Tetrahedron Letters,Vol.27,No.47,pp 5703-5706,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CYCLOADDITION REACTIONS OF BENZOTHIETE AND HETERO DIENOPHILES FOR THE SYNTHESIS OF HETEROCYCLIC SYSTEMS

Dominic Jacob, Hans Peter-Niedermann and Herbert Meier*
Institut für Organische Chemie der Universität Mainz
J.-J. Becherweg 18 - 22, D-6500 Mainz 1

Abstract: Benzothiete (1) undergoes cycloaddition reactions with hetero dienophiles with NN-, NO- or CO- double bonds, leading to six-membered heterocyclic ring systems of 2H-3,4-dihydro-1,2,3-benzothiadiazine (3), 4H-3,1,2-benzoxathiazine (4) and 4H-3,1-benzoxathiin.

Studies on the synthesis and the chemical reactivity of benzothiete (1) and its derivatives are of special interest due to its synthetic capability [1,2]. The valence isomerization between the benzenoid structure 1 and the o-quinoidal form 2 is responsible for a lot of addition and cycloaddition processes. The 8π-component 2 possesses a high-lying HOMO (-8.96 eV)[3], which can interfere with the low-lying LUMO of the "hetero dienophile". Such a frontier orbital control explicates not only the relative low activation barrier of these cycloaddition reactions, but also the observed regiospecifity. Polar dienophiles add exclusively in a way that the positive site is connected to the sulfur and the negative site to the CH_2-group of 2.

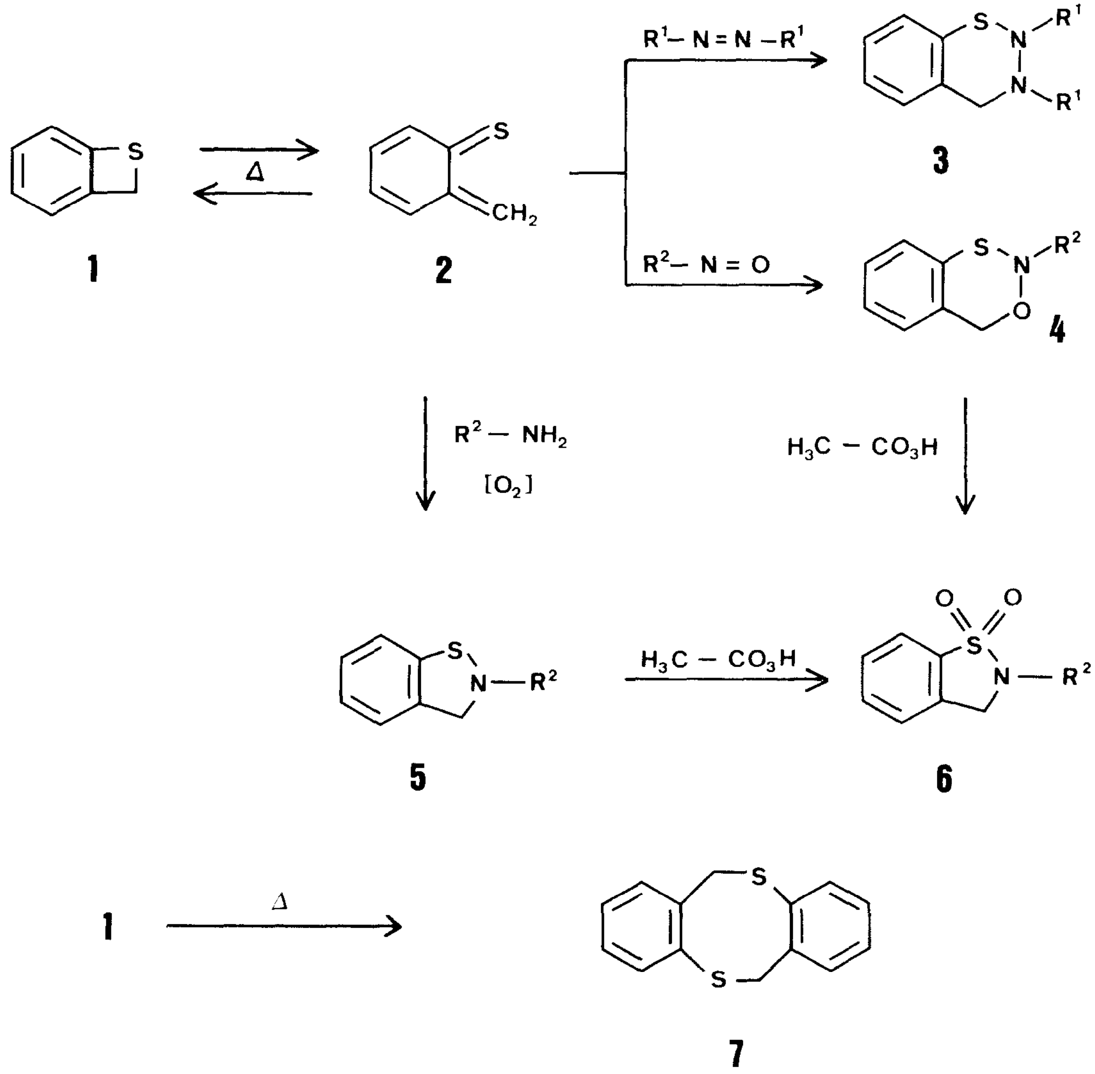
Refluxing a solution of benzothiete (1) in toluene in the presence of 1.25 equivalents of azodicarboxylic acid diester affords the derivatives of 2H-3,4-dihydro-1,2,3-benzothiadiazine (3).

3a: $R^1 = CO_2C_2H_5$, yield 77%, colourless liquid[4]
3b: $R^1 = CO_2CH_2\text{-}C_6H_5$, yield 90%, m. p. 84 °C
3c: $R^1 = CO_2C(CH_3)_3$, yield 73%, m. p. 115 °C
3d: $R^1 = CO_2C_6H_5$, yield 84%, m. p. 130 °C.

In a similar experiment nitroso compounds are added to benzothiete (1) furnishing the derivatives of 4H-3,1,2-benzoxathiazines (4).

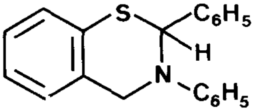
4a: $R^2 = C_6H_5$, yield 60%, m. p. 141 °C [5]
4b: $R^2 = o\text{-}CH_3\text{-}C_6H_4$, yield 63%, m. p. 104 °C
4c: $R^2 = o\text{-}Cl\text{-}C_6H_4$, yield 82%, m. p. 118 °C

In both the reactions a small part of 1 is dimerized to 1,5-dibenzo [b,f] dithiocin (7, m.p. 170°C, yield: 6-16 %). Higher cyclic oligomers are not observed under these conditions [6].



Oxidation of 4a with peracetic acid leads to 2-phenyl-2,3-dihydrobenz [d] isothiazole-1,1-dioxide (6a, yield 43 %) by ring contraction. 6a is also obtained via the ring enlargement 1 → 5a performed by the nucleophilic attack of aniline under air[2] and subsequent peracetic acid oxidation 5a → 6a (yield 75 %).

Besides dienophiles with two hetero atoms N or N and O, dienophiles with one hetero atom can be used for the cycloaddition with benzothiete. Schiff bases like N-benzylidene aniline form 3,4-dihydro-2H-1,3-benzothiazines 8[7] in a yield of about 70 % and mesoxalic acid diethyl ester furnishes 79 % of 4H-3,1-benzoxathiin-2,2-dicarboxylic acid diethyl ester (9)[8].



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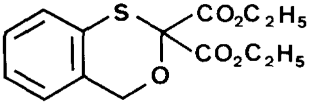

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On the whole, benzothiete (1) reacts as 8π-component in the o-quinoidal form 2 with suitable CN-, CO-, NN- and NO double bonds in a thermally allowed $[_{\pi}8_{s} + {}_{\pi}2_{s}]$-cycloaddition. Benzo-condensed 6-membered ring systems containing two or three hetero atoms (S, N, O) are formed in a very convenient way and in good yields. Whereas there are a few 2H-3,4-dihydro-1,2,3-benzothiadiazines 3 already mentioned in the literature $^{9-12)}$, to our knowledge the 3,1,2-oxathiazine system 4 is new and a single example of the oxathiin system 9 was prepared recently$^{13,14)}$. Like $3^{9-12)}$, these classes of compounds will certainly gain some interest concerning their pharmacological activity$^{15)}$.

Acknowledgement: This work was supported by the Fonds der Chemischen Industrie. D.J. thanks the German Academic Exchange Service (DAAD) for the award of a fellowship.

References and Notes:

1) K. Kanakarajan and H. Meier, J. Org. Chem. 48, 881 (1983) and references cited therein.

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3) MNDO calculation, unpublished.

4) An exemplary spectroscopic characterization shall be given for 3a. The compound exists at room temperature in two conformations in the approximate ratio 2 : 1. IR (direct phase): 2970, 1710, 1730, 1370, 1210, 750 cm^{-1}. ^1H-NMR ($CDCl_3$) : δ = 1.27 (m, 6H, CH_3), 4.23 (m, 4H, OCH_2), 4.52/5.16 (AB, ^2J = 16.0 Hz, CH_2 major component), 4.65/5.03 (AB, ^2J = 16.0 Hz, CH_2 minor component), 6.97 - 7.20 (m, 4H, $H_{arom.}$); ^{13}C-NMR ($CDCl_3$) : δ = 14.4/14.5 (CH_3), 44.5/45.5 (CH_2, broad), 62.8/64.2 (OCH_2), 122.9/125.2/126.0/126.5/127.2/128.1/128.9/132.3 ($C_{arom.}$), 154.5 (CO, broad), 155.6 (CO). MS (70 eV): m/z = 296 ($M^{+\cdot}$; 44 %), 224 (51), 151 (45).

5) Exemplary spectroscopic characterization of 4a: IR (KBr): 1590, 1500, 1305, 1280, 1110, 1070, 1050, 740 cm^{-1}. ^1H-NMR ($CDCl_3$) : δ = 4.89/5.25 (AB, ^2J = 15.5 Hz, 2H, CH_2), 7.04 7.83 (m, 9H, $H_{arom.}$); ^{13}C-NMR ($CDCl_3$) : δ = 55.1 (CH_2), 116.9 (C_o, phenyl), 122.6/123.4/124.6/128.8/131.6 (C-5,6,7,8 and C_p, phenyl), 129.6 (C_m, phenyl), 138.4/142.0/144.9 (C-4a,8a and C_i, phenyl). MS (70 eV): m/z = 229 ($M^{+\cdot}$; 100 %), 212 (90), 137 (59), 109 (50), 77 (72).

6) Compare also lit.[1,2].

7) Publication in preparation.

8) IR (direct phase): 1740, 1260, 1210, 935, 900 cm^{-1}. ^1H-NMR ($CDCl_3$) : δ = 1.22 (t, 6H, CH_3), 4.23/4.25 (AB-part of ABX_3, 4H, ethyl CH_2), 4.82 (s, 2H, CH_2), 7.20 - 7.35 (m, 4H, $H_{arom.}$); ^{13}C-NMR ($CDCl_3$) : δ = 13.8 (CH_3), 62.8 (ethyl-CH_2), 68.0 (C-4), 126.3/126.6/128.3/128.5 (C-5,6,7,8), 131.1/134.8 (C-4a,8a). MS (70 eV): m/z = 296 ($M^{+\cdot}$, 18 %), 224 (13), 223 (100), 167 (18), 136 (20), 123 (62), 122 (48), 121 (63).

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13) C.W. Perkins, S.R. Wilson and J.C. Martin, J. Am. Chem. Soc. 107, 3209 (1985).

14) Satisfactory analytical and spectroscopic data have been obtained from all isolated compounds.

15) This is also true for the cycloadducts with hetero dienophiles containing a NS- or PS-double bond. First successful experiments of such cycloaddition processes are in current investigation.

(Received in Germany 22 July 1986)