THE 1,3-DIPOLAR CYCLOADDITION AS AN APPROACH TO NOVEL TRICYCLIC O,N- AND S,N-HETEROCYCLES[1]

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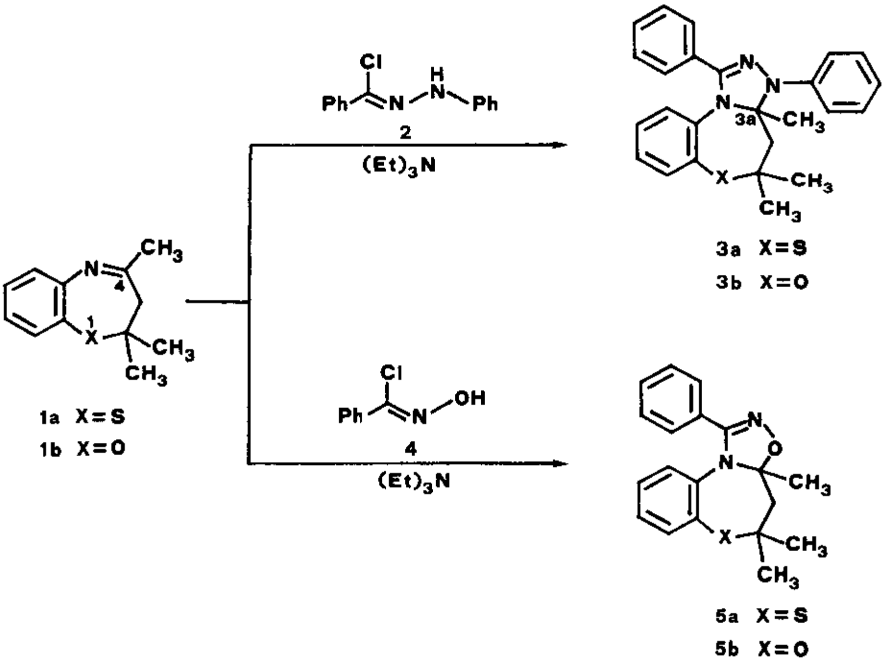
Abstract - A synthetic pathway to previously unknown tricyclic [1,5]benzothiazepines, [1,5]benzoxazepines, and [1,2,4]oxadiazolo[5,4-c][1,4]benzothiazine via 1,3-dipolar cycloaddition is described.

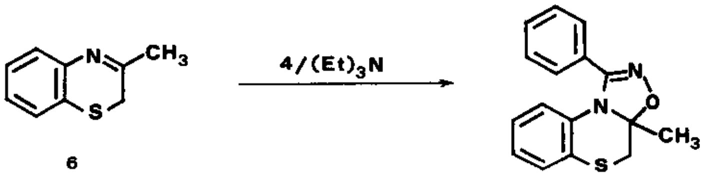
Various 1,5-benzothiazepines such as diltiazeme, nictiazeme, and tiazesime possess coronary vessel dilating and antidepressive activity, respectively. Based on previous results with benzodiazepine derivatives the addition of a third ring to bond [d] may be expected to enhance the activity or modify the activity profile.

The present investigation deals with the applicability of 1,3-dipolar cycloadditions as an access to such tricyclic ring systems. For stability reasons we chose 1,5-benzothiazepine $1a^2$ as dipolarophile, which was subjected to the reaction with benzonitrile N-phenylimine and benzonitrile oxide generated in situ from 2^3 and 4^4, respectively, with triethylamine. The structures of the cycloadducts 3a and 5a were confirmed by elemental analysis, mass and nmr spectra.



The removal of the imine double bond due to the cycloaddition was revealed in the ^{1}H-nmr spectra by a diamagnetic shift of the signal of the methyl group adjacent to the benzothiazepine nitrogen (1a: CH_3-C-4: 2.37 ppm; 3a: CH_3-C-3a: 1.29 ppm; 5a: CH_3-C-3a: 1.27 ppm). Likewise, in the ^{13}C-nmr spectra of the tricyclic compounds the C-3a signal experienced a similar shift (1a: C-4: 173.38 ppm; 3a: C-3a: 87.60 ppm; 5a: C-3a: 99.38 ppm). Moreover, the fixed conformation of the resulting tricyclic ring systems caused a split of the previous 1a-methylene singlet into an AB-system in the ^{1}H-nmr spectra of the reaction products.

To evaluate the wide applicability of this reaction, both dipoles were reacted in a similar manner with the oxygen containing compound 1b[5] and the 1,4-benzothiazine 6[6], respectively. Benzonitrile N-phenylimine only with 1b showed reaction to give 3b, whereas the benzonitrile oxide in both reactions gave the expected cycloadducts 5b and 7.



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7

EXPERIMENTAL

All melting points are measured with a Kofler hot-stage apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT-311 instrument (70 eV) and nmr spectra on a Bruker AC 80 spectrometer using TMS as internal standard in $CDCl_3$.

General Procedure for the Formation of Triazolo-fused Heterocycles 3a and 3b

To a stirred solution of 1 (10 mmol) and N-phenylbenzohydrazonic acid chloride (2, 2.53 g, 11 mmol) in anhydrous THF (100 ml), a solution of triethylamine (1.10 g, 11 mmol) in anhydrous THF (20 ml) was added dropwise over 10 min. After heating the mixture for 20 h, the solvent was evaporated under reduced pressure and the residue was dispersed in ether (100 ml). Triethylamine hydrochloride was filtered off, the solvent was removed in vacuo and the residue was recrystallized.

3,3a,4,5-Tetrahydro-3a,5,5-trimethyl-1,3-diphenyl[1,2,4]triazolo[3,4-d][1,5]benzothiazepine (3a): 1a (2.05 g) afforded 3.11 g (78%) of 3a as white crystals; mp (from ethanol) 135°C; ms: m/z 399 (M^+, 0.1), 384 (0.6), 343 (0.8), 230 (30), 194 (18), 91 (100); ^{1}H-nmr: δ 1.29 (s, 3H, CH_3), 1.46 (s, 6H, 2 CH_3), 2.34 and 2.66 (AB-system, J = 14.4 Hz, 2H, CH_2), 6.87 - 7.61 (m, 12 H, aromat.), 7.84 - 8.01 (m, 2H, aromat.) ppm; ^{13}C-nmr: δ 31.50 (3 CH_3), 42.18 (C-4), 53.32 (C-5), 87.60 (C-3a), 113.45 - 134.70 (17 C, aromat), 143.35 (C-1 of N-phenyl ring), 148.28 (C-1) ppm; Anal. Calcd. for $C_{25}H_{25}N_3S$: C, 75.15; H, 6.36; N, 10.52. Found: C, 74.91; H, 6.37; N, 10.49.

3,3a,4,5-Tetrahydro-3a,5,5-trimethyl-1,3-diphenyl[1,2,4]triazolo[3,4-d][1,5]benzoxazepine (3b): 1b (1.89 g) afforded 2.79 g (73%) of 3b as white crystals; mp (from ethanol) 110°C; ms: m/z 383 (M^+, 8), 368 (40), 327 (41), 194 (56), 91 (100); ^{1}H-nmr: δ 1.24 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.90 and 2.50 (AB-system, J = 15.6 Hz, 2H, CH_2), 6.89 - 7.50 (m, 14 H, aromat) ppm; Anal. Calcd. for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.12;

H, 6.63; N, 10.76.

General Procedure for the Formation of Oxadiazolo-fused Heterocycles 5a, 5b, and 7

To a stirred solution of 1 (10 mmol) or 6 (1.63 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in anhydrous THF (80 ml), a solution of benzohydroximic acid chloride (4, 1.55 g, 10 mmol) in anhydrous THF (20 ml) was added dropwise over 20 min at 0°C. After stirring at 0°C for 2 h, the solution was allowed to stand at 20°C for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (100 ml) and water (30 ml). The organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated. The crude product was recrystallized.

4,5-Dihydro-3a,5,5-trimethyl-1-phenyl-3aH-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine (5a): 1a (2.05 g) afforded 1.46 g (45%) of 5a as white crystals; mp (from 80% ethanol) 119 - 121°C; ms: m/z 324 (M^+, 14), 309 (8), 268 (79), 226 (84), 225 (100), 150 (18), 149 (52); ^{1}H-nmr: δ 1.27 (s, 3H, CH_3), 1.42 (s, 6H, 2 CH_3), 2.11 and 2.46 (AB-system, J = 14.4 Hz, 2H, CH_2), 6.71 - 7.54 (m, 9 H, aromat.) ppm; ^{13}C-nmr: δ 25.58 (CH_3), 30.36 (CH_3), 31.66 (CH_3), 42.35 (C-4), 53.56 (C-5), 99.38 (C-3a), 125.72 - 135.34 (12 C, aromat.), 154.41 (C-1) ppm; Anal. Calcd. for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.34; H, 6.28; N, 8.41.

4,5-Dihydro-3a,5,5-trimethyl-1-phenyl-3aH-[1,2,4]oxadiazolo[5,4-d][1,5]benzoxazepine (5b): 1b (1.89 g) afforded 1.82 g (59%) of 5b as white crystals; mp (from 70% ethanol) 104°C; ms: m/z 308 (M^+, 19), 293 (24), 252 (90), 210 (100), 209 (55), 134 (31), 133 (23); ^{1}H-nmr: δ 1.32 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.90 and 2.17 (AB-system, J = 15.4 Hz, 2H, CH_2), 6.87 - 7.54 (m, 9H, aromat.) ppm; ^{13}C-nmr: δ 27.11 (CH_3), 28.38 (CH_3), 28.78 (CH_3), 46.31 (C-4), 78.23 (C-5), 99.04 (C-3a), 124.04 - 132.52 (12 C, aromat.), 155.62 (C-1) ppm; Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.00; H, 6.65; N, 9.22.

3a,4-Dihydro-3a-methyl-1-phenyl[1,2,4]oxadiazolo[5,4-c][1,4]benzothiazine (7): From 6 1.07 g (38%) of 7 were obtained as white crystals; mp (from ethanol) 214°C; ms: m/z 282 (M^+, 55), 163 (100); ^{1}H-nmr: δ 1.57 (s, 3H, CH_3), 3.10 and 3.57 (AB-system, J = 13.5 Hz, 2H, CH_2), 6.47 - 7.83 (m, 9H, aromat.) ppm; Anal. Calcd. for $C_{16}H_{14}N_2OS$: C, 68.06; H, 4.99; N, 9.92. Found: C, 67.72; H, 5.11; N, 9.84.

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