 (C-4), 111.1 (C-3), 142.4 (C-5), 146.3 (C-2), 151.3 (C-1'), 168.3 (C=O). For similar reactions with saturated ketones, see Lottes, A. C.; Landgrebe, J. A.; Larsen, K. *Tetrahedron Lett.* **1989**, *30*, 4089.

[9] (a) Acetal **13** was prepared from furfural and ethylene glycol (Later, there appeared a similar protocol: Lu, T.-J.; Yang, J.-F.; Sheu, L.-J. *J. Org. Chem.* **1995**, *60*, 2931). (b) $CuSO_4$-catalyzed reaction (heptane/70 °C) of acetal **13** produced dioxane **14** in 28 % yield: Molchanov, A. P.; Serkina, T. G.; Badovskaya, L. A.; Kostikov, R. R. *J. Org. Chem. USSR* (Engl. Transl.)**1992**, *28*, 1874.

[10] Typical procedure: *Reaction of acetal* **13** *with EDA*.
A solution of ethyl diazoacetate (502 mg, 4.4 mmol) in 3 ml of dry CH_2Cl_2 was added slowly to a green solution of acetal **13** (740 mg, 5.3 mmol) and $[Rh_2(OAc)_4]$ (5 mg) in CH_2Cl_2 (20 ml) at r.t. over a 10-h period. It then was concentrated and filtered through a short *Florisil* column to remove the catalyst. The crude material was taken up in CH_2Cl_2 (20 ml) and stirred at r.t. with a catalytic amount of I_2 (two crystals) for 12 h. The solution was washed sequentially with 10% $Na_2S_2O_3$ and brine, and then dried (Na_2SO_4). The products (**14** and **18**) were separated by SiO_2 chromatography (10 % Et_2O-light petroleum ether).

[11] **13**: ^{13}C NMR δ 64.7 (CH_2s), 97.3 (C-acetal), 77.4 (C-3), 108.3 (C-4), 109.8 (C-3), 142.8 (C-5), 152.8 (C-2). **14**: ^{1}H NMR δ 1.09 (*t*, 3, *J* = 7.1 Hz, Me), 3.80-3.97 (*m*, 4, CH_2s), 4.06 (*q*, 2, *J* = 7.1 Hz, CH_3CH_2), 4.40 (*d*, 1, *J* = 8.8 Hz, H-2), 4.70 (*d*, 1, *J* = 8.8 Hz, H-3), 6.35 (*dd*, 1, *J* = 1.6, 3.3 Hz, H-3'), 6.38 (*d*, 1, *J* = 3.3 Hz, H-4'), 7.43 (br. *s*, 1, H-5'); ^{13}C NMR δ 13.5 (Me), 60.9 (CH_3CH_2), 65.5 and 65.8 (CH_2s), 72.2 (C-2), 77.4 (C-3), 109.2 (C-4'), 110.0 (C-3'), 142.7 (C-5'), 149.5 (C-2'), 167.9 (C=O). **18**: ^{1}H NMR δ 1.30 (*t*, 3, *J* = 7.1 Hz, Me), 3.90-4.12 (*m*, 8, CH_2s), 4.21 (*q*, 2, *J* = 7.1 Hz, CH_3CH_2), 4.94 (*s*, 1, H-7), 5.96 (*d*, 1, *J* = 15.4 Hz, H-5), 6.11 (*d*, 1, *J* = 11.4, 15.4 Hz, H-2), 6.59 (*dd*, 1, *J* = 11.2, 15.4 Hz, H-4), 7.28 (*dd*, 1, *J* = 11.2, 15.4 Hz, H-3); ^{13}C NMR δ 14.1 (Me), 60.2 (CH_3CH_2O), 65.6 and 65.7 (CH_2s), 104.2 (C-7), 106.8 (C-6), 123.2 (C-2), 129.7 (C-4), 136.6 (C-5), 142.7 (C-3), 166.4 (C=O). **19**: ^{1}H NMR δ 1.35 (*s*, 3, Me), 3.62-4.05 (*m*, 4, CH_2s), 3.82 (*s*, 3, OMe), 5.19 (*s*, 1, H-3), 6.38 (*dd*, 1, *J* = 1.6, 3.3 Hz, H-3'), 6.45 (*d*, 1, *J* = 3.3 Hz, H-4'), 7.43 (br. *s*, 1, H-5'). **20**: ^{1}H NMR δ 1.95 (*s*, 3, Me), 3.76 (*s*, 3, OMe), 3.90-4.12 (*m*, 8, CH_2s), 4.95 (*s*, 1, H-7), 6.07 (*d*, 1, *J* = 15.2 Hz, H-5), 6.79 (*dd*, 1, *J* = 11.6, 15.2 Hz, H-4), 7.19 (*d*, 1, *J* = 11.6 Hz, H-3); ^{13}C NMR δ 12.8 (Me), 51.8 (OMe), 65.7 and 65.8 (CH_2s), 104.4 (C-7), 107.1 (C-6), 127.3 (C-5), 129.0 (C-2), 135.3 (C-4), 136.8 (C-3), 168.6 (C=O).

[12] (a) Sangsari, F. H.; Chastrette, F.; Chastrette, M.; Blanc, A.; Mattioda, G. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 15. (b) Chastrette, F.; Bracoud, C.; Chastrette, M.; Mattioda, G.; Christidis, Y. *Bull. Soc. Chim. Fr.* **1983**, 33.