SYNTHESIS AND REACTIONS OF A NOVEL FURO[3,4-d]THIAZOLE

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Abstract - The synthesis of a novel furo[3,4-d]thiazole (6) and some cycloadditions are reported. Density functional theoretical calculations are in accord with the reactivity of this system.

Cycloaddition reactions with α-quinodimethane (1 → 2, A = benzo)1 and heteroanalogues thereof2 (A = pyridino,3 pyridazino,4 quinolino,5 quinoxalino,6 furo,7 thiopheno,8 pyrazolo,9 thiazolo,10 isothiazolo,11 oxazolo,12 indolo13) offer an attractive route to polycyclic systems as also do their more stable counterparts 3 (A = benzo,14 furo,14,15 thiopheno,14,16 isoxazolo,14 oxazolo,17 indolo14,18).

Recent work on a 2,3-dimethylenethiazole (1, A = thiazolo)10 prompts us to report our preliminary results on the synthesis and reactions of a furo[3,4-d]thiazole (6). The starting material (4) is available by reductive acylation of the known19 dimethyl α-nitrosoacetonedicarboxylic acid.20 Treatment of 4 with phosphorus pentasulfide21 yields thiazole (5a).22 Diazogen group transfer (Regitz reaction)23 with 4-azidosulfonylbenzoic acid and DBU in acetonitrile gives 5b,24 which was subjected to the conditions of a Hamaguchi-Ibata reaction25 (Rh2(OAc)4, 1,2-dichloroethane, reflux). Furo[3,4-d]thiazole (6) was obtained as a crystalline compound,26 which could be stored for several weeks without significant decomposition. Up to now furo[3,4-d]thiazoles seem not to have been reported in the literature.
In line with expectations 6 reacts with electron poor dienophiles like N-phenylmaleimide and 1,4-naphthoquinone to give 7 and 8, respectively. On treatment of 6 with dimethyl acetylenedicarboxylate (DMAD) compound (11) was obtained. This type of reaction is well known for other c-annulated furans. Probably 9 is formed in the primary reaction step. Ring opening (to 10) with subsequent migration of an ester group gives 11. Surprisingly the reaction of 6 with \( p \)-benzoquinone proceeds in a similar manner. Compound (12) was obtained as red crystals with mp 140 °C. The structure of 12 was determined unequivocally by an X-Ray investigation.

Although the exact geometry of furo[3,4-\( d \)]thiazoles is unknown, density functional theoretical methods (DFT) have been proven to be of considerable value in the prediction of geometric and energetic data of organic compounds. According to these calculations the furo[3,4-\( d \)]thiazole is entirely planar. Bond lengths for both 6 and the parent compound (13) are given in Scheme 2.
Scheme 2. Calculated bond lengths (in Å) for 6 (R¹ = Me, R² = OMe, R³ = CO₄Me) and 13 (R¹ = R² = R³ = H; values in parentheses) (E(6) = -1102.18038 a. u.; E (13): -720.45081 a. u.).

Although quantitative investigations are still lacking the furo[3,4-d]thiazole (6) seems to be less reactive in Diels-Alder reactions than the corresponding benzo[c]furan. DFT calculations for the model reactions (1) and (2) and the corresponding reactions of 13 with ethene (to 20) and acetylene (to 21) revealed the following results (Table 1).

(a) Furo[3,4-d]thiazole (13) is less reactive than benzo[c]furan (14) (both with ethene and acetylene); (b) In strongly related reactions (to 16/20 and 19/21, respectively) the heats of reaction can serve as a measure of reactivity.
Table 1: Heats of reaction ($\Delta E$) and transition state energies ($\Delta E(ts)$) (values in kcal/mol)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta E$</th>
<th>$\Delta E(ts)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>-29.8\textsuperscript{b}</td>
<td>15.4</td>
</tr>
<tr>
<td>19</td>
<td>-34.4\textsuperscript{c}</td>
<td>17.8</td>
</tr>
<tr>
<td>20</td>
<td>-19.6\textsuperscript{d}</td>
<td>19.7</td>
</tr>
<tr>
<td>21</td>
<td>-21.6\textsuperscript{e}</td>
<td>21.9</td>
</tr>
</tbody>
</table>

\textsuperscript{a}B3LYP/6-31G*. \textsuperscript{b}For reaction (1). \textsuperscript{c}For reaction (2). \textsuperscript{d}For the reaction of 13 with ethene (to 20). \textsuperscript{e}For the reaction of 13 with acetylene (to 21).

The transition states of 20 and 21 are shown in Figure 1 and Figure 2. In line with expectations the transition states are nearly symmetrical with slightly pyramidalized (bent) reaction centers.

Figure 1: Transition state geometry of 20. 

Figure 2: Transition state geometry of 21.

C(7)-C(10): 2.19Å  
C(6)-C(9): 2.22 Å

C(7)-C(10): 2.21Å  
C(6)-C(9): 2.23 Å

The results shown in Scheme 2 and Table 1 underline the validity and reliability of DFT calculations also reported by other authors\textsuperscript{14e,37,38,39} in theoretical studies of ground and transition states of organic molecules (reactions).
ACKNOWLEDGMENT

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REFERENCES AND NOTES


21. Colorless crystals; yield 29%; mp 61 °C; IR (KBr) ν 1734, 1708, 1502, 1436 cm⁻¹; UV (MeCN) λ log(e) 205 (4.271), 248 (3.844); ¹H NMR (CDCl₃) δ 7.22 (s, 3H), 3.76 (s, 3H), 3.93 (s, 3H), 4.30 (s, 2H); ¹³C NMR (CDCl₃) δ 19.24 (q), 32.42 (t), 52.33 (q), 52.52 (q), 139.83 (s), 141.50 (s), 162.60 (s), 164.42 (s), 170.09 (s); MS (70 eV) m/z 229 (44, M⁺), 197 (100), 170 (61), 154 (16). HRMS calcd for C₉H₁₅N₀₂S: 229.04088, found: 229.04178.
22. Colorless crystals; yield 33%; mp 141 °C; IR (KBr) ν 1763, 1721, 1693, 1570, 1504 cm⁻¹; UV (MeCN) λ log(e) 214 (4.078), 232 (4.044, sh); ¹H NMR (CDCl₃) δ 2.90 (s, 3H), 4.04 (s, 3H), 7.38-7.54 (m, 5H); ¹³C NMR (CDCl₃) δ 20.41 (q), 51.18 (q), 59.46 (q), 121.31 (s), 127.60 (s), 136.50 (s), 149.97 (s), 157.94 (s), 168.43 (s); MS (70 eV) m/z 382 (78, M⁺), 353 (16), 322 (100); HRMS calcd for C₉H₁₅NO₄S: 227.02522, found: 227.02522.
for C_{19}H_{14}N_{2}O_{5}S: 382.06235, found: 382.06285.

28. Yellow needles; yield 27%; mp 175 °C; IR (KBr) v 1724, 1666, 1592, 1560, 1297 cm^{-1}; UV (MeCN) λ log(e) 251 (4.609), 272 (4.690) 372 (3.812); \(^{1}H\) NMR (CDCl\(_3\)) δ 2.92 (s, 3H), 4.07 (s, 3H), 4.42 (s, 3H), 7.72-7.83 (m, 2H), 8.17-8.20 (m, 1H), 13C NMR (CDCl\(_3\)) δ 20.63 (q), 53.34 (q), 63.15 (q), 122.26 (s), 123.82 (s), 126.80 (d), 127.21 (d), 128.75 (s), 132.83 (s), 133.56 (d), 134.49 (d), 134.91 (s), 141.62 (s), 150.29 (s), 155.22 (s), 168.75 (s), 170.77 (s), 181.86 (s), 182.42 (s); MS (70 eV) m/z 367 (100, M\(^{+}\)), 338 (93), 306 (11), 279 (12); HRMS calcd for C_{19}H_{14}N_{2}O_{5}S: 367.05145, found: 367.05135.


30. Yellow prisms; yield 43%; mp 111 °C; IR (KBr) v 1785, 1745, 1670, 1436, 1365 cm^{-1}; UV (MeCN) λ log(e) 245 (4.434), 350 (3.586); \(^{1}H\) NMR (CDCl\(_3\)) δ 2.87 (s, 3H), 3.80 (s, 6H), 3.86 (s, 3H), 4.12 (s, 3H), 13C NMR (CDCl\(_3\)) δ 20.42 (q), 52.32 (q), 53.73 (q), 62.07 (q), 71.50 (s), 118.21 (s), 131.84 (s), 154.04 (s), 157.81 (s), 164.34 (s), 176.70 (s), 180.09 (s); MS (70 eV) m/z 369 (18, M\(^{+}\)), 338 (14), 325 (31), 310 (100); HRMS calcd for C_{19}H_{15}NO_{5}S: 369.05185, found: 369.05205.

31. IR (KBr) v 3380, 1742, 1660, 1641, 1575 cm^{-1}; UV (MeCN) λ log(e) 235 (4.277), 262 (4.113, sh), 328 (3.812), 455 (3.687); \(^{1}H\) NMR (CDCl\(_3\)) δ 2.41 (s, 3H), 3.70 (s, 3H), 4.29 (s, 3H), 6.86 (d, 1H), 7.10 (d, 1H), 8.72 (s, 1H, exchange with D\(_2\)O), 11.01 (s, 1H, exchange with D\(_2\)O); 13C NMR (CDCl\(_3\)) δ 21.06 (q), 54.59 (q), 62.52 (q), 109.70 (s), 116.10 (s), 120.88 (d), 129.70 (d), 135.83 (s), 143.25 (s), 148.70 (s), 156.41 (s), 167.00 (s), 167.17 (s), 194.60 (s); MS (70eV) m/z 335 (10, M\(^{+}\)), 320 (14), 276 (100), 261 (36).

32. Space group: monoclinic, P2\(_{1}\)/n. Cell dimensions: a = 8.2815 (8) Å, b = 14.540 (2) Å, c = 12.277 (3) Å, α = 90.00°, β = 94.35 (1)°, γ = 90.00°. 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 101141. 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).


36. The reactions (1) and (2) have also been investigated computationally by other authors using the same functional and basis set. Our results differ slightly from the values reported.


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