INTRAMOLECULAR CYCLOADDITIONS WITH ISOBENZOFURANS - XII[1] - SYNTHESIS AND REACTIONS OF FURO[3,4-*d*]ISOXAZOLES

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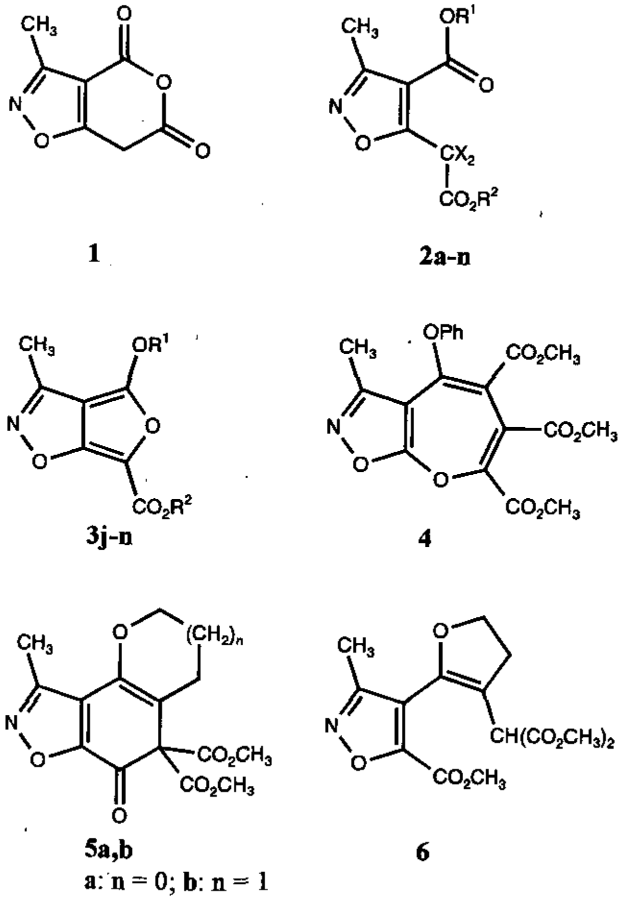
Abstract - The synthesis of furo[3,4-*d*]isoxazoles (**3**) and inter- and intramolecular cycloaddition reactions (to **4**, **5a,b**) are reported. The structures of **3k**, **5b** and **6** have been clarified by X-ray crystallography. Quantum chemical calculations (AM1, PM3, *ab initio*, density functional methods) concerning the geometry and the different reactivity of benzo[*c*]furans and furo[3,4-*d*]isoxazoles were performed.

Furo[3,4-*d*]isoxazoles (e.g., **3**) are virtually unknown,[2] although without any doubt these species are involved as intermediates in the synthesis of annulated isoxazoles.[3,4] In this paper we report the generation and reaction of compounds of this type. Regioselective solvolytic ring opening of anhydride (**1**) with methanol yields **2b**;[3] this compound can also be obtained from acid (**2a**) by selective esterification (MeOH/H_2SO_4; 89%). Subsequent treatment with phenol/DMAP/DCC[5] yields **2e**[6] (50%, colorless oil; ir (film): 1743 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 2.55 ppm (s, 3H, CH_3), 3.74 (s, 3H, CO_2CH_3), 4.21 (s, 2H, CH_2), 7.13-7.17 (m, 2H, *o*-arCH), 7.25-7.31 (m, 1H, *p*-arCH), 7.39-7.46 (m, 2H, *m*-arCH)), which was reacted with tosyl azide/triethylamine(MeCN, room temperature)[7] to give **2j** (86%; yellow crystals, mp 70°C; ir (KBr): 2136 cm^{-1}, 1727, 1715; ^{1}H nmr ($CDCl_3$): δ = 2.56 ppm (s, 3H, CH_3), 3.88 (s, 3H, CO_2CH_3), 7.14-7.19 (m, 2H, *o*-arCH), 7.26-7.33 (m, 1H, *p*-arCH), 7.40-7.47 (m, 2H, *m*-arCH)). It is well known that nitrogen extrusion from compounds of this type yields *c*-annulated furans (*Hamaguchi-Ibata* reaction).[8] Treatment of **2j** with $Rh_2(OAc)_4$ (0.9 mol%, 1,2-dichloroethane, reflux, 75 min) yields **3j** (72%, colorless crystals, mp 119°C; ir (KBr): 1715 cm^{-1}, 1648; uv (MeCN) λ (log ϵ): 212 nm (4.261), 258 (sh, 4.099), 266 (4.139), 295 (4.319); ^{1}H nmr ($CDCl_3$): δ = 1.55 ppm (s, 3H, CH_3),[9] 3.91 (s, 3H, CO_2CH_3), 7.26-7.31 (m, 2H, *o*-arCH), 7.36-7.42 (m, 1H, *p*-arCH), 7.48-7.55 (m, 2H, *m*-arCH); ^{13}C nmr ($CDCl_3$): δ = 10.07 ppm (q, $\underline{C}H_3$), 51.57 (q, $CO_2\underline{C}H_3$), 102.64 (s, C-3a), 111.84 (s, C-6), 120.16 (d, *o*-arC), 127.39 (d, *p*-arC), 130.76 (d, *m*-arC), 147.85 (s, C-6a), 151.25 (s, C-3), 153.83 (s, O-arC), 157.33 (s, $\underline{C}O_2CH_3$), 161.59 (s, C-4)), which on reaction with DMAD ($CHCl_3$, reflux, 3 h) gives an oxepino[3,2-*d*]isoxazole (**4**) (38%, slightly yellow crystals, mp 147°C; ir (KBr): 1739 cm^{-1}, 1617; uv (MeCN) λ (log ε): 215 nm (4.495), 325 (3.789); ^{1}H nmr ($CDCl_3$): δ = 2.05 ppm (s, 3H, CH_3), 3.55 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 6.96-7.01 (m, 2H, *o*-arCH), 7.07-7.13 (m, 1H, *p*-arCH), 7.26-7.36 (m, 2H, *m*-arCH)).

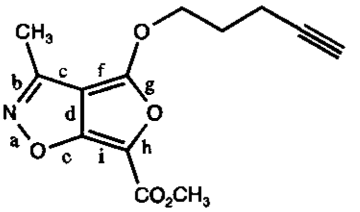
Scheme 1.



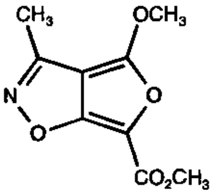
2, 3	X	R^1	R^2
a	H	H	H
b	H	H	CH_3
c	H	CH_3	CH_3
d	H	CH_3	H
e	H	Ph	CH_3
f	H	$-(CH_2)_3-C\equiv CH$	CH_3
g	H	$-(CH_2)_3-C\equiv C-CO_2CH_3$	CH_3
h	H	$-(CH_2)_2-C\equiv C-CO_2CH_3$	CH_3
i	H	CH_3	$-CH_2-C\equiv CH$
j	N	Ph	CH_3
k	N	$-(CH_2)_3-C\equiv CH$	CH_3
l	N	$-(CH_2)_3-C\equiv C-CO_2CH_3$	CH_3
m	N	$-(CH_2)_2-C\equiv C-CO_2CH_3$	CH_3
n	N	CH_3	$-CH_2-C\equiv CH$

Furoisoxazole (**3k**) was prepared quite similarly by reaction of **2b** with 4-pentyn-1-ol using again the *Neises-Steglich* conditions[5] and treatment of **2k**[12] with $Rh_2(OAc)_4$ (0.8 mol%, 1,2-dichloroethane, reflux, 3 h). The compound was obtained as fine colorless needles with mp 75°C.[13] An X-ray investigation of **3k**[14] reveals that the heterocyclic ring system is essentially planar. Quantum chemical calculations on the semiempirical (AM1, PM3)[10a] as well as the *ab initio*[10b] and the density functional[19-21] level show (Table 1) that the latter methods - especially, when Becke's three parameter[22] DFT exchange functional in combination with the Lee, Yang, and Parr correlation functional (BECKE3LYP)[23] together with a 6-31 G* basis[10b] is used - lead to a very good agreement between experimental and calculated values.

Table 1: Bond distances (in Å) of **3k** and **7** (obs. *vs.* calc.).[a,b]



3k



7

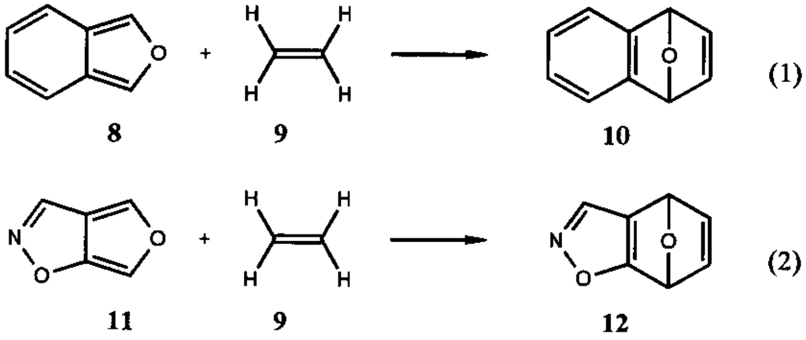
bond	AM1[c]	PM3[c]	RHF/6-31G*[d]	RHF/6-311G**[d]	BLYP/ 6-31G*[d]	BECKE3LYP/ 6-31G*[d]	obs.[c,e]
a	1.347	1.517	1.407	1.401	1.485	1.445	1.474
b	1.341	1.319	1.275	1.272	1.323	1.307	1.300
c	1.456	1.446	1.449	1.443	1.442	1.437	1.432
d	1.479	1.457	1.402	1.402	1.424	1.413	1.395
e	1.389	1.355	1.318	1.315	1.357	1.342	1.348
f	1.378	1.379	1.361	1.360	1.391	1.380	1.372
g	1.387	1.375	1.307	1.304	1.362	1.342	1.345
h	1.432	1.416	1.403	1.402	1.434	1.414	1.412
i	1.371	1.376	1.354	1.353	1.388	1.376	1.361

[a] Semiempirical calculations (AM1, PM3) were performed with the program system MOPAC.[16] [b] *Ab initio* calculations were performed with the program systems GAUSSIAN92[17] and GAUSSIAN92/DFT.[18] [c] For **3k**. [d] For 7. [e] X-ray.

Interestingly enough **3k** did not undergo an intramolecular cycloaddition as did **3l** (*vide infra*). If (as in **3l, m**) the furoisoxazole carries an electron deficient triple bond spontaneous intramolecular cycloaddition reactions are observed. The preparation of **2l** was accomplished by reaction of **2b** with methyl 6-hydroxyhex-2-yn-1-carboxylate[24]/DMAP/DCC[5] (to get **2g**[25]) and subsequent diazogroup transfer.[7,26] Nitrogen extrusion ($Rh_2(OAc)_4$, toluene, reflux, 5 h) resulted in the formation of **5b**.[27] Quite obviously a furoisoxazol (**3l**) is generated in the first step. Intramolecular cycloaddition with subsequent ring opening yields **5b**.[28] The structure of **5b** has been clarified definitely by X-ray crystallography.[29] Compound (**5a**) was prepared quite similarly by reaction of **1b** with methyl 5-hydroxypentyn-1-carboxylate[24]/DMAP/DCC[5] (to **2h**[30]), subsequent diazogroup transfer[7] (to **2m**),[31] and decomposition (0.5 mol% $Rh_2(OAc)_4$, 1,2-dichloroethane, reflux, 2 h). If during workup (chromatography) methanol is used as eluent compound (**6**)[32] is obtained. The formation of **6** can be rationalized by solvolytic ring opening reaction of **5a**. It is also possible to prepare furoisoxazoles with an unsaturated moiety at C-6 (e. g., **3n**). Selective saponification of **2c**, which is in turn available from **2a** ($SOCl_2$/MeOH/40°C; colorless oil, 75%) with potassium hydroxide/MeOH (reflux, 4 h),[33] esterification with 2-propyn-1-ol/DMAP/DCC[5] (to **2i**),[34] diazogroup transfer[7] (to **2n**)[35] and subsequent treatment with $Rh_2(OAc)_4$ (0.49 mol%, 1,2-dichloroethane, reflux, 2 h) yields **3n**.[36]

Generally speaking in $[\pi 4 + \pi 2]$ cycloadditions furo[3,4-*d*]isoxazoles are less reactive than the corresponding benzo[*c*]furans (isobenzofurans).[37] These findings are in line with expectations. Following a similar reasoning as *Rickborn* and coworkers[38] on various levels of theory (semiempirical, *ab initio*, density functional theory) the calculated exothermicity of reaction (2) ($\Delta\Delta H_f°(1) = \Delta H_f°(\mathbf{10}) - (\Delta H_f°(\mathbf{8}) + \Delta H_f°(\mathbf{9}))$ or $\Delta E(1) = \Delta E(\mathbf{10}) - (E(\mathbf{8}) + E(\mathbf{9})$, resp.) is *less* than the corresponding value of reaction (1) (Table 2).

Table 2: Calculated reaction enthalpies ($\Delta\Delta H_f°$) and reaction energies (ΔE) for reactions (1) and (2).



method	$\Delta\Delta H(1)$ $(\Delta E(1))^a$	$\Delta\Delta H(2)$ $(\Delta E(2))^a$	$\Delta\Delta\Delta H$ $(\Delta\Delta E)^{a,c}$
AM1	34.8	22.9	11.9
PM3	32.5	21.1	11.4
6-31G*	36.9	28.0	8.9
MP2/6-31G*//6-31G*	44.3	37.4	6.9
DFT[b]	21.5	12.2	9.3

[a] In kcal/mol. [b] Density functional method (BLYP/6-31G*); [c] $\Delta\Delta\Delta H(\Delta\Delta E) = \Delta\Delta H(1)\ (\Delta E(1)) - \Delta\Delta H(2)\ (\Delta E(2))$.

ACKNOWLEDGEMENT

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12. **2f**: 56%, colorless oil; ir (film): 1748 cm^{-1}, 1722; ^1H nmr ($CDCl_3$): δ=1.95 ppm (tt, 2H,$^3J_1$=6.4 Hz, $^3J_2$=7.0 Hz, CH_2-$C\underline{H}_2$-CH_2) 2.00 (t, 1H, ^4J=2.7 Hz, C≡C$\underline{H}$), 2.34 (td, 2H, $^3J_1$=7.0 Hz, $^4J_2$=2.7 Hz, $C\underline{H}_2$-C≡CH), 2.49 (s, 3H, CH_3), 3.75 (s, 3H, CO_2CH_3), 4.15 (s, 2H, $C\underline{H}_2CO_2CH_3$), 4.39 (t, 2H, ^3J=6.3 Hz, OCH_2). - **2k**: 83%, yellow oil; ir (film): 2130 cm^{-1}, 1725, 1714.
13. **3k**: ir (KBr): 3267 cm^{-1}, 1702, 1654, 1595; uv (MeCN) λ (log ϵ): 214 nm (4.311), 267 (4.199), 295 (4.289); ^1H nmr ($CDCl_3$): δ=2.02 *ppm* (*t, 1H*, J=2.7 Hz, -C≡CH), 2.01-2.15 (*m*, 2H, $C\underline{H}_2$-CH_2-C≡CH), 2.38-2.47 (m, 2H, -$C\underline{H}_2$-C≡CH), 2.43 (s, 3H, CH_3), 4.63 (t, 2H, J=6.1 Hz, OCH_2); ^{13}C nmr ($CDCl_3$): δ = 11.18 ppm (q, CH_3), 14.86 (t, $\underline{C}H_2$-C≡CH), 27.76 (t, $\underline{C}H_2$-CH_2-C≡CH), 51.37 (q, $CO_2\underline{C}H_3$), 69.86 (d, C≡$\underline{C}$H), 70.97 (t, OCH_2), 82.01 (s, $\underline{C}$≡CH), 101.17 (s, C-3a), 111.59 (s, C-6), 148.81 (s, C-4), 151.18 (s, C-3), 157.40 (s, $\underline{C}O_2CH_3$), 162.38 (s, C-6a); ms (70 eV): calcd for $C_{13}H_{13}NO_5$: 263.0793, found 263.0792.
14. Space group P1. Cell dimensions: a = 10.1710 (13) Å, b = 10.729 (3) Å, c = 13.429 (2) Å, α = 69.070° (14), β = 86.220° (11), γ= 66.270° (13). CSD number[15]: 404654.
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25. **2g**: Colorless oil, 62%; ir (film): 2238 cm^{-1}, 1744; ^1H nmr ($CDCl_3$): δ = 2.02 ppm (tt, 2H, J_1=7.2 Hz, J_2=6.2 Hz, CH_2-$C\underline{H}_2$-

CH_2), 2.48 (s, 3H, CH_3), 2.50 (t, 2H, J=7.2 Hz, CH_2-$C\equiv C$), 3.75 (s, 6H, CO_2CH_3), 4.13 (s, 2H, $C\underline{H}_2$-CO_2CH_3), 4.37 (t, 2H, J=6.2 Hz, OCH_2).

26. **2l**: Yellow oil, 83%; ir (film): 2238 cm^{-1}, 2131, 1735, 1714; ^1H nmr ($CDCl_3$): δ = 2.03 ppm (tt, 2H, J_1=6.3 Hz, J_2=7.1 Hz, CH_2-$C\underline{H}_2$-CH_2), 2.46 (s, 3H, CH_3), 2.50 (t, 2H, J=7.1 Hz, CH_2-$C\equiv C$), 3.75 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 4.40 (t, 2H, J=6.3 Hz, OCH_2).
27. **5b**: Yellow crystals, mp 161°C, 17%; ir (KBr): 1751 cm^{-1}, 1737; ^1H nmr ($CDCl_3$): δ = 1.96-2.05 ppm (m, 2H, CH_2-$C\underline{H}_2$-CH_2), 2.24-2.30 (m, 2H, OCH_2-CH_2-$C\underline{H}_2$), 2.50 (s, 3H, CH_3), 3.80 (s, 6H, CO_2CH_3), 4.19-4.25 (m, 2H, OCH_2); ^{13}C nmr ($CDCl_3$): δ = 11.25 ppm (q, CH_3), 21.60 (t, C-7), 22.02 (t, C-6), 53.66 (q, $CO_2C\underline{H}_3$), 66.43 (t, C-5), 74.24 (s, C-8), 109.26 (s, C-7a), 124.95 (s, C-3a), 142.27 (s, C-3b), 156.69 (s, C-3), 156.98 (s, C-9a), 164.98 (s, $\underline{C}O_2CH_3$), 177.87 (s, C-9).
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29. Space group: $P2_1/a$. Cell dimensions: a = 8.458 (2) Å, b = 17.842 (6) Å, c= 10.518 (2) Å, α = 90°, β = 110.11° (2), γ = 90°. CSD number[15]: 404649.
30. **2h**: Colorless oil, 69%; ir (film): 2242 cm^{-1}, 1747, 1719; ^1H nmr ($CDCl_3$): δ = 2.50 ppm (s, 3H, CH_3), 2.78 (t, 2H, J=6.3 Hz, CH_2-$C\equiv C$), 3.74 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 4.15 (s, 2H, $C\underline{H}_2$-CO_2CH_3), 4.41 (t, 2H, J=6.3 Hz, OCH_2).
31. **2m**: Fine yellow needles, mp 84°C, 80%, ir (KBr): 2242 cm^{-1}, 2137, 1725, 1707; ^1H nmr ($CDCl_3$): δ = 2.48 ppm (s, 3H, CH_3), 2.80 (t, 2H, J=6.3 Hz, CH_2-$C\equiv C$), 3.77 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 4.42 (t, 2H, J=6.3 Hz, OCH_2).
32. **6**: Colorless needles, mp 102°C; ir (KBr): 1750 cm^{-1}, 1726, 1613; ^1H nmr ($CDCl_3$): δ = 2.31 (s, 3H, CH_3), 3.06 (t, 2H, J=9.6 Hz, CH_2-$C\equiv C$), 3.75 (s, 6H, CO_2CH_3), 3.91 (s, 3H, CO_2CH_3), 4.04 (s, 1H, CH), 4.53 (t, 2H, J=9.6 Hz, OCH_2); ^{13}C nmr ($CDCl_3$): δ = 10.34 (q, CH_3), 31.59 (t, CH_2-$\underline{C}H_2$-C=C), 50.09, (d, CH), 52.71 (q, $CO_2\underline{C}H_3$), 52.93 (q, $CO_2\underline{C}H_3$), 70.17 (t, $C\underline{H}_2$-CH_2-C=C), 109.34 (s, CH_2-CH_2-$\underline{C}$=C), 114.36 (s, C-4), 143.30 (s, CH_2-CH_2-C=$\underline{C}$), 156.60 (s, C-5), 156.81 (s, C-3), 161.10 (s, $\underline{C}O_2CH_3$), 167.85 (s, $\underline{C}O_2CH_3$). - X-ray data: Space group P1. Cell dimensions: a = 7.873 (2) Å, b = 13.382 (4) Å, c= 16.028 (2) Å, α = 108.34° (2), β = 90.42° (2), γ = 97.92° (2). CSD number[15]: 404749.
33. **2d**: ir (KBr): 3600-2800 cm^{-1}, 1718, 1618; ^1H nmr ($CDCl_3$): δ = 2.45 ppm (s, 3H, CH_3), 3.85 (s, 3H, CO_2CH_3), 4.10 (s, 2H, CH_2), 9.56 (s, 1H, CO_2H); ^{13}C nmr ($[D_6]$ DMSO): δ = 11.09 ppm (q, CH_3), 33.09 (t, $\underline{C}H_2$-CO_2CH_3), 52.66 (q, OCH_3), 109.46 (s, C-4), 159.29 (s, C-3), 161.68 (s, CO_2CH_3), 168.22 (s, C-5), 171.56 (s, CO_2H).
34. **2i**: Colorless oil, 62%; ir (film): 2128 cm^{-1}, 1753, 1729; ^1H nmr ($CDCl_3$): δ = 2.47 (s, 3H, CH_3), 2.50 (t, 1H, ^4J=2.5 Hz, $C\equiv CH$), 3.86 (s, 3H, CO_2CH_3), 4.16 (s, 2H, CH_2-CO), 4.75 (d, 2H, ^4J=2.5 Hz, OCH_2)
35. **2n**: Yellow oil, 96%: ir (film): 2135 cm^{-1}, 1726, 1714; ^1H nmr ($CDCl_3$): δ = 2.46 (s, 3H, CH_3), 2.53 (t, 1H, ^4J= 2.5 Hz, $C\equiv CH$), 3.88 (s, 3H, CO_2CH_3), 4.89 (d, 2H, ^4J=2.5 Hz, OCH_2).
36. **3n**: Colorless needles, mp 139°C, 68%; ir (KBr): 3252 cm^{-1}, 2126, 1710, 1648; uv (MeCN) λ (log ϵ): 213 nm (4.321), 268 (4.172), 294 (4.295); ^1H nmr ($CDCl_3$): δ = 2.42 ppm (s, 3H, CH_3), 2.51 (t, 1H, ^4J=2.5 Hz, $C\equiv CH$), 4.23 (s, 3H, OCH_3), 4.88 (d, 2H, ^4J=2.5 Hz,OCH_2); ^{13}C nmr ($CDCl_3$): δ = 11.06 (q, CH_3), 51.64 (q, OCH_3), 58.74 (t, OCH_2), 74.91 (d, $C\equiv\underline{C}H$), 77.91 (s, $\underline{C}\equiv CH$), 110.11 (s, C-3a), 111.28 (s, C-6), 149.74 (s, C-4), 151.28 (s, C-3), 155.97 (s, $\underline{C}O_2CH_2$), 163.27 (s, C-6a).
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