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Reactions of Ethyl Diazoacetate with β-Methylfurans

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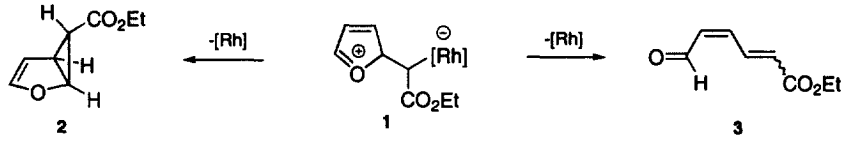
Abstract: Reactions of β-methylfuran and 2,4-dimethylfuran with ethyl diazoacetate in the presence of $[Rh_2(OAc)_4]$ catalyst, followed by iodine-induced isomerization, yielded furan ring-unravelled products. The results are compared with those of α-methylfurans.

Keywords: Furans; carbenes and carbenoids; cyclopropanation; diazo compounds.

An early intermediate on route of the $[Rh_2(OAc)_4]$-catalyzed interaction between ethyl diazoacetate (EDA) and furan is rhodium complex **1**, a substance capable of extruding rhodium and yielding the preponderant products (**2** and **3**). Since an early carbon-carbon bond is that formed between the carbenoid carbon and the furan α-carbon,[1] furan α-substituents would be expected to decrease the rate of such bond formation. In accord with this concept, EDA reaction with α -methylfuran proceeds on the unsubstituted side of the furan nucleus vs. the methylated side in 19:1 ratio.[1] It now became of interest to ascertain the site selectivity of a β-methyl group, leading to the following study of the reaction of β-methylfuran[2,3] and 2,4-dimethylfuran[4].



2 **1** **3**

The dimethylated furan (**4b**) could be prepared by two means. (a) Condition modification of the condensation of chloroacetone with ethyl acetoacetate[5] (dry HCl, -5 °C, 12 h; Et_3N, Et_2O, 0 °C, 52 h; 57 % yield) furnished furoate **5a**, whose hydrolysis (refluxing aq. NaOH, 2 h; 84 % yield) led to acid **5b**[5] and decarboxylation[6] of the latter produced **4b**. (b) 2-Bromo-4-methylfuran (**6a**),[7] prepared from ester **6b**,[8] was converted (^{t}BuLi, Et_2O, -78 °C; MeI, -78 °C to r.t., 56 % yield) into **4b**.[9]

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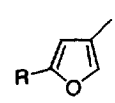
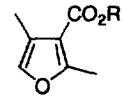
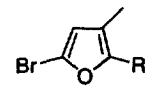


4a: R = H
b: R = Me

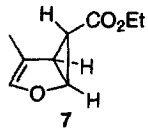


5a: R = Et
b: R = H



6a: R = H
b: R = CO_2Me

The reaction of β-methylfuran (**4a**) with EDA under $[Rh_2(OAc)_4]$ catalysis afforded a mixture of cyclopropane **7** and 1,4-diacyl-1,3-butadienes in 92 % of mass recovery. Treatment of the mixture with I_2 converted it into four aldehydoesters, - **8**, **9a**, **10a**[10] and **11a**. Aldehydoesters **8a** and **9a** are the products of [Rh]=$CHCO_2Et$ interaction with the furan on its unsubstituted side, whereas substances **10a** and **11a** are derived from action on the side of the substituent. The **[8+9a]/[10a+11a]** ratio proved to be in the range of 1.5:1 to 2:1, indicating low site selectivity in the **4a**-EDA reaction.[11]



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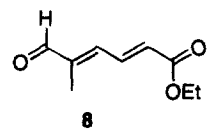

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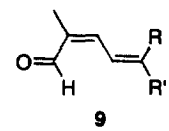

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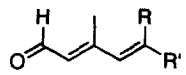

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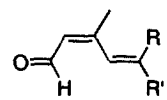

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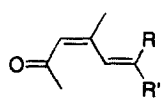
a: R = H, R' = CO_2Et; **b**: R = CO_2Et, R' = H

$[Rh_2(OAc)_4]$-induced reaction of 2,4-dimethylfuran (**4b**) and EDA furnished[12] ketoesters **12a** and **12b** (and traces of aldehydoesters **14a** and **14b**), whose I_2 treatment led to ketoesters **12a** (20 % yield) and **13** (62 % yield).[13] Thus, in this case nearly exclusive site selectivity favoring the β-methyl side of the furan nucleus was exhibited.



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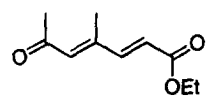

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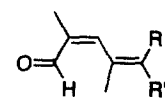

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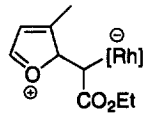
a: R = H, R' = CO_2Et; **b**: R = CO_2Et, R' = H

The extraordinary difference of behavior of α- and β-methylfurans may have both steric and electronic justifications. In view of complex **1** being an early intermediate along the carbenoid-furan reaction route, its

formation in the presence of an α-methyl group constitutes a high-energy *ipso* attack, but in the presence of a β-methyl substitutent a lower energy *ortho* attack. Furthermore, in complex **1** an *ortho*-methyl group (cf. **15**) would stabilize the furanyl positive charge, but only with the carbenoid interaction having taken place on the methylated side of the furan ring. In contrast, an α-methyl function (cf. **16**) stabilizes the positive charge only if the carbenoid interacts on the opposite side of the furan ring.



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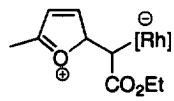

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References and Notes

[1] Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203.

[2] Burness, D.M. *Org. Synth.* **1959**, *39*, 49.

[3] For a reaction of **4a** with an α-diazo-β-lactam see Matlin, S.A.; Chan, L.; Catherwood, B. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 89.

[4] a) Ancerewicz, J.; Vogel, P. *Helv. Chim. Acta* **1996**, *79*, 1393. b) Reichstein, T.; Zschokke, H.; Georg, A. *Helv. Chim. Acta* **1931**, *14*, 1393.

[5] Alexander, E.R.; Baldwin, S. *J. Am. Chem. Soc.*, **1951**, *73*, 356.

[6] Shepard, A.F.; Winslow, N.R.; Johnson, J.R.; *J. Am. Chem. Soc.* **1930**, *52*, 2083.

[7] Knight, D.W.; Rustidge, D.C. *J. Chem. Soc, Perkin Trans. 1*, **1981**, 679.

[8] Grigg, R.; Knight, J.A.; Sargent, M.V. *J. Chem. Soc. (C)*, **1966**, 976.

[9] NMR (300 MHz, $CDCl_3$) data:
5a: ^{13}C NMR δ 9.9 (4-CH_3), 14.2 (CH_3CH_2 and 2-CH_3), 59.7 (CH_2), 113.4 (C-4), 121.0 (C-3), 137.0 (C-5), 159.9 (C-2), 164.6 (C=O). **5b**: ^{13}C NMR δ 9.9 (4-CH_3), 14.6 (2-CH_3), 112.8 (C-4), 121.5 (C-3), 137.8 (C-5), 162.0 (C-2), 170.9 (C=O). **6b:** ^{13}C NMR δ 11.3 (CH_3), 51.5 (OMe), 116.7 (C-4), 126.3 (C-3), 133.4 (C-5), 152.0 (C-2), 158.6 (C=O). *5-Bromo-3-methyl-2-furoic acid*: ^{13}C NMR (DMSO-d_6) δ 10.6 (CH_3), 115.9 (C-4), 124.9 (C-3), 131.9 (C-5), 142.0 (C-2), 159.1 (C=O). **6a:** ^{13}C NMR δ 9.8 (CH_3), 113.6 (C-3), 121.6 (C-4), 122.9 (C-2), 140.9 (C-5). **4b:** ^{13}C NMR δ 9.6 (4-CH_3), 13.3 (2-CH_3), 108.2 (C-3), 120.6 (C-4), 137.2 (C-5), 152.0 (C-2).

[10] a) Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841. b) Severin, Th.; Lerche, H. *Chem. Ber.* **1976**, *109*, 1171.

[11] **7:** ^1H NMR δ 0.99 (*d*, 1, *J* = 2.4 Hz, H-6), 1.26 (*t*, 3, *J* = 7.2 Hz, CH_3CH$_2$), 1.79 (*d*, 3, *J* = 0.9 Hz, CH_3), 2.65 (*dd*, 1, *J* = 2.4, 5.4 Hz, H-5), 4.12 (*q*, 2, *J* = 7.2 Hz, CH_2), 4.78 (*d*, 1, *J* = 5.4, H-1), 6.11 (br. *s*, 1, H-3). ^{13}C NMR δ 10.0 (CH_3), 13.8 (CH_3CH_2), 21.6 (C-6), 34.7 (C-5), 60.2 (CH_2), 66.8 (C-1), 116.2 (C-4), 141.0 (C-3), 172.7 (C=O). **8:** ^1H NMR δ 1.32 (*t*, 3, *J* = 7.1 Hz, CH_3CH$_2$), 1.95 (*d*, 3, *J* = 0.9 Hz, CH_3), 4.26 (*q*, 2, *J* = 7.1 Hz, CH_2), 6.26 (*d*, 1, *J* = 15.3 Hz, H-2), 6.90 (br. *d*, 1, *J* = 11.6 Hz, H-4), 7.68 (*dd*, 1, *J* = 11.6, 15.3 Hz, H-3), 9.50 (*s*, 1, H-6). **9a:** ^1H NMR δ 1.32 (*t*, 3, *J* = 7.1 Hz, CH_3CH$_2$), 1.93 (*s*, 3, CH_3), 4.25 (*q*, 2, *J* = 7.1 Hz, CH_2), 6.13 (*d*, 1, *J* = 15.0 Hz, H-2), 7.05 (*d*, 1, *J* = 12.4 Hz, H-4), 8.18 (*dd*, 1, *J* = 12.4, 15.0 Hz, H-3), 10.42 (*s*, 1, H-6). ^{13}C NMR δ 13.8 (CH_3CH_2), 16.4 (CH_3), 60.4 (CH_2), 126.8 (C-2), 135.2 (C-3), 140.5 (C-5), 140.9 (C-4), 165.6 (C-1), 189.5 (C-6). **9b:** ^1H NMR δ 1.33 (*t*, 3, *J* = 7.1 Hz, CH_3CH$_2$), 1.96 (*s*, 3, CH_3), 4.24 (*q*, 2, *J* = 7.1 Hz, CH_2), 5.98 (*d*, 1, *J* = 11.4 Hz, H-2), 7.55 (*t*, 1, *J* = 11.9 Hz, H-3),

8.24 (*d*, 1, *J* = 12.4, H-4), 10.39 (*s*, 1, H-6). ^{13}C NMR δ 14.1 (CH_3CH_2), 17.0 (CH_3), 60.5 (CH_2), 120.3 (C-2), 134.9 (C-3), 137.8 (C-4), 140.9 (C-5), 165.4 (C-1), 190.0 (C-6). **10a:** ^{1}H NMR δ 1.33 (*t*, 3, *J* = 7.0 Hz, CH_3CH_2), 2.32 (*s*, 3, CH_3), 4.26 (*q*, 2, *J* = 7.0 Hz, CH_2), 6.17 (*d*, 1, *J* = 7.8 Hz, H-5), 6.35 (*d*, 1, *J* = 15.9 Hz, H-2), 7.36 (*d*, 1, *J* = 15.9 Hz, H-3), 10.18 (*d*, 1, *J* = 7.8 Hz, H-6). ^{13}C NMR δ 12.6 (CH_3), 13.9 (CH_3CH_2), 60.6 (CH_2), 124.3 (C-2), 133.6 (C-5), 145.9 (C-3), 150.5 (C-4), 165.5 (C-1), 190.8 (C-6). **10b:** ^{1}H NMR δ 1.33 (*t*, 3, *J* = 7.1 Hz, CH_3CH_2), 2.35 (*s*, 3, CH_3), 4.26 (*q*, 2, *J* = 7.1 Hz, CH_2), 5.95 (*d*, 1, *J* = 7.8 Hz, H-5), 5.98 (*d*, 1, *J* = 12.1 Hz, H-2), 6.81 (*d*, 1, *J* = 12.1 Hz, H-3), 10.09 (*d*, 1, *J* = 7.8 Hz, H-6). ^{13}C NMR δ 14.1 (CH_3CH_2), 16.2 (CH_3), 60.7 (CH_2), 123.2 (C-2), 129.6 (C-5), 142.6 (C-3), 154.3 (C-4), 165.2 (C-1), 190.8 (C-6). **11a:** ^{1}H NMR δ 1.34 (*t*, 3, *J* = 7.1 Hz, CH_3CH_2), 2.15 (*s*, 3, CH_3), 4.28 (*q*, 2, *J* = 7.1 Hz, CH_2), 6.09 (br. *d*, 1, *J* = 7.9 Hz, H-5), 6.26 (*d*, 1, *J* = 15.7 Hz, H-2), 8.24 (*d*, 1, *J* = 15.7 Hz, H-3), 10.28 (*d*, 1, *J* = 7.9 Hz, H-6). ^{13}C NMR δ 13.6 (CH_3CH_2), 20.1 (CH_3), 60.4 (CH_2), 125.0 (C-2), 132.6 (C-5), 137.3 (C-3), 150.1 (C-4), 165.3 (C-1), 189.2 (C-6). **11b:** ^{1}H NMR δ 1.34 (*t*, 3, *J* = 7.1 Hz, CH_3CH_2), 2.13 (*s*, 3, CH_3), 4.27 (*q*, 2, *J* = 7.1 Hz, CH_2), 6.07 (*d*, 1, *J* = 8.1 Hz, H-5), 6.10 (*d*, 1, *J* = 12.1 Hz, H-2), 6.85 (*d*, 1, *J* = 12.1 Hz, H-3), 9.70 (*d*, 1, *J* = 8.0 Hz, H-6). ^{13}C NMR δ 13.9 (CH_3CH_2), 23.7 (CH_3), 60.7 (CH_2), 123.8 (C-2), 128.3 (C-5), 140.8 (C-3), 157.5 (C-4), 164.2 (C-1), 191.4 (C-6).

[12] Typical procedure: *Reaction of 2,4-dimethylfuran with EDA.*
A solution of ethyl diazoacetate (0.83 g, 7.3 mmol) in 5 ml of dry CH_2Cl_2 was added slowly to a green solution of 2,4-dimethylfuran (1.4 g, 14.6 mmol) and [$Rh_2(OAc)_4$] (ca. 5-10 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 purified (SiO_2, 1-6% Et_2O-light petroleum ether) or 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 (**13** and **12a**) were separated by SiO_2 chromatography.

[13] **12a:** ^{1}H NMR δ 1.32 (*t*, 3, *J* = 7.1 Hz, CH_3CH_2), 2.02 (*d*, 3, *J* = 0.9 Hz, CH_3), 2.26 (*s*, 3, H-7), 4.24 (*q*, 2, *J* = 7.1 Hz, CH_2), 6.18 (*d*, 1, *J* = 16.1 Hz, H-2), 6.28 (br. *s*, 1, H-5), 8.40 (*d*, 1, *J* = 16.1 Hz, H-3). ^{13}C NMR δ 14.0 (CH_3CH_2), 20.2 (CH_3), 31.5 (C-7), 60.4 (CH_2), 124.1 (C-2), 130.3 (C-5), 140.5 (C-3), 144.7 (C-4), 166.2 (C-1); 197.9 (C-6). **12b:** ^{1}H NMR δ 1.27 (*t*, 3, *J* = 7.1 Hz, CH_3CH_2), 2.09 (*s*, 3, CH_3), 2.19 (*s*, 3, H-7), 4.14 (*q*, 2, *J* = 7.1 Hz, CH_2), 5.85 (*d*, 1, *J* = 12.3 Hz, H-2), 6.16 (br. *s*, 1, H-5), 7.07 (*d*, 1, *J* = 12.3 Hz, H-3). ^{13}C NMR δ 13.8 (CH_3CH_2), 23.2 (CH_3), 30.3 (C-7), 59.9 (CH_2), 119.2 (C-2), 125.1 (C-5), 146.1 (C-3), 151.0 (C-4), 165.2 (C-1), 197.0 (C-6). **13:** ^{1}H NMR δ 1.32 (*t*, 3, *J* = 7.1 Hz, CH_3CH_2), 2.23 (br. *s*, 3, CH_3), 2.28 (*s*, 3, H-7), 4.24 (*q*, 2, *J* = 7.1 Hz, CH_2), 6.26 (*d*, 1, *J* = 15.7 Hz, H-2), 6.39 (br. *s*, 1, H-5), 7.26 (*d*, 1, *J* = 15.7 Hz, H-3). ^{13}C NMR δ 13.5 (CH_3), 14.0 (CH_3CH_2), 31.8 (C-7), 60.5 (CH_2), 124.1 (C-2), 131.7 (C-5), 146.4 (C-4), 147.1 (C-3), 166.0 (C-1), 198.7 (C-6). **14a:** ^{1}H NMR δ 1.24 (*t*, 3, *J* = 7.1 Hz, CH_3CH_2), 1.89 (*d*, 3, *J* = 1.2 Hz, 5-CH_3), 2.10 (br. *s*, 3, 3-CH_3), 4.12 (*q*, 2, *J* = 7.1 Hz, CH_2), 5.95 (*t*, 1, *J* = 1.2 Hz, H-2), 7.24 (br. *s*, 1, H-4), 9.82 (*s*, 1, H-6). **14b:** ^{1}H NMR δ 1.24 (*t*, 3, *J* = 7.1 Hz, CH_3CH_2), 1.85 (*d*, 3, *J* = 0.9 Hz, 5-CH_3), 2.14 (*d*, 3, *J* = 0.9 Hz, 3-CH_3), 4.12 (*q*, 2, *J* = 7.1 Hz, CH_2), 5.90 (*t*, 1, *J* = 1.2 Hz, H-2), 7.65 (br. *s*, 1, H-4), 9.55 (*s*, 1, H-6).