1,3-Dipolar cycloaddition of nitrilimines to 2,4-disubstituted-3*H*-1,5-benzodiazepines: remarkable effect of C4-substituent on diastereoselectivity

Khadija Nabih,[a] Abdesselam Baouid,*[a] Aissa Hasnaoui,[a] Mohamed Selkti[b] and Philippe Compain*[c]

[a] *Laboratoire de Chimie des Substances Naturelles et des Hétérocycles, département de chimie, Faculté des Sciences-Semlalia, B.P. 2390, Université Cadi Ayyad, Marrakech, Morocco. E-mail: baouid.abdesselam@caramail.com*

[b] *Laboratoire de Cristallographie et RMN Biologiques, UMR 8015 CNRS-Faculté de Pharmacie, 4 avenue de l'Observatoire, 75270, Paris cedex 6, France*

[c] *Institut de Chimie Organique et Analytique (CNRS UMR 6005), Rue de Chartres, BP 6759, 45067, Orléans cedex 2, France. E-mail: philippe.compain@univ-orleans.fr*

Received* (*in Montpellier, France*) *9th April 2003, Accepted 3rd June 2003
First published as an Advance Article on the web 5th September 2003

The one-step synthesis of new bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5] benzodiazepines by way of completely regio- and diastereoselective 1,3-dipolar cycloaddition of nitrilimines to 2,4-dimethyl-3*H*-1,5-benzodiazepines is reported and a tentative rationalization for the observed diastereoselectivity, which underline the key effect of the C4-dipolarophile substituent, is proposed.

Introduction

Owing to their remarkable Central Nervous System (CNS) depressant activity, benzodiazepines[1-4] have been the object of intense investigation in medicinal chemistry and are now one of the most widely prescribed class of psychotropics.[5] More recently, the area of biological interest of 1,5-benzodiazepines[6] has been extended to various diseases such as cancer,[7] viral infection (HIV)[8] and cardiovascular disorders.[9] The 1,5-benzodiazepine core is indeed a ''privileged scaffold''[10] found in compounds active against a variety of target types including peptide hormones (such as CCK),[11] interleukin converting enzymes (ICE)[12] and potassium blockers (I_k)[9b] (examples are given Fig. 1).

Results and discussion

In addition, readily available 2,4-disubstituted-3*H*-1,5-benzodiazepines **1**[13] are useful synthons for the rapid construction of polyheterocyclic systems due to the presence of two possible dipolarophile sites. This structural feature could allow the diversity-oriented synthesis[14] of small libraries of benzodiazepine-based compounds for pharmacological testing on a wide range of biological targets.[15] To achieve this aim and as part of our continuing studies on 1,3-dipolar cycloaddition to diazepines,[16] we decided to explore the reactivity of 2,4-dimethyl-3*H*-1,5-benzodiazepines **1a**–**b** toward nitrilimines (Fig. 2).[17] It is noteworthy that according to the substituent in C7, the two dipolarophile sites are chemically equivalent (R_1 = H) or different (R_1 = Me).

To study the influence of nitrilimine substituents, we first turned our attention to *N*-aryl-*C*-ethoxycarbonylnitrilimines prepared *in situ* from ethylarylhydrazono-α-bromoglyoxylate **2** by base-induced dechlorination.[18] Reaction with 1,5-benzodiazepines **1** in benzene at room temperature provided the tetraheterocycles **3** in reasonable to very good yields (Table 1). These bis-adducts resulted from a double regiospecific 1,3-dipolar cycloaddition of the nitrilimines to the two dipolarophile sites C=N.

The structure of **3** was determined on the basis of mass, NMR spectral data (^{1}H and ^{13}C) and X-ray crystallographic

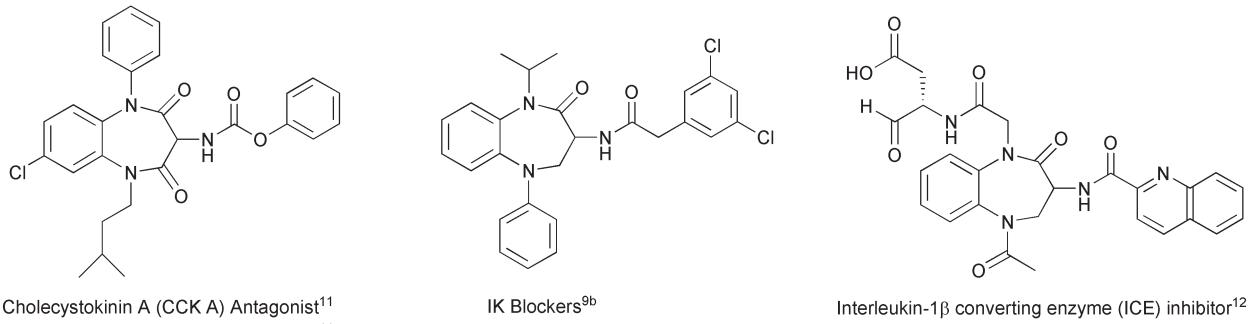
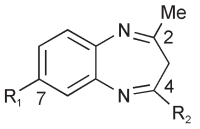


Fig. 1 Examples of 1,5-benzodiazepine-based compounds of biological interest.

 DOI: 10.1039/b303995c



1a R_1 = H, R_2=Me
1b R_1 = Me, R_2=Me

Fig. 2 2,4-Dimethyl-3*H*-1,5-benzodiazepine **1a-b**.

analysis. In particular, the chemical shift observed for the quaternary carbons C3a and C4a around δ 88 unambiguously rules out the formation of the alternative regioisomer, for which chemical shifts of about δ 50 would be expected.[19] The regiochemistry of the cycloaddition was that expected from frontier molecular orbital theory, considering dipole LUMO-dipolarophile HOMO interactions.[20] Contrary to what was found previously for benzodiazepine **1c** (R_2 = Ph),[16b,d] the formation of the mono-adduct was never observed even though equimolecular amounts or a large excess of dipolarophile were used. The reaction was found to be completely diastereoselective and the obtained bis-adducts **3a**–**f** were characterized by the *anti* relationship of the two triazolo rings fused to the benzodiazepine framework on the basis of ^{1}H and 2D NOESY NMR experiments.[21] In the case of the tetracycles **3a**–**c**, the *trans* isomers obtained have a C_2 symmetry axis, so that the methylene protons in C4 are equivalent and resonate as an only singlet. In addition, the structure of the cycloadduct **3b** was unambiguously determined on the basis of X-ray crystallographic analysis of a single crystal (Fig. 3).[22] The X-ray data indicate that the central 7-membered ring is quasi-planar; C4, the two aromatic carbons and endocyclic nitrogen atoms are in the same plan.

In the tetraheterocycles **3d**–**f** obtained from non-symmetrical benzodiazepine **1b**, methylene protons in C4 appear as a broad AB system. Irradiation of the C3a or C4a methyl groups of **3d**–**f** enhanced the intensity of H4A or H4B protons respectively. A *cis* stereochemistry would require that the two methyl groups could possibly produce NOE effect on only one of the adjacent geminal methylene protons.

When the C4 substituent is a phenyl (dienophile **1c**), we observed in a previous study[16d] that for one case (dipole **2c**), the diastereomeric excess of the cycloaddition reaction dropped to 36%. This puzzling singularity prompted us to explore the scope of the reaction with more sterically demanding diarylnitrilimines which were obtained *in situ* by the action of triethylamine on *N*-phenylarylohydrazonoyl chloride **4**.

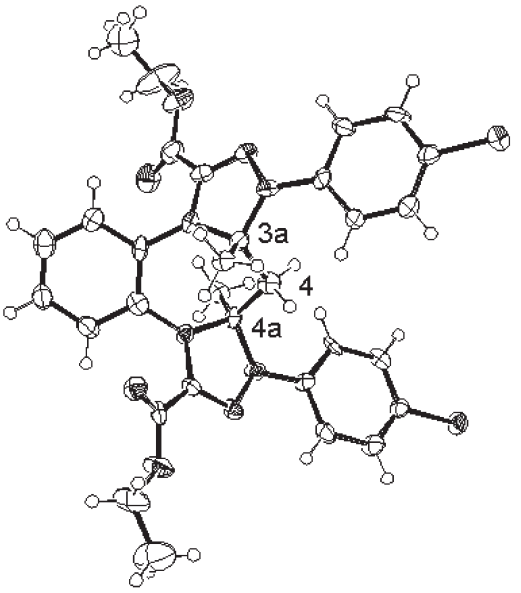
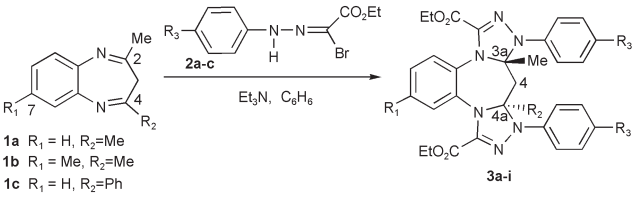


Fig. 3 Perspective ORTEP view of compound **3b**.

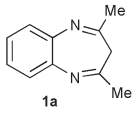
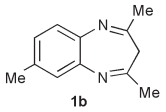
After stirring for 2 days at room temperature in benzene, cycloaddition reactions with 1,5-benzodiazepines **1a**–**b** furnished only one type of bis-cycloadducts **5** with complete regioselectivity and the same direction of addition to the imines as for the formation of tetraheterocycles **3** (Table 2).

The reaction was also found to be completely diastereoselective and gave the *trans* stereoisomers with respect to the relative stereochemistry of their C3a- and C4a-substituents. As for ethoxycarbonylnitrilimines, the mono-adducts were never detected whatever the experimental conditions explored. Comparison of these results with those observed for 2-methyl-4-phenyl-3*H*-benzodiazepine **1d** (R_2 = Ph),[16b] showed a remarkable effect of the C4-substituent on the diastereoselectivity of the 1,3-dipolar cycloaddition (entries 7 to 9). In this case, the diastereomeric excess dramatically dropped as far as 17%. With 1,5-benzodiazepines **1a**–**b**, the intermediate monocycloadduct may adopt a pseudo boat conformation

Table 1 Reaction of dipolarophiles **1a**–**b** with **2a**–**c**

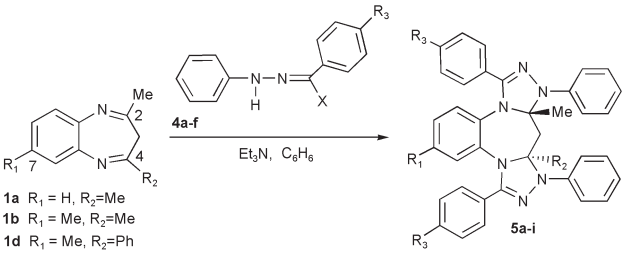


1a R_1 = H, R_2=Me
1b R_1 = Me, R_2=Me
1c R_1 = H, R_2=Ph

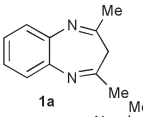
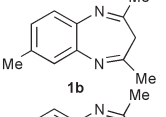
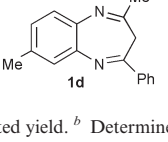
Entry	Dipolarophile	R_3	Dipole	Product	Yield(%)[a]	d.e. (%)[b]
1		Me	**2a**	**3a**	45	>95
2		Cl	**2b**	**3b**	50	>95
3	**1a**	NO_2	**2c**	**3c**	65	>95
4		Me	**2a**	**3d**	88	>95
5		Cl	**2b**	**3e**	60	>95
6	**1b**	NO_2	**2c**	**3f**	70	>95

[a] Isolated yield. [b] determined by ^{1}H NMR of the crude product.

Table 2 Reaction of dipolarophiles **1a**–**b** with **4a**–**f**



1a R_1 = H, R_2=Me
1b R_1 = Me, R_2=Me
1d R_1 = Me, R_2=Ph

Entry	Dipolarophile	R_3	X	Dipole	Product	Yield(%)[a]	d.e. (%)[b]
1		H	Cl	**4a**	**5a**	60	>95
2		Me	Cl	**4b**	**5b**	33	>95
3	**1a**	Cl	Cl	**4c**	**5c**	40	>95
4		H	Cl	**4a**	**5d**	84	>95
5		Me	Cl	**4b**	**5e**	56	>95
6	**1b**	Cl	Cl	**4c**	**5f**	60	>95
7[c]		H	Br	**4d**	**5g**[c]	35[d]	17
8[c]		NO_2	Br	**4e**	**5h**[c]	34[d]	62
9[c]	**1d**	Cl	Br	**4f**	**5i**[c]	38[d]	46

[a] Isolated yield. [b] Determined by ^{1}H NMR of the crude product. [c] See ref. 16*b*. [d] Inseparable mixture of *trans* and *cis* cycloadducts.

A,[25] in which the addition of the dipole to the less hindered face of the imine, opposite to the first formed triazole, gave the *trans* diastereoisomer (Fig. 4).

According to our previous work on 2-methyl-4-phenyl-3*H*-1,5-benzodiazepines **1d**, we assumed that the first intermediate of the process is the monocycloadduct which results from the dipole reaction with the most reactive imine function N1=C2.[16b,d] The loss in stereofacial discrimination may be rationalized by partial destabilization of the pseudo boat conformation **A** due to peri nonbonded interaction between the C4a- and N3-phenyl groups. The monocycloadduct may adopt a pseudo chair conformation **B**, in equilibrium with **A**, in which attack of the dipole on the less hindered face, opposite to the pseudo axial C3a-Me group, led to the *cis* diastereoisomer.

Conclusion

In conclusion, we have achieved an efficient one-step synthesis of new bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepines by way of completely regio- and diastereoselective 1,3-dipolar cycloaddition of nitrilimines to 2,4-dimethyl-3*H*-1,5-benzodiazepines. The steric course of this reaction was found to be dependent on the conformations of the benzodiazepine ring in the intermediate monocycloadduct. These conformations are controlled by peri nonbonded interaction according to the nature of the C4-substituent. This strategy is currently being extended to other dipoles and to various C4-substituents with the goal of generating a small library of new tetraheterocycles[26] of biological interests with a controlled stereochemistry.

Experimental

General

Melting points were taken in an open capillary tube on a Buchi 510 apparatus and are uncorrected. Spectra were recorded with the following instruments: ^{1}H NMR spectra: Brücker AC-250, ^{13}C NMR spectra: Brücker WP-200, Mass spectra: Jeol JMS DX 300. TMS was used as an internal reference. Column chromatography was carried out using E-Merck silica gel $60F_{254}$. Reagents and solvents were purified in the usual way.

General procedure for preparation of products 3, 5

To a solution of 1,5-benzodiazepine **1a**–**b**[13] (2.9 mmol) and ethylhydrazono-α-bromoglyoxylate **2**[18] or *N*-phenylarylohydrazonoyl chloride **4**[27] (4.6 mmol) in dry benzene (30 mL), triethylamine (0.8 mL, 6 mmol) dissolved in dry benzene (10 mL) was added dropwise. After stirring for 48 hours at room temperature, the mixture was washed several times with water (25 mL) and dried over anhydrous sodium sulfate. The organic layers were concentrated and the residue was chromatographed on a silica gel column (eluent: hexane/ethyl acetate), the isolated products were then recrystallized from ethanol.

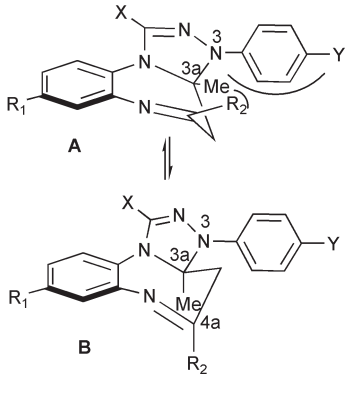


Fig. 4 Postulated conformations of intermediate monocycloadducts.

1,7-Diethoxycarbonyl-3a,4a-dimethyl-3,5-diparatolyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 3a. 3a is isolated from **2a** (R_3 = CH_3) and 1,5-benzodiazepine **1a** (R_1 = H). Yield 45%; m.p.: 148–150 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 6H, 2CH_3-CH_2-O), 1.74 (s, 6H, CH_3-C-3a, CH_3-C-4a), 2.29 (s, 6H, 2CH_3-Ar), 2.88 (s, 2H, CH_2-4), 4.31 (m, 4H, 2CH_3-CH_2-O), 6.87–7.25 (m, 12H, *H*-Ar); ^{13}C NMR ($CDCl_3$): δ 14.05 (2CH_3-CH_2-O), 20.72 (2CH_3-Ar), 24.14 (CH_3-C-3a, CH_3-C-4a), 44.01 (CH_2-4), 61.92 (2CH_3-CH_2-O), 88.50 (*C*-3a, *C*-4a), 118.79, 125.13, 125.32, 129.61, 132.43, 138.29, 139.23 (*C*=), 158.52 (2CO_2Et); MS(IS): *m*/*z* 580 ($[M]^+$, 100%).

3,5-Di-*p*-chlorophenyl-1,7-diethoxycarbonyl-3a,4a-dimethyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 3b. 3b is isolated from **2b** (R_3 = Cl) and 1,5-benzodiazepine **1a** (R_1 = H). Yield 50%; m.p.: 180–181 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 6H, 2CH_3-CH_2-O), 1.80 (s, 6H, CH_3-C-3a, CH_3-C-4a), 2.80 (s, 2H, CH_2-4), 4.25 (m, 4H, 2CH_3-CH_2-O), 6.75–7.2 (m, 12H, *H*-Ar); ^{13}C NMR ($CDCl_3$): δ 14.40 (2CH_3-CH_2-O), 25.07 (CH_3-C-3a, CH_3-C-4a), 44.30 (CH_2-4), 62.62 (2CH_3-CH_2-O), 88.57 (*C*-3a, *C*-4a), 119.19, 125.35, 125.99, 127.90, 129.55, 131.72, 138.95, 140.39 (*C*=), 158.65 (2CO_2Et); MS(IS): *m*/*z* 621 ($[M]^+$, 100%).

1,7-Diethoxycarbonyl-3a,4a-dimethyl-3,5-di-*p*-nitrophenyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 3c. 3c is isolated from **2c** (R_3 = NO_2) and 1,5-benzodiazepine **1a** (R_1 = H). Yield 65%; m.p.: 288–290 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 6H, 2CH_3-CH_2-O), 2.15 (s, 6H, CH_3-C-3a, CH_3-C-4a), 3.00 (s, 2H, CH_2-4), 4.30 (m, 4H, 2CH_3-CH_2-O), 6.75–8.00 (m, 12H, *H*-Ar); ^{13}C NMR ($CDCl_3$): δ 14.38 (2CH_3-CH_2-O), 26.02 (CH_3-C-3a, CH_3-C-4a), 46.67 (CH_2-4), 63.36 (2CH_3-CH_2-O), 88.04 (*C*-3a, *C*-4a), 114.32, 124.44, 126.11, 126.27, 129.42, 139.45, 141.17, 145.74 (*C*=), 158.34 (2CO_2Et); MS(IS): *m*/*z* 642 ($[M]^+$, 90%), 263 (100%).

1,7-Diethoxycarbonyl-3a,4a,10-trimethyl-3,5-di-*p*-tolyl-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 3d. 3d is isolated from **2a** (R_3 = CH_3) and 1,5-benzodiazepine **1b** (R_1 = CH_3). Yield 88%; m.p.: 175-177 °C (ethanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 6H, 2CH_3-CH_2-O), 1.72 (s, 6H, CH_3-C-3a, CH_3-C-4a), 2.28 (s, 9H, 3CH_3-Ar), 2.77 (d, J = 14.8 Hz, 1H, AB, CH_2-4), 2.95 (d, J = 14.8 Hz, 1H, AB, CH_2-4), 4.31 (m, 4H, 2CH_3-CH_2-O), 6.64-7.26 (m, 11H, *H*-Ar); ^{13}C NMR ($CDCl_3$): δ 14.16 (2CH_3-CH_2-O), 20.77, 20.82, 21.13 (3CH_3-Ar), 23.89, 24.45 (CH_3-C-3a, CH_3-C-4a,), 44.04 (CH_2-4), 61.97 (2CH_3-CH_2-O), 88.25, 88.60 (*C*-3a, *C*-4a), 118.42, 119.27, 124.75, 125.80, 126.01, 128.65, 129.69, 132.14, 132.73, 133.25, 135.84, 138.40, 138.80, 139.35, 139.45 (*C*=), 158.59, 158.76 (2CO_2Et); MS(IS): *m*/*z* 595 ($[M + H]^+$, 100%).

3,5-Di-*p*-chlorophenyl-1,7-diethoxycarbonyl-3a,4a,10-trimethyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 3e. 3e is isolated from **2b** (R_3 = Cl) and 1,5-benzodiazepine **1b** (R_1 = CH_3). Yield 60%; m.p.: 187–189 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 6H, 2CH_3-CH_2-O), 1.83 (s, 6H, CH_3-C-3a, CH_3-C-4a), 2.29 (s, 3H, CH_3-Ar), 2.77 (br d, 1H, AB, CH_2-4), 2.91 (br d, 1H, AB, CH_2-4), 4.31 (m, 4H, 2CH_3-CH_2-O), 6.62-7.26 (m, 11H, *H*-Ar); ^{13}C NMR ($CDCl_3$): δ 14.08 (2CH_3-CH_2-O), 21.06 (CH_3-Ar), 24.40, 24.95 (CH_3-C-3a, CH_3-C-4a,), 43.91 (CH_2-4), 62.21 (2CH_3-CH_2-O), 87.92, 88.23 (*C*-3a, *C*-4a),

118.36, 119.13, 124.65, 125.59, 126.11, 127.13, 127.66, 127.97, 129.18, 132.06, 136.03, 138.64, 138.99, 140.13 (*C*=), 158.30, 158.43 (2*C*O$_2$Et); MS(IS): *m*/*z* 635 ([M]$^+$, 100%).

1,7-Diethoxycarbonyl-3a,4a,10-trimethyl-3,5-di-*p*-nitrophenyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 3f. 3f is isolated from **2c** (R$_3$ = NO$_2$) and 1,5-benzodiazepine **1b** (R$_1$ = CH$_3$). Yield 70%; m.p.: 282–283 °C (ethanol); ^{1}H NMR (CDCl$_3$): *δ* 1.37 (t, 6H, 2C*H*$_3$-CH$_2$-O), 2.20 (s, 6H, C*H*$_3$-C-3a, C*H*$_3$-C-4a), 2.30 (s, 3H, C*H*$_3$-Ar), 3.08 (br d, 1H, AB, C*H*$_2$-4), 3.16 (br d, 1H, AB, C*H*$_2$-4), 3.70 (m, 4H, 2CH$_3$-C*H*$_2$-O), 6.70-8.13 (m, 11H, *H*-Ar); ^{13}C NMR (CDCl$_3$): *δ* 14.12 (2*C*H$_3$-CH$_2$-O), 21.05 (*C*H$_3$-Ar), 25.60, 25.67 (*C*H$_3$-C-3a, *C*H$_3$-C-4a,), 46.38 (*C*H$_2$-4), 63.02 (2CH$_3$-*C*H$_2$-O), 87.58, 87.66 (*C*-3a, *C*-4a), 113.91, 114.10, 124.30, 125.06, 125.83, 126.33, 126.65, 129.21, 136.29, 139.28, 139.41, 140.75, 140.86, 145.54 (*C*=), 158.15, 158.16 (2*C*O$_2$Et); MS(IS): *m*/*z* 657 ([M + H]$^+$, 28%), 210 (100%).

3a,4a-Dimethyl-1,3,5,7-tetraphenyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 5a. 5a is isolated from **4a** (R$_3$ = H) and 1,5-benzodiazepine **1a** (R$_1$ = H). Yield 60%, mp: 176–178 °C (ethanol); ^{1}H NMR (CDCl$_3$): *δ* 1.60 (s, 6H, C*H*$_3$-C-3a, C*H*$_3$-C-4a), 2.93 (s, 2H, C*H*$_2$-4), 6.91–7.46 (m, 24H, *H*-Ar); ^{13}C NMR (CDCl$_3$): *δ* 22.50 (*C*H$_3$-C-3a, *C*H$_3$-C-4a), 42.04 (*C*H$_2$-4), 86.64 (*C*-3a, *C*-4a), 118.51, 121.71, 126.41, 127.25, 128.51, 128.81, 129.03, 129.46, 143.93, 148.96 (*C*=); MS(IS): *m*/*z* 561 ([M + H]$^+$, 80%), 197 (100%).

3a,4a-Dimethyl-3,5-diphenyl-1,7-di-*p*-tolyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 5b. 5b is isolated from **4b** (R$_3$ = CH$_3$) and 1,5-benzodiazepine **1a** (R$_1$ = H). Yield 33%; m.p.: 210–212 °C (ethanol); ^{1}H NMR (CDCl$_3$): *δ* 1.58 (s, 6H, C*H*$_3$-C-3a, C*H*$_3$-C-4a), 2.35 (s, 6H, 2C*H*$_3$-Ar), 2.93 (s, 2H, C*H*$_2$-4), 6.90–7.35 (m, 22H, *H*-Ar); ^{13}C NMR (CDCl$_3$): *δ* 21.55 (*C*H$_3$-C-3a, *C*H$_3$-C-4a, 2*C*H$_3$-Ar), 42.16 (*C*H$_2$-4), 86.51 (*C*-3a, *C*-4a), 118.50, 121.68, 126.01, 126.28, 127.26, 129.01, 129.19, 139.61, 144.07, 149.04 (*C*=); MS(IS): *m*/*z* 589 ([M + H]$^+$, 100%).

1,7-Di-*p*-chlorophenyl-3a,4a-dimethyl-3,5-diphenyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 5c. 5c is isolated from **4c** (R$_3$ = Cl) and 1,5-benzodiazepine **1a** (R$_1$ = H). Yield 40%; m.p.: 249–250 °C (ethanol); ^{1}H NMR (CDCl$_3$): *δ* 1.59 (s, 6H, C*H*$_3$-C-3a, C*H*$_3$-C-4a), 2.95 (s, 2H, C*H*$_2$-4), 6.94–7.33 (m, 22H, *H*-Ar); ^{13}C NMR (CDCl$_3$): *δ* 21.58 (*C*H$_3$-C-3a, *C*H$_3$-C-4a), 41.84 (*C*H$_2$-4), 86.85 (*C*-3a, *C*-4a), 118.38, 121.95, 122.21, 127.30, 128.35, 128.81, 129.12, 135.45, 143.67, 148.11 (*C*=); MS(IS): *m*/*z* 629 ([M]$^+$, 100%).

3a,4a,10-Trimethyl-1,3,5,7-tetraphenyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 5d. 5d is isolated from **4a** (R$_3$ = H) and 1,5-benzodiazepine **1b** (R$_1$ = CH$_3$). Yield 84%; m.p.: 187–188 °C (ethanol); ^{1}H NMR (CDCl$_3$): *δ* 1.57, 1.62 (2 × s, 2 × 3H, C*H*$_3$-C-3a, C*H*$_3$-C-4a), 2.14 (s, 3H, C*H*$_3$-Ar), 2.84 (br d, 1H, AB, C*H*$_2$-4), 2.95 (br d, 1H, AB, C*H*$_2$-4), 6.66–7.48 (m, 23H, *H*-Ar); ^{13}C NMR (CDCl$_3$): *δ* 21.18 (*C*H$_3$-C-3a, *C*H$_3$-C-4a, *C*H$_3$-Ar), 41.92 (*C*H$_2$-4), 86.21, 86.85 (*C*-3a, *C*-4a), 117.81, 118.93, 121.14, 121.99, 127.16, 127.37, 128.46, 128.52, 128.82, 129.01, 129.04, 129.42, 143.95, 144.04, 149.09, 149.35 (*C*=); MS(IS): *m*/*z* 575 ([M + H]$^+$, 100%).

3a,4a,10-Trimethyl-3,5-diphenyl-1,7-di-*p*-tolyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 5e. 5e is isolated from **4b** (R$_3$ = CH$_3$) and 1,5-benzodiazepine **1b** (R$_1$ = CH$_3$). Yield 56%; m.p.: 258–260 °C (ethanol); ^{1}H NMR (CDCl$_3$): *δ* 1.55, 1.59 (2 × s, 2 × 3H, C*H*$_3$-C-3a, C*H*$_3$-C-4a), 2.15 (s, 3H, C*H*$_3$-Ar), 2.35 (s, 6H, 3C*H*$_3$-Ar), 2.84 (br d, 1H, AB, C*H*$_2$-4), 2.93 (br d, 1H, AB, C*H*$_2$-4), 6.66–7.37 (m, 21H, *H*-Ar); ^{13}C NMR (CDCl$_3$): *δ* 21.20, 21.55 (*C*H$_3$-C-3a, *C*H$_3$-C-4a, 3*C*H$_3$-Ar), 41.95 (*C*H$_2$-4), 86.06, 86.69 (*C*-3a, *C*-4a), 117.86, 119.03, 120.95, 126.02, 126.23, 127.16, 127.35, 128.98, 129.12, 129.17, 139.51, 139,53, 144.08, 144.17, 149.19, 149.43 (*C*=); MS(IS): *m*/*z* 603 ([M + H]$^+$, 100%).

1,7-Di-*p*-chlorophenyl-3a,4a,10-trimethyl-3,5-diphenyl-3a,4a,8,13-tetrahydro-4*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]benzodiazepine 5f. 5f is isolated from **4c** (R$_3$ = Cl) and 1,5-benzodiazepine **1b** (R$_1$ = CH$_3$). Yield 60%; m.p.: 270–271 °C (ethanol); ^{1}H NMR (CDCl$_3$): *δ* 1.55, 1.62 (2 × s, 2 × 3H, C*H*$_3$-C-3a, C*H*$_3$-C-4a), 2.19 (s, 3H, C*H*$_3$-Ar), 2.80 (br d, 1H, AB, C*H*$_2$-4), 2.93 (br d, 1H, AB, C*H*$_2$-4), 6.65-7.64 (m, 21H, *H*-Ar); ^{13}C NMR (CDCl$_3$): *δ* 21.26 (*C*H$_3$-C-3a, *C*H$_3$-C-4a, *C*H$_3$-Ar), 41.70 (*C*H$_2$-4), 86.42, 87.03 (*C*-3a, *C*-4a), 127.31, 127.52, 128.23, 128.49, 128.75, 128.82, 129.09, 129.12, 135.39, 143.68, 143.77 (*C*=); MS(IS): *m*/*z* 643 ([M]$^+$, 19%), 214 (100%).

Crystallographic structural determination

Data for **3b** were collected, at room temperature, using a Kappa CCD diffractometer with an Mo-K$_\alpha$ irradiation source. The structure was solved by direct methods using SHELXS 97.[23] Refinement, based on F^2, was carried out by full matrix least squares with SHELXL-97[24] software. The asymmetric unit contains two crystallographically independent molecules. Non hydrogen atoms were refined anisotropically. The hydrogen atoms were positioned geometrically and refined riding on their carrier atom with isotropic thermal displacement parameters fixed at 1.2 times those of their parent atoms. Convergence was reached at $R_1 = 0.061$ for 4097 reflections ($I > 2\sigma(I)$), $wR2 = 0.155$ for all data and $S = 1.06$ for 775 parameters. The residual electron density in the final difference Fourrier does not show any feature above 0.673 e.Å^{-3} and below −0.318 e.Å^{-3}.

CCDC reference number 208973. See http://www.rsc.org/suppdata/nj/b3/b303995c/ for crystallographic files in CIF or other electronic format.

Acknowledgements

The authors express their gratitude to Dr Martine Nierlich for assistance with crystallographic studies.

References

1 G. A. Archer and L. H. Sternbach, *Chem. Rev.*, 1968, **68**, 747.
2 T. A. Hamor and I. L. Martin in *Progress in Medicinal Chemistry*, eds. G. P. Ellis and G. B. West, Elsevier Science Publishers, Amsterdam, 1983, vol. 20.
3 R. Langnickel, R. Bluth and T. Ott, *Pharmazie*, 1986, **41**, 689.
4 A. L. Parola, H. I. Yamamura and H. E. Laird, *Life Sci.*, 1993, **52**, 1329.
5 S. Michelini, G. B. Cassano, F. Frare and G. Perugi, *Pharmacopsychiatry*, 1996, **29**, 127.
6 (*a*) J. Knabe, H. P. Buech and S. Bender, *Arch. Pharm.*, 1995, **328**, 59; (*b*) R. N. Brogden, R. C. Heel, T. M. Speight and G. S. Avery, *Drugs*, 1980, **20**, 161.
7 K. S. Atwal, J. L. Bergey, A. Hedberg and S. Moreland, *J. Med. Chem.*, 1987, **30**, 635.
8 (*a*) V. Merluzzi, K. D. Hargrave, M. Labadia, K. Grozinger, M. Skoog, J. C. Wu, C.-K. Shih, K. Eckner, S. Hattox, J. Adams, A. S. Rosenthal, R. Faanes, R. J. Eckner, R. A. Koup and J. L. Sullivan, *Science*, 1990, **250**, 1411; (*b*) M. Di Braccio, G. Grossi, G. Roma, L. Vargiu, M. Mura and M. E. Marongiu, *Eur. J. Med. Chem.*, 2001, **36**, 935.
9 (*a*) W. Werner, J. Baumgart, G. Burckhardt, W. F. Fleck, K. Geller, W. Gutsche, H. Hanschmann, A. Messerschmidt and W. Roemer, *Biophys. Chem.*, 1990, **35**, 271; (*b*) D. A. Claremon, N. Liverton, H. G. Selnick and G. R. Smith, PCT Int. Appl. WO 9640653.

10 For a presentation of the concept of "privileged scaffold" see B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber and P. S. Anderson, *J. Comb. Chem.*, 2000, **5**, 513.

11 M. E. Tranquillini, P. G. Cassara, M. Corsi, G. Curotto, D. Donati, G. Finizia, G. Pentassuglia, S. Polinelli, G. Tarzia, A. Ursini and F. T. M. Van Amsterdam, *Arch. Pharm.*, 1997, **330**, 353.

12 M. J. Batchelor, D. Bebbington, G. W. Bemis, W. H. Fridman, R. J. Gillespie, J. M. C. Golec, D. J. Lauffer, D. J. Livingston, S. S. Matharu, M. D. Mullican, M. A. Murcko, R. Murdoch, and R. E. Zelle, PCT US Appl. US96-598332.

13 J. A. Barltrop, C. G. Richards, D. M. Russel and G. J. Ryback, *J. Chem. Soc.*, 1959, 1132.

14 S. L. Schreiber, *Science*, 2000, **287**, 1964.

15 It has been shown that the addition of fused 5-membered heterocycles onto 1,4-benzodiazepines increases their CNS depressant activity. J. B. Hester Jr., A. D. Rudzik and B. V. Kamdar, *J. Med. Chem.*, 1971, **14**, 1078.

16 (*a*) A. Baouid, S. Elhazazi, A. Hasnaoui, P. Compain, J.-P. Lavergne and F. Huet, *New J. Chem.*, 2001, **25**, 1479; (*b*) M. Essaber, A. Baouid, A. Hasnaoui, A. Benharref and J.-P. Lavergne, *Synth. Commun.*, 1998, **28**, 4097; (*c*) R. Benelbaghdadi, A. Hasnaoui, J.-P. Lavergne, M. Giorgi and M. Pierrot, *Synth. Commun.*, 1998, **28**, 4221; (*d*) A. Baouid, A. Benharref, A. Hasnaoui and J.-P. Lavergne, *Bull. Soc. Chim. Belg.*, 1994, **103**, 743; (*e*) R. Jalal, M. El Messaoudi, A. Hasnaoui, M. Esseffar, M. Selkti, J.-P. Lavergne and P. Compain, *New J. Chem.*, 2002, **26**, 1545.

17 For a review on nitrilimines see G. Bertrand and C. Wentrup, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 527.

18 B. Sharp and C. S. Hamilton, *J. Am. Chem. Soc.*, 1946, **68**, 588.

19 M. Begtrup, J. Elguero, R. Faure, P. Camps, C. Estopa, D. Ilavsky, A. Fruchier, C. Marzin and J. Mendoza, *Magn. Reson. Chem.*, 1988, **26**, 134.

20 (*a*) J. Bastide and O. Henri-Rousseau, *Bull. Chem. Soc. Fr.*, 1973, 2290; (*b*) K. N. Houk, J. Sims, R. E. Duke Jr., R. W. Strozier and J. K. George, *J. Am. Chem. Soc.*, 1973, **95**, 7301.

21 For a related example of *anti* addition see M. C. Aversa, P. Bonaccorsi, P. Giannetto and D. A. Leigh, *J. Heterocycl. Chem.*, 1989, **26**, 1619.

22 Single crystals suitable for X-ray crystallographic measurement were obtained by slow evaporation of solution of compound **3b** in CH_2Cl_2/ethanol (20 : 80) mixture. Crystal Data for **3b**: formula $C_{31}H_{30}Cl_2N_6O_4$ monoclinic, space group $P2_1/c$; $a = 16.749(3)$, $b = 23.587(5)$, $c = 17.758(4)$ Å, $\beta = 116.76(3)^\circ$, $V = 6264(2)$ Å^3, $Z = 8$, 4102 independent reflections, 4097 with $I > 2\sigma(I)$, $R1 = 0.0614$, $wR2 = 0.1549$. The structure was solved by SHELXS-97[23] and refined using SHELXL-97.[24].

23 G. M. Sheldrick, *SHELXS-97, Program for solution of crystal structures*, University of Göttingen, Germany, 1997.

24 G. M. Sheldrick and T. R. Schneider, *SHELXL, High resolution refinement*, in *Methods in Enzymology, 277*, eds. C. W. Carter, Jr and L. M. Sweet, Academic Press, San Diego, 1997, pp. 319–343.

25 H. Tucker and D. J. Le Count, *Comprehensive Heterocyclic Chemistry II*, eds. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Elsevier Science Inc.; New York, 1996, Vol. 9, pp. 151–182.

26 For a recent review on the combinatorial synthesis of bicyclic privileged scaffold including 1,5-benzodiazepine-2-ones see D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.

27 R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, 1962, **17**, 3.