

Reactions of Ethyl Diazoacetate with β -Methylfurans

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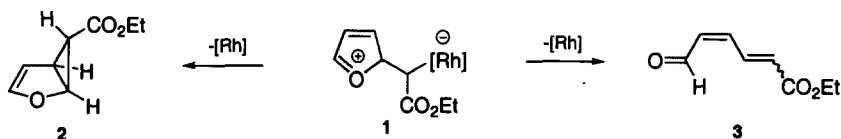
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Abstract: Reactions of β -methylfuran and 2,4-dimethylfuran with ethyl diazoacetate in the presence of $[\text{Rh}_2(\text{OAc})_4]$ catalyst, followed by iodine-induced isomerization, yielded furan ring-unravalled products. The results are compared with those of α -methylfurans.
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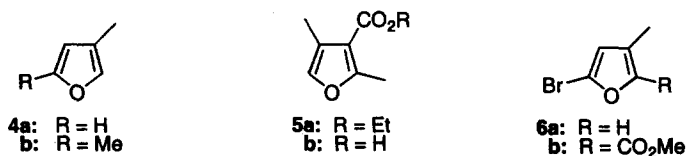
Keywords: Furans; carbenes and carbenoids; cyclopropanation; diazo compounds.

An early intermediate on route of the $[\text{Rh}_2(\text{OAc})_4]$ -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-dimethylfuran⁴.

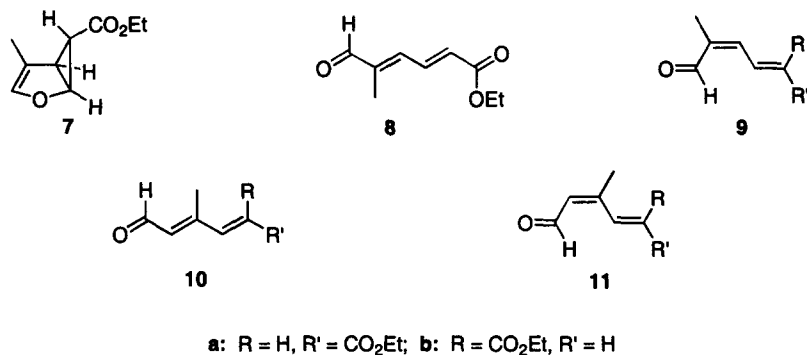


The dimethylated furan (**4b**) could be prepared by two means. (a) Condition modification of the condensation of chloroacetone with ethyl acetoacetate⁵ (dry HCl, -5 °C, 12 h; Et₃N, Et₂O, 0 °C, 52 h; 57 % yield) furnished furoate **5a**, whose hydrolysis (refluxing aq. NaOH, 2 h; 84 % yield) led to acid **5b**⁵ and decarboxylation⁶ of the latter produced **4b**. (b) 2-Bromo-4-methylfuran (**6a**),⁷ prepared from ester **6b**,⁸ was converted (^tBuLi, Et₂O, -78 °C; MeI, -78 °C to r.t., 56 % yield) into **4b**.⁹

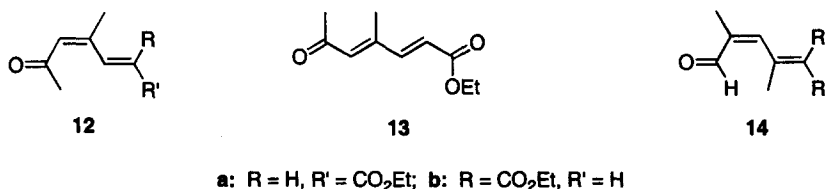
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The reaction of β -methylfuran (**4a**) with EDA under $[\text{Rh}_2(\text{OAc})_4]$ catalysis afforded a mixture of cyclopropane **7** and 1,4-diacyl-1,3-butadienes in 92 % of mass recovery. Treatment of the mixture with I_2 converted it into four aldehydoesters, - **8**, **9a**, **10a**¹⁰ and **11a**. Aldehydoesters **8a** and **9a** are the products of $[\text{Rh}]=\text{CHCO}_2\text{Et}$ interaction with the furan on its unsubstituted side, whereas substances **10a** and **11a** are derived from action on the side of the substituent. The $[\text{8}+\text{9a}]/[\text{10a}+\text{11a}]$ ratio proved to be in the range of 1.5:1 to 2:1, indicating low site selectivity in the **4a**-EDA reaction.¹¹



$[\text{Rh}_2(\text{OAc})_4]$ -induced reaction of 2,4-dimethylfuran (**4b**) and EDA furnished¹² 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.



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 substituent 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.



References and Notes

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- [9] NMR (300 MHz, CDCl₃) data:
5a: ¹³C NMR δ 9.9 (4-CH₃), 14.2 (CH₃CH₂ and 2-CH₃), 59.7 (CH₂), 113.4 (C-4), 121.0 (C-3), 137.0 (C-5), 159.9 (C-2), 164.6 (C=O). **5b**: ¹³C NMR δ 9.9 (4-CH₃), 14.6 (2-CH₃), 112.8 (C-4), 121.5 (C-3), 137.8 (C-5), 162.0 (C-2), 170.9 (C=O). **6b**: ¹³C NMR δ 11.3 (CH₃), 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*: ¹³C NMR (DMSO-d₆) δ 10.6 (CH₃), 115.9 (C-4), 124.9 (C-3), 131.9 (C-5), 142.0 (C-2), 159.1 (C=O). **6a**: ¹³C NMR δ 9.8 (CH₃), 113.6 (C-3), 121.6 (C-4), 122.9 (C-2), 140.9 (C-5). **4b**: ¹³C NMR δ 9.6 (4-CH₃), 13.3 (2-CH₃), 108.2 (C-3), 120.6 (C-4), 137.2 (C-5), 152.0 (C-2).
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- [11] **7**: ¹H NMR δ 0.99 (*d*, 1, *J* = 2.4 Hz, H-6), 1.26 (*t*, 3, *J* = 7.2 Hz, CH₃CH₂), 1.79 (*d*, 3, *J* = 0.9 Hz, CH₃), 2.65 (*dd*, 1, *J* = 2.4, 5.4 Hz, H-5), 4.12 (*q*, 2, *J* = 7.2 Hz, CH₂), 4.78 (*d*, 1, *J* = 5.4, H-1), 6.11 (*br. s*, 1, H-3). ¹³C NMR δ 10.0 (CH₃), 13.8 (CH₃CH₂), 21.6 (C-6), 34.7 (C-5), 60.2 (CH₂), 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, CH₃CH₂), 1.95 (*d*, 3, *J* = 0.9 Hz, CH₃), 4.26 (*q*, 2, *J* = 7.1 Hz, CH₂), 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, CH₃CH₂), 1.93 (*s*, 3, CH₃), 4.25 (*q*, 2, *J* = 7.1 Hz, CH₂), 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). ¹³C NMR δ 13.8 (CH₃CH₂), 16.4 (CH₃), 60.4 (CH₂), 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, CH₃CH₂), 1.96 (*s*, 3, CH₃), 4.24 (*q*, 2, *J* = 7.1 Hz, CH₂), 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**: ^1H 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**: ^1H 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**: ^1H 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**: ^1H 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 $[\text{Rh}_2(\text{OAc})_4]$ (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% $\text{Na}_2\text{S}_2\text{O}_3$ and brine, and then dried (Na_2SO_4). The products (**13** and **12a**) were separated by SiO_2 chromatography.

- [13] **12a**: ^1H 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**: ^1H 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**: ^1H 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**: ^1H 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**: ^1H 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).