# A Convenient Synthesis of Novel [1,2,4]Triazolo[4,3-*a*][1,5]benzodiazepine Derivatives

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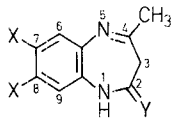
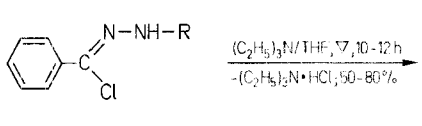
A synthetic approach to the previously unknown 3a,4,5,6-tetrahydro-3*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine system via [3 + 2]-cycloaddition of nitrile imines to 2,3-dihydro-1*H*-1,5-benzodiazepines is described. In an analogous way, the 3a,4,4a,5-tetrahydro-3*H*-bis[1,2,4]triazolo[4,3-*a*:3′,4′-*d*][1,5]benzodiazepine system is prepared from 3*H*-1,5-benzodiazepines.

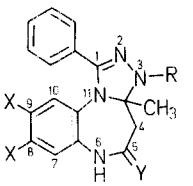
Several benzodiazepine derivatives containing additional rings are compounds of pharmacological interest[1]. In connection with our investigations on possible approaches to novel benzodiazepine derivatives with an additional fused heterocyclic ring[2], we have tested the C=N bond of 1,5-benzodiazepine systems as a dipolarophile in 1,3-dipolar cycloadditions of nitrile imines. The reactions of 2,3-dihydro-1*H*-1,5-benzodiazepines[3-7] (**1**) with benzonitrile *N*-phenylimine[8] and with benzonitrile *N*-ethoxycarbonylimine[9] (generated *in situ* from the hydrazonic chlorides **2a, b**) in boiling tetrahydrofuran afforded the 3a,4,5,6-tetrahydro-3*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines **3aa, 3ab, 3ba,** and **3ca** in satisfactory yields. However, the reaction of 1,5-benzodiazepine derivative **1b** with nitrile imine precursor **2b** under the same conditions failed to give the expected cycloadduct **3bb** in practically useful yields.



**1a** Y = 2 $CH_3$, X = H
**1b** Y = O, X = H
**1c** Y = 2 $CH_3$, X = Cl



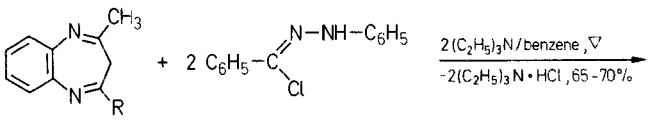
**2a** R = $C_6H_5$
**2b** R = $-COOC_2H_5$



| 3 | Y | R | X |
|---|---|---|---|
| aa | 2 $CH_3$ | $C_6H_5$ | H |
| ba | O | $C_6H_5$ | H |
| ab | 2 $CH_3$ | $-COOC_2H_5$ | H |
| bb | O | $-COOC_2H_5$ | H |
| ca | 2 $CH_3$ | $C_6H_5$ | Cl |

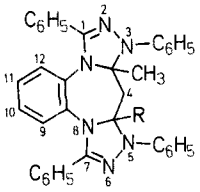
We extended the investigation to the 2,4-disubstituted 3*H*-1,5-benzodiazepines **4a,b**[11,12,13] and found that these compounds react with benzonitrile *N*-phenylimine (from **2a**) in an analogous manner to give the cycloadducts **5a, b.**

To our knowledge, cycloadducts of the types **3** and **5** have previously not been reported. Up to now, only few publications have appeared on the synthesis and biological activity of more highly unsaturated [1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines derivatives[14].



**4a** R = $CH_3$
**4b** R = $C_6H_5$

**2a**



**5a** R = $CH_3$
**5b** R = $C_6H_5$

The structures of products **3** and **5**, which were assigned on the basis of element analyses, mass spectrometry, and $^1$H- and $^{13}$C-N.M.R. spectrometry. The structures suggest a 1,3-dipolar cycloaddition mechanism in the formation of compounds **3** and **5**.

The N.M.R. spectra of adducts **3** and **5** were compared with those of the starting 1,5-benzodiazepine derivatives **1** and **4**[4-7,12,13]. The signals of the H- and C-atoms in the spectra of compounds **1** and **4** are all found in the spectra of products **3** and **5**, respectively. In addition, the proton resonances of the moiety —N=C($CH_3$)— in products **1** and **4** were shifted to higher field for the saturated moieties N—C($CH_3$) in products **3** and **5**; an analogous shift of the C-4 resonance in **1** upon conversion into **3** (C-3a in **3**) was observed due to saturation of the C=N double bond. These results provide further evidence for the suggested cycloaddition. The signals of the methylene protons appear as a singlet in the spectra of the bicyclic compounds **1** and **4** whereas they appear as AB systems in the spectra of the cycloadducts **3** and **5b** and as a broad singlet ($\delta$ = 2.94 ppm) in the case of **5a**. The $^1$H-N.M.R. spectra in deuteriochloroform of **1a** and **1c** show a single sharp peak at $\delta$ = 1.34 and 1.33 ppm, respectively, for the geminal methyl groups 2-$CH_3$ which resonate as two distinct singlets (5-$CH_3$) at $\delta$ = 1.46 and 1.21 ppm in **3aa**, 1.48 and 1.20 ppm in **3ab**, and 1.38 and 1.13 ppm in **3ca**. These data are indicative of a fixed conformation of the cycloadducts in solution: when the $^1$H-N.M.R. spectrum of **3aa** was recorded over a range of temperatures between − 88 and + 150 °C, no positive evidence for a change in the conformation of the 7-membered ring was observed, apart from some line broadening which occurred at higher temperatures. Single-crystal X-ray analysis of **3aa**[15] shows chair conformation of the 7-membered ring, as suggested for 2,2,4-trimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine[5]. The regioselectivity obtained in the reaction under investigation is that predicted from perturbation theory[10].

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Element analyses were performed on a Perkin-Elmer 240 analyzer. Mass spectra were obtained on a Hitachi RMU 6 spectrometer. I.R. spectra were recorded on a Perkin-Elmer 225 spectrometer. $^1$H-N.M.R. spectra were recorded on a Varian EM 360 A 60MHz and $^{13}$C-N.M.R. spectra on a Varian FT 80 20MHz instrument. The C-assignments given with the $^{13}$C-N.M.R. data are based on off-resonance and gated decoupling experiments.

**3a,5,5-Trimethyl-1-phenyl-3a,4,5,6-tetrahydro-3*H*-[1,2,4]triazolo-[4,3-*a*][1,5]benzodiazepines 3aa, 3ab, and 3ca and 3a-Methyl-5-oxo-1,3-diphenyl-3a,4,5,6-tetrahydro-3*H*-[1,2,4]triazolo[4,3-*a*-]benzodiazepine (3ba); General Procedure:**

To a stirred solution of the 1,5-benzodiazepine derivative **1** (6 mmol) and the benzenecarbohydrazonic chloride **2** (6 mmol) in anhydrous tetrahydrofuran (50 ml) [anhydrous benzene can also be used in the

present reactions], a solution of triethylamine (607.2 mg, 6 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise over a few minutes. The mixture is then refluxed for 10–20 h, the optimum reaction time being determined by T.L.C. monitoring (silica gel). Tetrahydrofuran is then evaporated at reduced pressure, and ether (100 ml) is added to the residue. Triethylamine hydrochloride is filtered off, the solvent is evaporated at reduced pressure, and the residue is chromatographed on a silica gel column [type 60 (70–230 mesh, 0.063–0.200 mm), petroleum ether with varying amounts of ether as eluent] to afford the product **3**.

*3a,5,5-Trimethyl-1,3-diphenyl-3a,4,5,6-tetrahydro-3H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine* **(3aa)**; yield: 70%; m.p. 148–150°C.

| | | | | |
|---|---|---|---|---|
| $C_{25}H_{26}N_4$ | calc. | C 78.50 | H 6.85 | N 14.65 |
| (382.5) | found | 78.60 | 6.84 | 14.55 |

M.S. (70eV): *m/e* = 382 ($M^+$, 20%), 368 (18), 367 (60), 326 (22), 195 (18), 194 (100), 133 (12), 132 (10), 118 (13), 92 (18), 91 (96), 77 (40), 65 (10), 64 (12), 41 (10).

I.R. (Nujol): $\nu$ = 3320 (NH); 1595 (C=N); 1460, 1377 $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 1.21, 1.46 (2s, 3H each, 2×5-$CH_3$); 1.67 (s, 3H, 3a-$CH_3$); 2.13, 2.52 (2d, 1H each, AB quartet, $J$ = −14.2 Hz, $CH_2$); 4.34 (br. s, 1H, NH); 6.5–7.8 ppm (m, 14 $H_{arom}$).

$^{13}$C-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 26.1 (3a-$CH_3$); 3.18 (2×5-$CH_3$); 48.9 (C-4); 52.3 (C-5); 85.1 (C-3a); 120.2 (C-10); 120.5 (C-8); 125.6 (C-6a); 127.2–130.0 (C-7, C-9, and phenyl CH); 130.9 (C-1'); 143.2 (C-10a); 144.0 (C-1 of *N*-phenyl ring); 147.6 ppm (C-1).

*3a-Methyl-5-oxo-1,3-diphenyl-3a,4,5,6-tetrahydro-3H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine* **(3ba)**; yield: 60%; m.p. 170–172°C.

| | | | | |
|---|---|---|---|---|
| $C_{23}H_{20}N_4O$ | calc. | C 74.98 | H 5.47 | N 15.21 |
| (368.4) | found | 74.85 | 5.50 | 15.30 |

I.R. (Nujol): $\nu$ = 3200 (NH); 1680 (C=O); 1600 (C=N) $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 1.73 (s, 3H, $CH_3$); 2.58, 2.91 (2d, 1H each, AB quartet, $J$ = −13.7 Hz, $CH_2$); 6.8–8.0 (m, 14 $H_{arom}$); 8.69 ppm (br. s, 1H, NH).

$^{13}$C-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 25.2 (3a-$CH_3$); 42.1 (C-4); 93.5 (C-3a); 120.3 (C-10); 121.3 (C-6a); 122.9 (C-8); 125.8–129.9 (C-7, C-9, and phenyl CH); 133.2 (C-1'); 136.0 (C-1 of *N*-phenyl ring); 143.7 (C-10a); 150.3 (C-1); 171.4 ppm (C-5).

*3-Ethoxycarbonyl-3a,5,5-trimethyl-1-phenyl-3a,4,5,6-tetrahydro-3H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine* **(3ab)**; yield: 50%; low-melting solid.

| | | | | |
|---|---|---|---|---|
| $C_{22}H_{26}N_4O_2$ | calc. | C 69.82 | H 6.93 | N 14.80 |
| (378.5) | found | 69.81 | 7.00 | 14.79 |

I.R. ($CHCl_3$): $\nu$ = 3350 (NH); 1680 (C=O); 1592 (C=N); 1373, 1340 $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 1.20, 1.48 (2s, 3H each, 2×5-$CH_3$); 1.36 (t, 3H, $J$ = 6.8 Hz, $CH_2$—$CH_3$); 1.76 (s, 3H, 3a—$CH_3$); 2.15, 2.69 (2d, 1H each, AB quartet, $J$ = −14.5 Hz, 4-$CH_2$); 3.59 (br. s, 1H, NH); 4.31 (q, 2H, O—$CH_2$); 6.5–7.6 ppm (m, 9 $H_{arom}$).

$^{13}$C-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 14.8 (—$CH_2$—$CH_3$); 25.8 (3a—$CH_3$); 30.6, 32.2 (2×5-$CH_3$); 46.1 (C-4); 52.5 (C-5); 61.6 (O—$CH_2$); 82.5 (C-3a); 120.7 (C-10); 120.9 (C-8); 126.6 (C-6a); 127.8–130.9 (C-7, C-9, and phenyl CH); 131.8 (C-1'); 144.2 (C-10a); 151.6 (C-1); 152.0 ppm (CO—O)

*8,9-Dichloro-3a,5,5-trimethyl-1,3-diphenyl-3a,4,5,6-tetrahydro-3H-1,2,4-triazolo[4,3-a][1,5]benzodiazepine* **(3ca)**; yield: 80%; m.p. 186–188°C.

| | | | | |
|---|---|---|---|---|
| $C_{25}H_{24}Cl_2N_4$ | calc. | C 66.52 | H 5.36 | N 12.41 |
| (451.4) | found | 66.81 | 5.38 | 12.15 |

I.R. ($CHCl_3$): $\nu$ = 3360 (NH); 1595 (C=N); 1485, 1400, 1385 $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 1.13, 1.38 (2s, 3H each, 2×5-$CH_3$); 1.67 (s, 3H, 3a-$CH_3$); 2.12, 2.52 (2d, 1H each, AB quartet, $J$ = −14.5 Hz, $CH_2$); 3.67 (br. s, 1H, NH); 6.7–8.2 ppm (m, 12 $H_{arom}$).

**3a-Methyl-1,3,5,7-tetraphenyl-3a,4,4a,5-tetrahydro-3*H*-bis[1,2,4-triazolo][4,3-*a*:3',4'-*d*][1,5]benzodiazepines 5a, b:**

Following the above general procedure, the 3*H*-1,5-benzodiazepines **4a, b** are subjected to the reaction with 2 molecular equivalents of *N*-phenylbenzenecarbohydrazonic chloride **(2a)**.

*3a,4a-Dimethyl-1,3,5,7-tetraphenyl-3a,4,4a,5-tetrahydro-3H-bis[1,2,4-triazolo][4,3-a:3',4'-d][1,5]benzodiazepine* **(5a)**; yield: 65%; m.p. 140–142°C.

| | | | | |
|---|---|---|---|---|
| $C_{37}H_{32}N_6$ | calc. | C 79.26 | H 5.75 | N 14.99 |
| (560.7) | found | 79.48 | 5.83 | 14.69 |

I.R. ($CHCl_3$): $\nu$ = 1595 (C=N); 1490, 1405, 1375 $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 1.61 (s, 6H, 3a-$CH_3$, 4a-$CH_3$); 2.94 (br. s, 2H, $CH_2$); 6.9–7.8 ppm (m, 24 $H_{arom}$).

*3a-Methyl-1,3,4a,5,7-pentaphenyl-3a,4,4a,5-tetrahydro-3H-bis[1,2,4-triazolo][4,3-a:3',4'-d][1,5]benzodiazepine* **(5b)**; yield: 70%; m.p. 250–252°C.

| | | | | |
|---|---|---|---|---|
| $C_{42}H_{34}N_6$ | calc. | C 81.00 | H 5.50 | N 13.49 |
| (622.8) | found | 81.20 | 5.58 | 13.22 |

I.R. ($CHCl_3$): $\nu$ = 1593 (C=N); 1490, 1400, 1380 $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 1.72 (s, 3H, $CH_3$); 3.28, 3.55 (2d, 1H each, AB quartet, $J$ = −14.7 Hz, $CH_2$); 6.3–7.8 ppm (m, 29 $H_{arom}$).

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1 Sternbach, L.H. *Prog. Drug Res.* **1978**, *22*, 229–266.
2 Aversa, M.C., Giannetto, P., Ferlazzo, A., Romeo, G. *J. Chem. Soc. Perkin Trans. 1* **1982**, 2701–2705.
3 Ried, W., Stahlhofen, P. *Chem. Ber.* **1957**, *90*, 815–824.
4 Acheson, R.M., Tully, W.R. *J. Chem. Soc.* [C] **1970**, 1117–1121.
5 Hunter, P.W.W., Webb, G.A. *Tetrahedron* **1973**, *29*, 147–153.
6 Radeglia, R., Jehn, W. *J. Prakt. Chem.* **1976**, *318*, 1049–1056.
7 Vernin, G., Domloj, H., Siv, C., Metzger, J., Archavlis, A., Llinas, J.R. *Chem. Scr.* **1980**, *16*, 157–162.
8 Huisgen, R., Seidel, M., Wallbillich, G., Knupfer, H. *Tetrahedron* **1962**, *17*, 3–29.
9 Bacchetti, T. *Gazz. Chim. Ital.* **1961**, *91*, 866–879.
10 Houk, K.N., Sims, J., Watts, C.R., Luskus, L.J. *J. Am. Chem. Soc.* **1973**, *95*, 7301–7315.
Bianchi, G., De Micheli, C., Gandolfi, R., in: *The Chemistry of Double-Bonded Functional Groups*, Patai, S., Ed., Suppl. A, Part 1, John Wiley & Sons, London, 1977, p. 369.
11 Thiele, J., Steimmig, G. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 955–975.
12 Staab, H.A., Vögtle, F. *Chem. Ber.* **1965**, *98*, 2701–2714.
13 Mannschreck, A., Rissmann, G., Vögtle, F., Wild, D. *Chem. Ber.* **1967**, *100*, 335–346.
14 Bauer, A., Weber, K.H., Donneberg, P., Kuhn, F.J. *German Patent (DOS)* 2 318 673, (1974), C.H. Boehringer Sohn; *C.A.* **1975**, *82*, 57747.
Moffett, R.B., Kamdar, B.V., Von Voigtlander, P.F. *J. Med. Chem.* **1976**, *19*, 192–193.
Chow, A.W., Gyurik, R.J., Parish, R.C. *J. Heterocyclic Chem.* **1976**, *13*, 163–164.
Szarvasi, E., Grand, M., Depin, J., Betbeder-Matibet, A. *Eur. J. Med. Chem. Chim. Ther.* **1978**, *13*, 113–119.
Fryer, R.I., Sternbach, L.H., Walser, A. *U.S. Patent* 4 111 934, (1978), Hoffmann-La Roche, Inc.; *C.A.* **1979**, *90*, 152253.
15 Aversa, M.C., Ferlazzo, A., Giannetto, P., Kohnke, F.H., Slawin, A.M.Z., Williams, D.J., to be published.