Letter

Synthesis of a novel heterocyclic ring system by way of highly regio- and chemoselective 1,3-dipolar cycloaddition of nitrilimines to 1,3,4-benzotriazepin-5-one derivatives

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The 1,3-dipolar cycloaddition reaction of nitrilimines to 3,4-dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-ones 1 led, with complete regio- and chemoselectivity, to [1,2,4]triazolo[1,3,4]-benzotriazepines 3, the structures of which were assigned by spectral methods and X-ray crystallographic analysis.

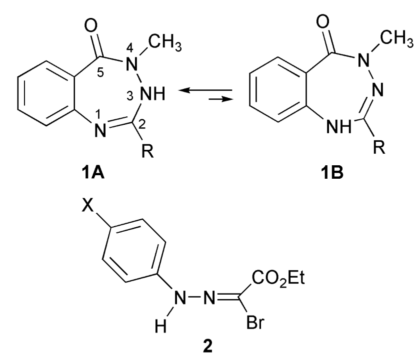
Owing to their well-established role as psychotherapeutics,[1] benzodiazepines have been the object of intense investigation in medicinal chemistry. The area of biological interest of this family of compounds has been extended recently to various diseases such as cancer,[2] viral infections (HIV)[3] and cardiovascular disorders.[4] Such a versatile biological activity of the benzodiazepine pharmacophore have prompted investigations into their nitrogen homologues, the benzotriazepines,[5] in order to find new therapeutical leads. The fusion of heterocyclic rings to different faces of the heptatomic nucleus was shown to enhance or modify activity profiles.[6]

The 1,3-dipolar cycloaddition reaction constitutes one of the most important classes of organic reactions and is a versatile and powerful preparative method for the synthesis of heterocyclic compounds.[7a–c] The five-membered cycloadducts involve a 4π-2π electron balance. The 2π unit is usually a system containing a double bond (A=B) or a triple bond (A≡B), where A and B could be any element of the main group. In view of such a myriad of possibilities, much effort has been devoted during the last two decades towards the development of synthetic methods using heteroatomic systems.[7] In addition, 1,3-dipolar cycloadditions are reactions of choice for performing "click chemistry",[8] a strategy introduced recently by Sharpless *et al.* to accelerate the discovery of substances with useful properties.

In this context and as part of our continuing studies on 1,2-diazepine and 1,2,4-triazepine ring systems,[9] we were interested in the reactivity of 1,3,4-benzotriazepin-5-ones **1** as dipolarophiles towards nitrilimines[10] in order to access rapidly new benzotriazepines of biological interest. In particular, it is noteworthy that **1** contains two possible dipolarophile sites: N1=C2 and C2=N3 according to the two tautomeric forms **1A** and **1B** that may exist in equilibrium, even though **1A** is the only form observed in solution (Scheme 1).[11,12]

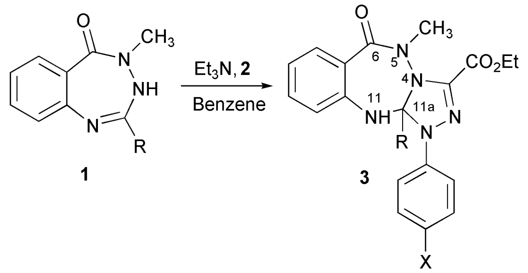
The reaction of 1,3,4-benzotriazepin-5-ones **1** with a slight excess of various *N*-aryl-*C*-ethoxycarbonylnitrilimines, generated *in situ* from ethylhydrazono-α-bromoglyoxylate **2** and triethylamine,[13] was performed in dry benzene at room temperature during one week (Table 1).

After purification by flash chromatography, [1,2,4]triazolo[1,3,4]benzotriazepines **3** were isolated in 18 to 44% yield; 50 to 75% of the dipolarophile **1a** and **1b** were recovered, respectively, along with slight amounts of nitrilimine dimerisation products. Heterocycles **3** result from a regiospecific 1,3-dipolar cycloaddition of nitrilimines to the C=N bond of **1B**. The formation of the isomeric triazolobenzotriazepines from the tautomeric form **1A**, by cycloaddition of the nitrilimine across the 1,2 position of the benzotriazepine ring instead of the 2,3 position, was never observed. The nature of the X substituent on the phenyl group of the nitrilimines had no remarkable influence on the reaction yield. In contrast, the R substituent directly bonded to the dipolarophile site had a dramatic influence on the reactivity of the dipolarophile. The reaction yields were approximatively halved for benzotriazepin-5-one **1b** (R = Ph) compared to **1a** (R = H). Moreover, for dipolarophile **1c** (R = Me), no conversion to the expected



Scheme 1

Table 1



Entry	1	R	2	X	3	Yield/%
1	**1a**	H	**2a**	CH_3	**3aa**	34
2	**1a**	H	**2b**	Cl	**3ab**	44
3	**1a**	H	**2c**	NO_2	**3ac**	36
4	**1b**	Ph	**2a**	CH_3	**3ba**	18
5	**1b**	Ph	**2b**	Cl	**3bb**	23

product was observed with dipoles **2a**–**c** (**1c** was completely recovered after flash chromatography). These results may be explained by steric hindrance, which prevents the approach of the nitrilimines to the dipolarophile site.

The structure elucidation of the cycloadducts **3aa**–**3bb**, were based on spectral data (^{1}H NMR, ^{13}C NMR and mass spectrometry) and X ray crystallographic analysis. Concerning the sense of addition of the nitrilimine dipoles, the chemical shift observed for C11a ($\delta \sim 91$ for R = H and $\delta \sim 105$ for R = Ph) Ph) ruled out unambiguously the formation of the other possible regioisomer, the C11a shift of which was expected to be around δ 60 and δ 90 for R = H and R = Ph, respectively. These results were confirmed by the singlet at δ 6.7–6.8 in the ^{1}H NMR spectra assigned to the proton at C11a for the benzotriazepines **3aa**–**3ac** (R = H). Even though the spectral data were in good agreement with the proposed structure, they did not enable a choice to be made between structure **3** and possible alternative regioisomeric structures (such as referred to above, by cycloaddition across the 1,2 positions of the benzotriazepine ring). The structure of the cycloadducts **3** could only be unambiguously determined on the basis of the X-ray crystallographic analysis of a single crystal of **3aa**[14] (Fig. 1) and **3ba**[15] (Fig. 2). The X-ray data indicate that the substitution of a proton by a phenyl group on C11a did not affect the arrangement of the triheterocyclic framework of **3** and that the central 7-membered ring was quasi-planar. Furthermore, the angle between the triazepine and the triazolo ring

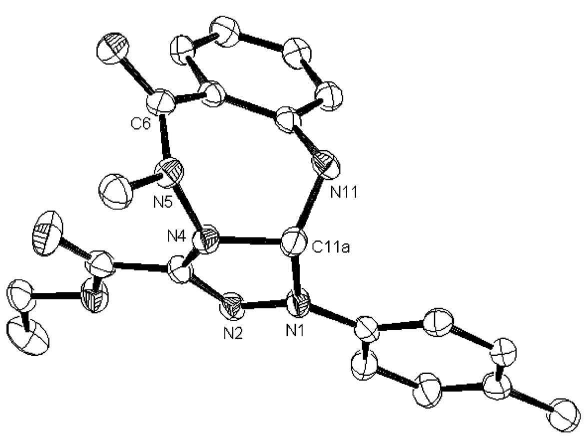


Fig. 1 Perspective ORTEP view of compound **3aa**.

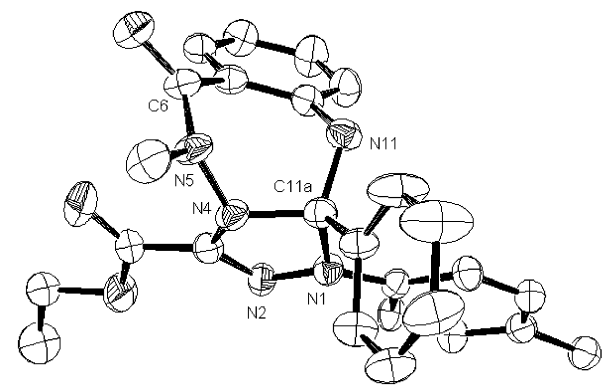
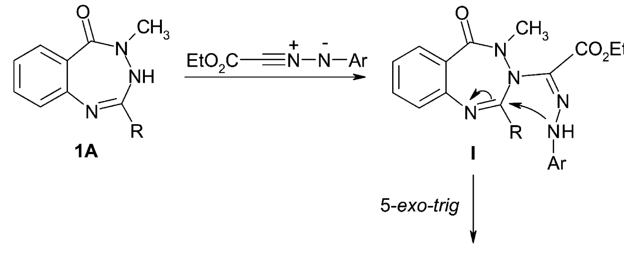


Fig. 2 Perspective ORTEP view of compound **3ba**.

was found to be in the same range for **3aa** and **3ba** (78° and 82°, respectively).

In all studied cases, the cycloaddition reaction was found to be completely regio- and chemoselective. The question of regioselectivity in 1,3-dipolar cycloadditions has been rationalized satisfactory by frontier molecular orbital (FMO) theory[16] and Sustmann has proposed a simple interaction model.[17] The sense of addition of the nitrilimine dipole to the C=N bond is that expected considering, for an electron-rich dipolarophile, the dipole LUMO-dipolarophile HOMO interactions.[16–18] The quite unexpected dramatic difference of reactivity between the two dipolarophile sites in the tautomeric forms **1A** and **1B**, which allowed the trapping of the imperceptible aminomethylene hydrazide **1B**, may be also explained with FMO theory.[19] Preliminary semiempirical calculations[20] indicated clearly that **1A** has a lower lying HOMO than **1B** ($\Delta E_{HOMO} \sim 1$ eV), resulting in a much less favored transition state arising from the dipole LUMO-dipolarophile HOMO interaction compared to **1B**. An alternative reaction pathway in two steps may, however, be formulated and involves a nucleophilic N–H addition of form **1A** on nitrilimines followed by a 5-*exo-trig* cyclization of the intermediate **I** to afford benzotriazepines **3** (Scheme 2). This mechanistic rationale could account for the observed regio- and chemoselectivity of the reaction but not for the complete recovery of compound **1c** (R = Me). As the nucleophilic N–H addition is not expected to be dramatically influenced by the R substituent, conversion of the starting material **1c** should therefore be observed and the intermediate **I** possibly isolated. This result argues in favor of the concerted cycloaddition pathway.

In conclusion, the 1,3-dipolar cycloaddition reaction of nitrilimines to 3,4-dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-ones **1** was found to be completely regio- and chemoselective and led to [1,2,4]triazolo[1,3,4]benzotriazepines **3**. The lower dipolarophile reactivity of *N*-iminomethyl hydrazide **1A** compared to its aminomethylene hydrazide tautomer **1B** allowed the trapping of the latter. This study is currently being



Scheme 2

extended to other dipoles with the goal of generating a small library of new benzotriazepine-based compounds of therapeutical interest. The new triheterocyclic structures **3** will be evaluated against various biological targets and the results obtained will be reported in due course.

Experimental

Uncorrected melting points were taken on a Buchi 510 apparatus. The ^{1}H NMR spectra were recorded with a Bruker WP 400 CW. Me_4Si was used as an internal standard and $CDCl_3$ as the solvent. The ^{13}C NMR spectra was measured on a Varian FT 80 (100 MHz). Mass spectra was recorded with a Jeol JMS DX 300. The X-ray structures were solved by SHELXS-97[21] and refined using SHELXL-97.[22] Column chromatography was carried out using E-Merck silica gel 60F 254. Reagents and solvents were purified in the usual way.

General procedure for the 1,3-dipolar cycloaddition reaction

Triethylamine (7.2 mmol) dissolved in dry benzene (10 ml) was added dropwise to a solution of 1,3,4-benzotriazepin-5-one **1** (5 mmol) and ethylhydrazono-α-bromoglyoxylate **2** (5.5 mmol) dissolved in dry benzene (30 ml). After stirring one week at room temperature, the reaction mixture was washed several times with water (25 ml) and the organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by chromatography on silica gel column (hexane–ethyl acetate). The isolated product **3** was recrystallized in ethanol.

Ethyl 5-methyl-6-oxo-1-(4-tolyl)-4,5,11,11a-tetrahydro-6*H*-[1,2,4]triazolo[3,4-b][1,3,4]benzotriazepine-3-carboxylate, 3aa. Yield: 34%. mp 174–176 °C (ethanol). ^{1}H NMR (400 MHz): 1.19 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 2.26 (s, 3H, $ArCH_3$), 3.45 (s, 3H, NCH_3), 4.16 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 4.71 (s, 1H, NH), 6.25 (d, $J = 7.6$ Hz, 1H, C10–H), 6.73 (s, 1H, C11a–H), 6.95–7.20 (m, 6H, ArH), 7.54 (d, $J = 7.5$ Hz, 1H, C7–H); ^{13}C NMR (100 MHz): 13.96 (OCH_2CH_3), 20.64 ($ArCH_3$), 37.32 (NCH_3), 61.84 (OCH_2), 91.85 (C11a), 115.76, 123.96, 124.84, 129.51, 129.85, 130.54, 131.76, 132.76, 138.60, 138.98, 139.90 (C3, CAr), 156.31 (CO_2Et), 172.21 (C6); MS (FAB) m/z: 380 $[M + H]^+$.

Ethyl 1-(4-chlorophenyl)-5-methyl-6-oxo-4,5,11,11a-tetrahydro-6*H*-[1,2,4]triazolo[3,4-b][1,3,4]benzotriazepine-3-carboxylate, 3ab. Yield: 44%. mp 183–185 °C (ethanol). ^{1}H NMR (400 MHz): 1.19 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 3.43 (s, 3H, NCH_3), 4.16 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 4.91 (s, 1H, NH), 6.27 (d, $J = 7.6$ Hz, 1H, C10–H), 6.71 (s, 1H, C11a–H), 6.97–7.23 (m, 6H, ArH), 7.53 (d, $J = 7.5$ Hz, 1H, C7–H); ^{13}C NMR (100 MHz): 13.89 ($O–CH_2–CH_3$), 37.22 (NCH_3), 62.00 (OCH_2), 91.43 (C11a), 116.52, 124.56, 125.27, 126.86, 129.17, 129.88, 130.46, 132.87, 139.35, 139.59 (C3, CAr), 156.20 (CO_2Et), 172.11 (C6); MS (FAB) m/z: 400 $[M + H]^+$.

Ethyl 5-methyl-1-(4-nitrophenyl)-6-oxo-4,5,11,11a-tetrahydro-6*H*-[1,2,4]triazolo[3,4-b][1,3,4]benzotriazepine-3-carboxylate, 3ac. Yield: 36%. mp 195–197 °C (ethanol); ^{1}H NMR (400 MHz): 1.23 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 3.47 (s, 3H, NCH_3), 4.22 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 4.88 (s, 1H, NH), 6.47 (d, $J = 7.5$ Hz, 1H, C10–H), 6.82 (s, 1H, C11a–H), 7.12–7.25 (m, 4H, ArH), 7.57 (d, $J = 7.2$ Hz, 1H, C7–H), 8.18 (d, $J = 9.2$ Hz, 2H, ArH); ^{13}C NMR (100 MHz): 13.97 (OCH_2CH_3), 37.31 (NCH_3), 62.57 (OCH_2), 90.50 (C11a), 113.50, 125.48, 125.76, 126.43, 130.58, 130.71, 133.26, 138.32, 141.10, 141.35, 145.92 (C3, CAr), 156.06 (CO_2Et), 171.80 (C6); MS (FAB) m/z: 411 $[M + H]^+$.

Ethyl 5-methyl-6-oxo-11a-phenyl-1-(4-tolyl)-4,5,11,11a-tetrahydro-6*H*-[1,2,4]triazolo[3,4-b][1,3,4]benzotriazepine-3-carboxylate, 3ba. Yield: 18.5%. mp 223–225 °C (ethanol); ^{1}H NMR (400 MHz): 1.30 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 2.29 (s, 3H, $ArCH_3$), 3.08 (s, 3H, NCH_3), 4.19–4.35 (m, 2H, OCH_2CH_3), 5.06 (s, 1H, NH), 6.18 (d, $J = 7.5$ Hz, 1H, C10–H), 6.90–7.60 (m, 9H, ArH), 7.68 (d, $J = 7.6$ Hz, 1H, C7–H), 7.95 (m, 2H, ArH); ^{13}C NMR (100 MHz): 14.49 (OCH_2CH_3), 21.12 ($ArCH_3$), 38.01 (NCH_3), 62.42 (OCH_2), 104.84 (C11a), 117.58, 123.83, 124.68, 128.06, 128.98, 129.54, 130.00, 130.34, 131.14, 132.85, 133.19, 137.20, 139.44, 139.95, 141.43 (C3, CAr), 156.83 (CO_2Et), 172.85 (C6); MS (FAB) m/z: 456 $[M + H]^+$.

Ethyl 1-(4-chlorophenyl)-5-methyl-6-oxo-11a-phenyl-4,5,11,11a-tetrahydro-6*H*-[1,2,4]triazolo[3,4-b][1,3,4]benzotriazepine-3-carboxylate, 3bb. Yield: 23%. mp 268–269 °C (ethanol); ^{1}H NMR (400 MHz): 1.35 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 3.07 (s, 3H, NCH_3), 4.25–4.35 (m, 2H, OCH_2CH_3), 5.11 (s, 1H, NH), 6.19 (d, $J = 7.5$ Hz, 1H, C10–H), 6.97–7.57 (m, 9H, ArH), 7.69 (d, $J = 7.72$ Hz, 1H, C7–H), 7.95 (m, 2H, ArH); ^{13}C NMR (100 MHz): 14.46 (OCH_2CH_3), 38.00 (NCH_3), 62.63 (OCH_2), 104.64 (C11a), 118.38, 123.89, 125.12, 127.87, 128.21, 129.26, 129.49, 129.76, 130.62, 131.24, 133.36, 137.76, 139.34, 140.51, 141.86 (C3, CAr), 156.69 (CO_2Et), 172.66 (C6); MS (FAB) m/z: 476 $[M + H]^+$.

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14 Crystal data for **3aa**: formula $C_{20}H_{21}N_5O_3$ monoclinic, space group $P2_1/c$; $a = 23.810(5)$, $b = 13.142(3)$, $c = 12.281(3)$ Å, $\beta = 99.48(3)°$, $V = 3290(1)$ Å^3, $Z = 8$, 6392 independent reflections, 3758 ($R_{int} = 0.063$) with $I > 2\sigma(I)$, $R_1 = 0.0665$, $wR_2 = 0.1637$. Compound **3aa** crystallizes with two independent molecules. CCDC reference number 194488. See http://www.rsc.org/suppdata/nj/b2/b204659h/ for crystallographic files in CIF or other electronic format.
15 Crystal data for **3ba**: formula $C_{26}H_{25}N_5O_3$ monoclinic, space group $P2_1/c$; $a = 8.063(2)$, $b = 14.142(3)$, $c = 19.642(4)$ Å, $\beta = 92.98(3)°$, $V = 2236(2)$ Å^3, $Z = 4$, 3662 independent reflections, 2021 ($R_{int} = 0.079$) with $I > 2\sigma(I)$, $R_1 = 0.0635$, $wR_2 = 0.1882$. CCDC reference number 194489. See http://www.rsc.org/suppdata/nj/b2/b204659h/ for crystallographic files in CIF or other electronic format.
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