Cycloaddition of Benzothiete and Electron-deficient Nitriles

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The *o*-quinoid 8π electron system **2**, generated by thermal ring opening of benzothiete (**1**), enters regiospecific [8π + 2π] cycloaddition reactions with electron-deficient nitriles **3a-d**, yielding the 4*H*-1,3-benzothiazines **4a-d**. A competitive dimerization of **1** leads to 1,5-dibenzo[*b*,*f*]dithiocin (**5**). Depending on the nitrile further competitive or subsequent reactions (**2** + **3b** → **7b**, **2** + **3d** → **4d** → **8d**) can occur. The cycloadducts **10e** and **11e** gained from **3e** anticipate a primary cleavage of **3e** to methylisothiocyanate **9e** which reacts at the C=N double bond as well as at the C=S double bond.

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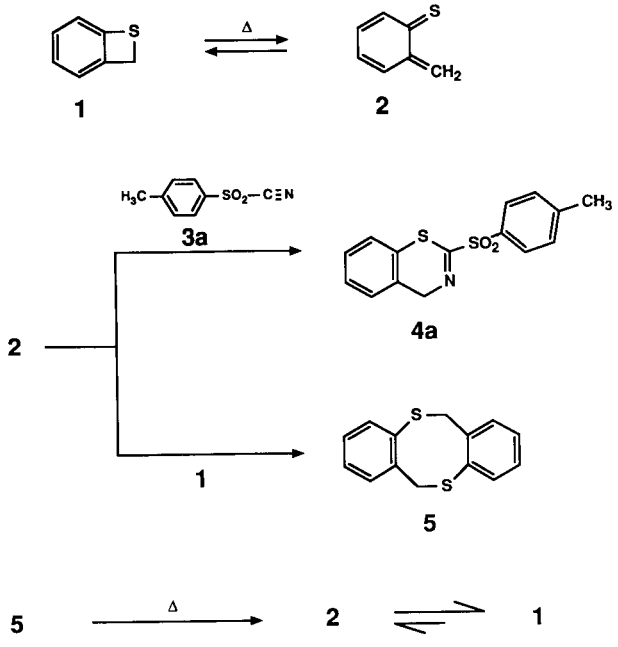
Hetero-Diels-Alder reactions provide a theoretically interesting and synthetically valuable access to six-membered heterocyclic ring systems [1,2]. Hetero atoms can be incorporated into the diene or into the dienophile or both.

Nitriles are relatively inert in such intermolecular [3-6] or intramolecular [7-9] cycloaddition processes and require high reaction temperatures. However, exceptions are established with sulfonyl cyanides [10-12] and with cyanamides and electron-deficient tetrazines [13]. A special case is also given by the cycloaddition of acetonitrile or acrylonitrile and push-pull dienes [14].

Now, we have investigated the chemical behaviour of benzothiete (**1**) in the presence of nitriles **3a-e**. Compound **1** is transformed by thermal (or photochemical) ring opening to an 8π electron component **2** which is capable of a variety of [8π + 2π] cycloaddition reactions [15-21], due to its extremely low-lying LUMO and its relatively high-lying HOMO [17]. The addition processes take always place at the exocyclic positions. Besides this periselectivity mostly regioselectivity is observed.

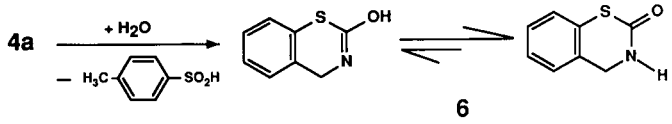
Scheme 1



Indeed, tosylnitrile **3a** furnishes in boiling toluene the 4*H*-1,3-benzothiazine **4a** in a yield of 57%. Additionally, the dimer **5** is formed, which again can be cleaved by pyrolysis to **1**.

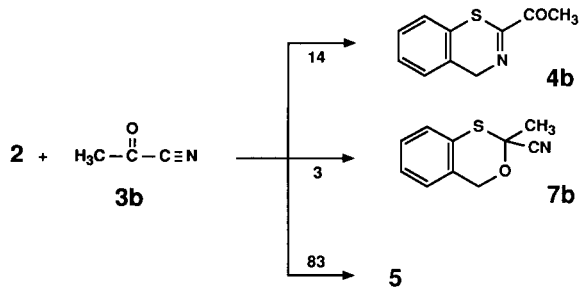
In the presence of traces of acid **4a** can hydrolyze to the 1,3-benzothiazin-2-one **6**. A quantitative transformation can be achieved by the action of aqueous acetic acid in toluene.

Scheme 2



The nitrile of pyruvic acid **3b** is much less reactive towards **2** than **3a**; *i.e.* the amount of dimer **5** is considerably higher. Furthermore, the carbonyl group of **3b** is involved in the cycloaddition leading to the 3,1-benzoxathiin **7b** as a side product.

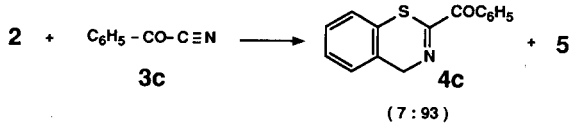
Scheme 3



Comparable to acetonitrile or benzonitrile the cyano group in **7b** is not capable to attack **2**.

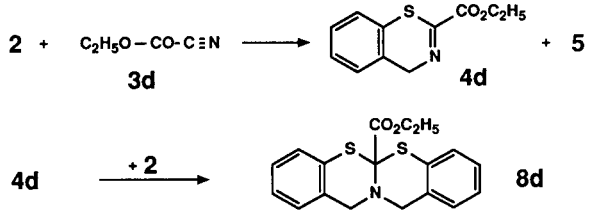
In contrast to **3b**, the benzoyl system **3c** reacts chemoselectively at the C≡N triple bond [22]. The poor yield is less important, because - as mentioned above - the dimer **5** can be cleaved and introduced once again into the reaction.

Scheme 4



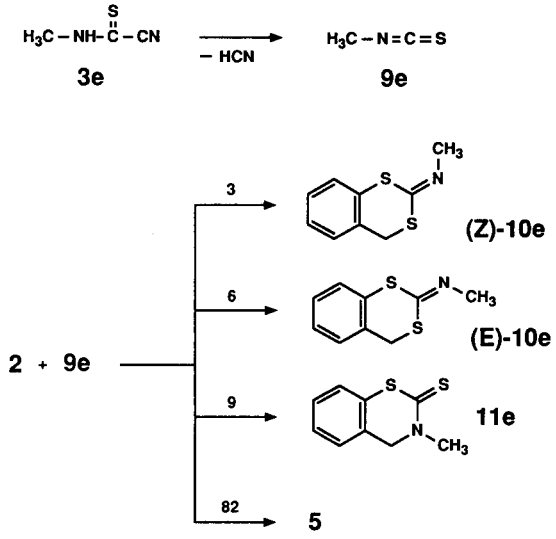
Cyanoformic acid ester **3d** and **2** yield the cycloadduct **4d** which can add a second molecule benzothiete. Thus, the tetracyclic ring system **8d** is formed. Principally the same 1,3-benzothiazino[2,3-*b*][1,3]benzothiazines are accessible by the reaction of *O*-acylated oximes with benzothiete [21].

Scheme 5



Finally, we have investigated the cyanide **3e**. Three different cycloadducts can be isolated. Due to an elimination of HCN, one carbon atom lacks in all of them. The simplest explanation is given by a primary formation of methyl isothiocyanate **9e**, which reacts at the C=S double bond as well as at the C=N double bond. The diastereoisomers of **10e** are generated in a ratio Z:E = 31:69. The differentiation was determined on the basis of NOE experiments. Irradiation into the signal of the methyl group leads in the case of (*E*)-**10e** to a significant increase of the singlet of the CH_2-group.

Scheme 6



EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus and are not corrected. The PFT-^{1}H- and ^{13}C-nmr spectra were run on a Bruker AMV400 in deuteriochloroform as the solvent and internal standard (δ = 7.2399 and δ = 76.999, respectively). The ir spectra were recorded on a Beckman Acculab 4, and the mass spectra on a Varian MAT 711 and on a CH 7A operating at 70 eV.

General Procedure.

Compound **1** (490 mg, 4.0 mmoles) [23-25] and 6.0-8.0 mmoles of the nitrile **3** were refluxed in dry toluene until tlc control (silica/toluene) indicated the disappearance of **1**. The solvent was removed under reduced pressure (12 torr) and the resulting residue separated by column chromatography (60 x 2 cm silica, toluene/ethyl acetate 10:1 - 10:2).

The first fractions consist of **5** [26] and unreacted **3**, then the products were isolated in the sequence as follows: **4a** (pure) or **6**/**4a**; **7b**/**4b**; **4c** (pure); **8d**/**4d**; and **11e**/**10e**.

2-(4-Methylphenylsulfonyl)-4*H*-1,3-benzothiazine (**4a**).

The compound was obtained as a colorless solid, mp 102°, yield 690 mg (57%); ^{1}H-nmr: δ 2.38 (s, 3H, CH_3), 4.77 (s, 2H, 4-H), 7.17-7.28 (ABCD, 4H, 5, 6, 7, 8-H), 7.30/7.86 (AA'BB', 4H, tosyl); ^{13}C-nmr: δ 21.6 (CH_3), 56.6 (C-4), 126.8/127.3/128.1/128.4 (C-5, 6, 7, 8) 129.4/129.8 (C-2' 3', tosyl), 128.4/128.5/133.6 (C-4a, 8a, 4'), 145.7 (C-1') 164.7 (C-2); ir (potassium bromide): 1660, 1440, 1310, 1295, 1145, 1080, 775, 660 cm^{-1}; ms: (70 eV) m/z (%) 303 (2) ($M^{+\cdot}$), 239 (58), 148 (16), 139 (34), 122 (77), 121 (100), 91 (57), 77 (19), 65 (23).

Anal. Calcd. for $C_{15}H_{13}NO_2S_2$: C, 59.38; H, 4.32. Found: C, 59.38; H, 4.25.

3,4-Dihydro-2*H*-1,3-benzothiazin-2-one (**6**).

The compound was obtained as a colorless solid, mp 146°, quantitative yield by treating **4a** with aqueous acetic acid in toluene; ^{1}H-nmr: δ 4.40 (s, 2H, 4-H), 7.01 (s, 1H, NH), 7.17-7.28 (ABCD, 4H, 5, 6, 7, 8-H); ^{13}C-nmr: δ 46.7 (C-4), 126.4/126.4/126.8/-128.2 (C-5, 6, 7, 8), 130.6/131.7 (C-4a, 8a), 168.9 (C-2); ir (chloroform): 3280, 1650, 1440, 1270, 1065, 1045 cm^{-1}; ms: (70 eV) m/z (%) 165 (40) ($M^{+\cdot}$), 123 (11), 122 (100), 121 (66), 78 (27).

Anal. Calcd. for C_8H_7NOS: C, 58.16; H, 4.27. Found: C, 58.10; H, 4.26.

2-Acetyl-4*H*-1,3-benzothiazine (**4b**).

The compound was obtained as a yellow oil, yield 107 mg (14%); ^{1}H-nmr: δ 2.50 (s, 3H, CH_3), 4.79 (s, 2H, 4-H), 7.23-7.33 (ABCD, 4H, 5, 6, 7, 8-H); ^{13}C-nmr: δ 24.9 (CH_3), 54.7 (C-4), 126.8/-126.9/127.8/127.8 (C-5, 6, 7, 8), 128.7/130.3 (C-4a, 8a), 162.2 (C-2), 195.0 (CO); ir (deuteriochloroform): 2120, 1695, 1590, 1440, 1350, 1235, 1030 cm^{-1}; ms (70 eV): m/z (%) = 191 (43) ($M^{+\cdot}$), 123 (11), 122 (100), 121 (59), 78 (20), 43 (59) (CH_3CO^+).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74. Found: C, 62.42; H, 4.77.

2-Cyano-2-methyl-4*H*-3,1-benzoxathiine (**7b**).

The compound was obtained as a yellow oil, yield 23 mg; ^{1}H-nmr: δ = 1.99 (s, 3H, CH_3), 4.97/5.18 (AB, ^2J = 15.4 Hz, 2H, 4-H), 7.09-7.24 (ABCD, 4H, 5,6,7,8-H); ^{13}C-nmr: δ = 27.8 (CH_3), 67.4 (C-4), 73.5 (C-2), 117.6 (CN), 125.9/126.2/127.4/128.1 (C-5,6,7,8), 128.3/128.6 (C-4a,8a); ir (chloroform): 1475, 1440, 1375, 1135, 1070, 1035 cm^{-1}; ms: (70 eV): m/z (%) = 191 (4) ($M^{+\cdot}$), 122 (29), 121 (100), 78 (94), 51 (66), 43 (92).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74. Found: C, 62.64; H, 4.85.

2-Benzoyl-4*H*-1,3-benzothiazine (**4c**).

The compound was obtained as a yellow oil, yield 71 mg (7%); ^{1}H-nmr: δ = 4.83 (s, 2H, 4-H), 8.08 (d, 2H, H_o, phenyl), 7.43 (t, 2H, H_m, phenyl), 7.58 (t, 1H$_p$, phenyl), 7.34 (ABCD, 4,5,6,7,8-H); ^{13}C-nmr: δ = 56.8 (C-4), 126.9/127.0/127.9/127.9 (C-5,6,7,8), 129.3/130.9/133.6 (C-4a,8a,1'), 133.9 (C_p, phenyl), 128.3 (C_m, phenyl), 130.9 (C_o, phenyl), 161.9 (C-2), 188.7 (CO); ir chloroform): 1655, 1590, 1440, 1275, 1000, 845 cm^{-1}; ms: (70 eV) m/z (%) = 253 (10) (M^+), 122 (30), 121 (26), 105 (100) ($C_7H_5O^+$), 77 (82), 51 (24).

Anal. Calcd. for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.53. Found: C, 70.87; H, 4.40; N, 5.52.

4*H*-1,3-Benzothiazine-2-carboxylic Acid Ethyl Ester (**4d**).

The compound was obtained as a colorless oil, yield 62 mg (7%); ^{1}H-nmr δ = 1.38 (t, 3H, CH_3), 4.39 (q, 2H, OCH_2), 4.82 (s, 2H, 4-H), 7.24-7.31 (ABCD, 4H, 5,6,7,8-H); ^{13}C-nmr: δ = 14.1 (CH_3), 56.8 (C-4), 63.1 (OCH_2), 126.5/127.1/127.9/128.2 (C-5,6,7,8), 128.5/128.9 (C-4a, 8a), 155.9 (C-2), 161.7 (CO); ir (chloroform): 1715, 1605, 1440, 1280, 1250, 1050 cm^{-1}; ms: (70 eV) m/z (%) 221 (21) ($M^{+\cdot}$), 149 (13), 123 (11), 122 (100), 121 (63), 78 (18).

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01. Found: C, 59.50; H, 4.96.

5a*H*, 11*H*, 13*H*-1,3-Benzothiazino[2,3-*b*][1,3]benzothiazine-5a-carboxylic Acid Ethyl Ester (**8d**).

The compound was obtained as a colorless solid, mp 113°, yield 69 mg (10%); ^{1}H-nmr: δ 1.22 (t, 3H, CH_3), 3.88/4.09 (AB, 4H, 11, 13-H), 4.24 (q, 2H, OCH_2), 7.09-7.24 (ABCD, 8H, 1, 2, 3, 4, 7, 8, 9, 10-H); ^{13}C-nmr: δ 13.9 (CH_3), 54.9 (C-11, 13), 62.9 (OCH_2), 79.5 (C-5a), 126.3/127.3/127.7/127.8 (C-1, 2, 3, 4, 7, 8, 9, 10), 132.8/134.4 (C-1, 2, 3, 4, 7, 8, 9, 10), 132.8/134.4 (C-4a, 6a, 10a, 13a), 168.8 (CO); ir (chloroform): 1725, 1460, 1435, 1230, 1100, 1020 cm^{-1}; ms: (70 eV) m/z (%) = 343 (16) ($M^{+\cdot}$), 272 (84), 270 (59), 268 (89), 220 (72), 122 (85), 121 (100), 78 (30).

Anal. Calcd. for $C_{18}H_{17}NO_2S_2$: C, 62.95; H, 4.99; N, 4.08. Found: C, 63.15; H, 5.16; N, 3.78.

2-Methylimino-4*H*-1,3-benzodithiin (*Z*/*E*-**10e**).

The mixture of stereo isomers was obtained as a yellow oil, yield 31 mg (4%), *Z*:*E* = 31:69; ^{1}H-nmr: (*E*) δ 3.23 (s, 3H, CH_3), 4.06 (s, 2H, 4-H), 7.24, 7.45 (ABCD, 4H, 5, 6, 7, 8-H); ^{1}H-nmr: (*Z*) δ 3.36 (s, 3H, CH_3), 3.99 (s, 2H, 4-H), 7.24-7.45 (ABCD, 4H, 5, 6, 7, 8-H); ^{13}C-nmr: (*E*) δ 35.3 (CH_3), 43.0 (C-4), 126.9/127.7/128.2/129.6 (C-5, 6, 7, 8), 134.3/136.0 (C-4a, 8a); ^{13}C-nmr: (*Z*) δ 34.7 (CH_3), 41.1 (C-4), 127.4/127.7/127.9/129.1 (C-5, 6, 7, 8), 133.1, 136.2 (C-4a, 8a), 160.5 (C-2); ir (deuteriochloroform): 2220, 1570, 1460, 1433, 1385, 990 cm^{-1}; ms: (70 eV) m/z (%) 195 (18) $M^{+\cdot}$), 156 (48), 155 (49), 154 (100), 153 (60), 122 (60), 121 (73), 78 (54), 77 (50), 69 (46), 63 (38).

Anal. Calcd. for $C_9H_9NS_2$: C, 55.35; H, 4.64; N, 7.17. Found: C, 55.24; H, 4.61; N, 7.00.

3-Methyl-3,4-dihydro-1,3-benzothiazine-2-thione (**11e**).

The compound was obtained as a pale yellow solid, mp 118-119°, yield 31 mg (4%); ^{1}H-nmr: δ 3.61 (s, 3H, CH_3), 4.59 (s, 2H, 4-H), 7.21-7.34 (ABCD, 4H, 5, 6, 7, 8-H); ^{13}C-nmr: δ 43.2 (CH_3), 58.2 (C-4), 123.8/126.2/127.4/128.9 (C-5, 6, 7, 8), 129.3/133.3 (C-4a, 8a), 190.6 (CS); ir (chloroform): 1490, 1320, 1095, 995 cm^{-1}; ms: (70 eV) m/z (%) 195 (62) ($M^{+\cdot}$), 154 (37), 122 (85), 121 (100), 78 (41), 71 (46), 57 (83), 55 (49), 43 (71).

Anal. Calcd. for $C_9H_9NS_2$: C, 55.35; H, 4.64. Found: C, 55.42; H, 4.72.

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