[4+3] CYCLOADDITIONS WITH *c*-HETEROANNULATED FURANS – SYNTHESIS OF NOVEL ANNULATED TROPONES

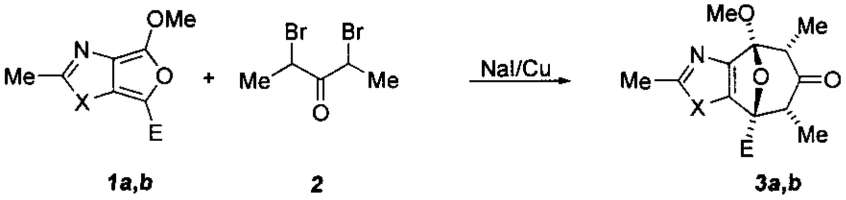
Stephan Reck,[a] Christian Näther,[b] and Willy Friedrichsen*[a]

[a]Institute of Organic Chemistry, Otto-Hahn-Platz 4, D-24098 Kiel, Germany
[b]Institute of Inorganic Chemistry, Otto-Hahn-Platz 6/7, D-24098 Kiel, Germany

Abstract - Furo[3,4-*d*]oxazole (**1a**) and furo[3,4-*d*]thiazole (**1b**) react with 1,3-dimethyloxyallyl cationic species to give the [4+3] cycloaddition products (**3a,b**). The ring opening reaction of these adducts with H_2SO_4/Et_2O yields the annulated hydroxytropones (**4a,b** or **5a,b**).

The [4+3] cycloaddition reactions of dienes (**A**) with allylic systems of type (**B**) have emerged as a powerful method for the construction of seven-membered rings. Especially furan and its derivatives thereof have been used frequently for this purpose.[1]

Recently we succeeded in the preparation of furo[3,4-*d*]oxazole (**1a**)[2a] and furo[3,4-*d*]thiazole (**1b**)[2b] using the *Hamaguchi-Ibata* methodology.[3] In this paper the [4+3] cycloaddition reactions of these compounds with an oxyallyl[4] derived from 2,5-dibromo-3-pentanone (**2**) are reported. Treatment of a mixture of **1a** and **2** with NaI/Cu in acetonitrile at room temperature (15 h) with subsequent chromatography (silica gel, *n*-pentane/Et_2O/CH_2Cl_2 = 4/1/1) yielded **3a**.[5] Compound (**3b**) was obtained similarly from **1b**.[6,7]



a: X = O, **b**: X = S, E = CO_2Me

Although several stereoisomers of **3a,b** are possible (*cis*, *trans*, *endo*, *exo*) according to literature data[9] a *cis-endo* structure can be anticipated. This was confirmed by an X-Ray structure determination for **3b** (Figure 1).[10] Experimental bond distances are in good agreement with density functional theoretical (DFT) values (see Table 1).[11]

Figure 1. Structure of compound **3b** (X-Ray).

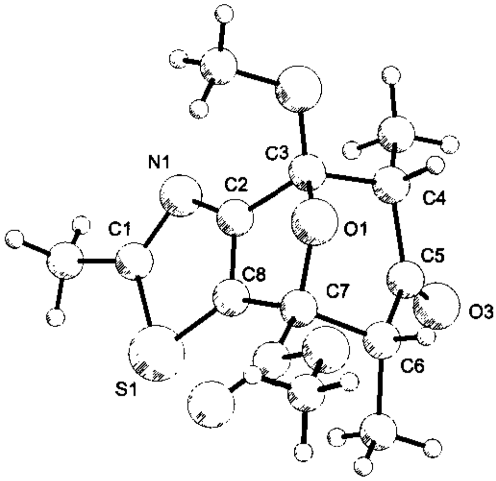
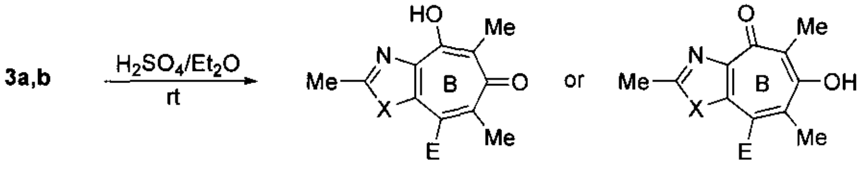


Table 1. Selected structure parameters of compound (**3b**) (X-Ray, DFT[a]).

bond	r (in Å)	bond	r (in Å)
C1-N1	1.312 (1.306)	C3-C4	1.532 (1.557)
C1-S1	1.759 (1.785)	C4-C5	1.532 (1.542)
N1-C2	1.371 (1.367)	C5-O3	1.208 (1.215)
C2-C3	1.521 (1.516)	C5-C6	1.534 (1.545)
C2-C8	1.348 (1.360)	C6-C7	1.552 (1.563)
C3-O1	1.455 (1.455)	C7-C8	1.504 (1.513)

[a] B3LYP/6-31G*, values in parentheses.[11]

Several methods have been reported for the cleavage of this type of oxygen bridge. Whereas TMSOTf/Et_3N[12] was unsuitable for this purpose, the ring opening of **3a** followed by elimination of methanol could be achieved very cleanly under acidic conditions with H_2SO_4(80%)/Et_2O (27/18 = v/v)[13] giving compound (**4a**) in 53% yield.[14] Although this compound exists as an enol, the exact structure (**4a** or **5a**) is not be determined with certainty.[15] The ring opening of **3b** could also been performed with H_2SO_4/Et_2O, although under these conditions the yield of **4b** (**5b**) was low.[16]



4a,b **5a,b**

a: X = O, **b**: X = S, E = CO_2Me

In summary we have shown that *c*-heteroannulated furans react with an oxyallyl system to give the [4+3] cycloadducts, which can be cleaved to the corresponding annulated hydroxytropones.

ACKNOWLEDGMENT

The continuous support of our work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

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5. **3a**: 53% colorless crystals; mp 98°C; IR (KBr) ν 1755, 1718 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.02 (d, 3H, *J* = 7.01 Hz, CH_3), 1.11 (d, 3H, *J* = 6.86 Hz, CH_3). 2.50 (s, 3H, CH_3), 2.97 (q, 1H, *J* = 6.91 Hz, CH), 3.08 (q, 1H, *J* = 6.99 Hz, CH), 3.55 (s, 3H, OCH_3), 3.94 (s, 3H, CO_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.2 (q, CH_3), 8.9 (q, CH_3), 14.8 (q, C-2-CH_3), 49.4 (d), 53.2 (q, OCH_3), 53.5 (q, OCH_3), 53.8 (d), 82.3 (s, C-1), 108.1 (s, C-7), 144.6 (s, C-6), 155.7 (s, C-4), 166.5 (s, C-2), 168.3 (s, CO_2CH_3), 205.3 (s, C-10); HRMS calcd for $C_{14}H_{17}NO_6$: 295.10559, found: 295.10560.
6. **3b** was obtained by chromatography (silica gel, cyclohexane/ethyl acetate 2/1); mp 130°C, yield 59%; IR (KBr) ν 1745, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99 (d, 3H, *J* = 6.90 Hz, CH_3), 1.12 (d, 3H, *J* = 6.89 Hz, CH_3), 2.72 (s, 3H, CH_3), 3.05 (q, 1H, *J* = 6.88 Hz, CH), 3.13 (q, 1H, *J* = 6.90 Hz, CH), 3.54 (s, 3H, OCH_3), 3.94 (s, 3H, CO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3 (q, CH_3), 9.5 (q, CH_3), 19.8 (q, C-4-CH_3), 50.6 (d, C-8), 53.0 (q, OCH_3), 53.3 (q, OCH_3), 54.6 (d, C-10), 84.5 (s, C-1), 109.1 (s, C-7), 134.7 (s, C-6), 159.1 (s, C-4), 167.5 (s, C-2), 173.5 (s, CO_2CH_3), 205.3 (s, C-10); HRMS calcd for $C_{14}H_{17}NO_5S$: 311.08281, found: 311.08260.
7. Treatment of **1b** with trimethyl (3,3-dimethoxy-2-hydroxy-2-trimethylsilylpropyl)silane or trimethyl (3,3-dimethoxy-2-methylenepropyl)silane ($TiCl_4$/dichloromethane; -78°C)[8] was unsuccessful.

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10. Space group: $P2_1/n$. Cell dimensions: a = 8.002(1) Å, b = 10.289(1) Å, c = 17.761(2) Å, α = 90°, β = 94.55° (2), γ = 90°. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 116075. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).
11. These calculations have been performed with the program system Gaussian 94, Rev. D.2, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1995.
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14. Yield: 53%; colorless needles; mp 193°C; IR (KBr) ν 3432, 1740, 1562, 1599 cm^{-1}; UV (MeCN) λ (log ε) 245 (4.415), 258 (4.354), 264 (4.304), 325 (3.746) nm; ^1H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 6H, 2 CH_3), 2.62 (s, 3H, C2-CH_3), 4.01 (s, 3H, CO_2CH_3), 7.37 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3 (q), 14.2 (q), 19.8 (q), 53.1 (q), 124.8 (s), 126.0 (s), 135.1 (s), 141.6 (s), 144.4 (s), 151.9 (s), 162.0 (s), 166.0 (s), 184.2 (s); MS (70 eV) m/z (%) 263 (59, M^+), 248 (100), 204 (31); HRMS calcd for $C_{13}H_{13}NO_5$: 263.07938, found: 263.07930.
15. According to DFT studies (B3LYP/6-31G*)[11] compound (**4b**) is more stable than **5b** by 4.3 kcal/mol (E(**4b**) = -1257.03027, E(**5b**) = -1257.02334 (in hartrees, gas phase)). Additionally, these calculations reveal that ring B in **4b** and **5b** is not planar.
16. Yield: 9%; colorless crystals; mp 118°C; obtained by chromatography (silica gel, cyclohexane/ethyl acetate/dichloromethane = (7/1/1); IR (KBr) ν 3308, 1716, 1560, 1313 cm^{-1}; UV (MeCN) λ (log ε) 262 (4.630), 270 (4.551, sh), 315 (3.814), 328 (3.821) nm; ^1H-NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.77 (s, 3H, C2-CH_3), 3.97 (s, 3H, CO_2CH_3), 8.46 (s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.6 (q), 19.1 (q), 20.1 (q), 53.1 (q), 125.0 (s), 128.7 (s), 131.3 (s), 140.4 (s), 146.7 (s), 153.7 (s), 166.4 (s), 169.0 (s), 185.2 (s); MS (70 eV) m/z (%) 279 (41, M^+), 264 (37), 251 (100), 236 (49); HRMS calcd for $C_{13}H_{13}NO_4S$: 279.05652, found: 279.05630.

Received, 25th January, 1999