

Intramolecular [2+3]-addition of an azide to a C=C double bond as a novel approach to piperazines

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Received 21 October 2004; revised 30 November 2004; accepted 10 December 2004

Available online 8 January 2005

Abstract—An intramolecular [2+3]-cycloaddition of an azide to a C=C double bond was carried out to obtain hexahydro-[1,2,3]triazolo[1,5-*a*]pyrazines. These compounds were used as intermediates to prepare 2-(halogenomethyl)piperazines that could serve as precursors for various condensed derivatives.

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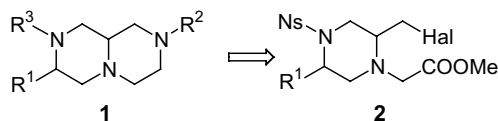
It was shown recently that hydrogenated pyrazino-[1,2-*a*]pyrazine derivatives **1** can serve as a new type of β -turn mimetic.¹ The shortest way to obtain the heterocyclic system **1** is the transformation of 1,4-protected piperazines **2** containing a functional group at one of the carbon atoms² (Scheme 1). However, methods for the synthesis of these monocyclic derivatives **2** include many steps and are extremely laborious, especially the preparation of 2,5-disubstituted piperazines.

In this letter we report a novel approach to the functionalized piperazines **2**, by formation of the hexahydro-[1,2,3]triazolo[1,5-*a*]pyrazine bicyclic system **6** (Scheme 2). As anticipated, the reactive 1,2,3-triazoline ring in this system provides the means for the introduc-

tion of various functional groups into the piperazine ring by the action of electrophilic reagents.

In order to synthesize the key bicyclic system **6**, we used an intramolecular [2+3] cycloaddition of an azide group to a C=C double bond (Scheme 2). Some examples of this reaction can be found in the literature,³ however, these cyclizations were often accompanied by nitrogen evolution and in essence resulted in the formation of a C–N bond. On the contrary, a distinctive feature of our approach is the isolation of the hexahydro-[1,2,3]triazolo[1,5-*a*]pyrazines **6**, which can then be readily transformed into the target piperazines **7** by the action of alkylating or acylating reagents.

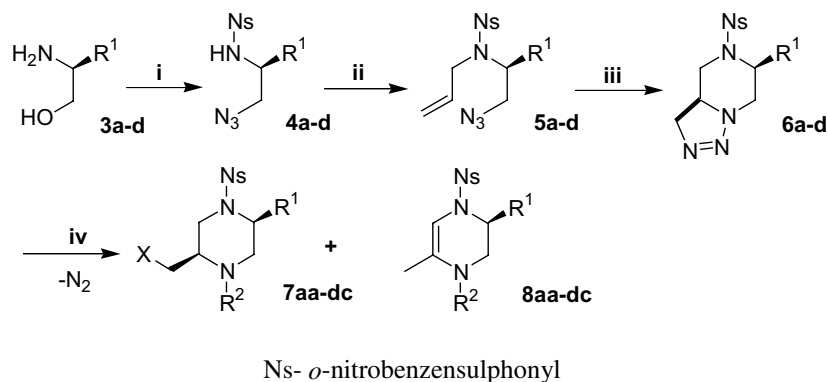
In order to synthesize bicyclic intermediates **6**, we used the readily available amino alcohols **3** as starting compounds. The transformation of the hydroxy group into the azide (**3**→**4**) was carried out by the conventional method after introducing an *N*-*o*-nitrobenzenesulfonyl group, chosen for this purpose as the most convenient for each step of the synthesis.⁴ The subsequent *N*-allylation of azides **4** was carried out under very mild conditions using K₂CO₃/18-crown-6 as base. It is noteworthy that *N*-allyl derivatives **5** turned out to be unstable. Upon isolation, they underwent polymerization within 1–2 h. We found that keeping *N*-allyl derivatives **5** in dilute solutions was optimal for the cyclization (**5**→**6**). The yields of triazolines **6** are shown



Scheme 1. Formation of the hydrogenated pyrazino[1,2-*a*]pyrazines. R¹ = alkyl; R², R³ = alkyl, aryl, etc.

Keywords: Piperazines; Azides; Intramolecular cycloaddition; 1,2,3-Triazolines.

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Scheme 2. Reagents and conditions: (i) (a) NsCl, aq NaHCO₃, EtOAc; (b) MsCl, TEA, CH₂Cl₂; (c) NaN₃, DMF; (ii) allyl bromide, K₂CO₃, 18-crown-6, MeCN; (iii) MeCN, 1–14 days rt; (iv) R²Hal, MeCN.

Table 1. Preparation of triazolines **6a–d**

	R ¹	Time, days	6 Yield (%)
6a	H	4–5	43
6b	Me	10–14	35
6c	<i>i</i> Pr	1–2	77
6d	Bn	6–9	34

in Table 1. It appears that bulky substituents R¹ facilitate the cyclization, and the best results were obtained with valinol as a starting amino alcohol (3, R¹ = *i*-Pr).

Triazolines **6** are crystalline compounds stable at 0 °C for several months. They can also be stored for a long time as solutions in aprotic solvents such as MeCN or CH₂Cl₂. The structures of compounds **6** were confirmed by ¹H NMR and ¹³C NMR spectroscopic analysis.⁵ The assignment of the ¹H and ¹³C NMR spectra involved ¹H–¹H COSY, ¹H–¹³C HMBC, and ¹H–¹³C HSQC experiments. In addition, X-ray crystallographic analysis unambiguously confirmed the structures of compounds **6a** and **6d** (Fig. 1).⁶ In all cases, a stereo-specific cyclization reaction occurred resulting in *cis*-2,5-disubstituted piperazine derivatives. The triazolines **6** turned out to be unstable in the presence of acids, even as weak as alcohols.⁷ Contact with silica gel gave rise to decomposition of **6** accompanied by violent nitrogen evolution, as has been reported for analogous triazolines.^{3a}

The target 2-(halogenomethyl)piperazines **7** were successfully synthesized from intermediates **6** in reactions with acyl chlorides, carbamoyl chlorides, and alkyl halides. It should be noted that while the reactions with acyl chlorides proceed almost instantly, alkyl halides reacted much more slowly. Thus, we succeeded in obtaining positive results only for the most reactive compounds, such as methyl iodide,⁸ benzyl bromide,⁹ allyl bromide, and ethyl bromoacetate. No reactions were observed with benzyl chloride, *n*-butyl bromide, and cyclopropylmethyl bromide. The best yield of compounds **7** was obtained using CbzCl as electrophile (Table 2). In most cases, tetrahydropyrazines **8** (which

Table 2. Preparation of halides **7aa–dc**

No.	R ¹	R ²	X	Yield (%)	Yield 8aa–dc (%)
7aa	H	CH ₂ Ph	Br	87	5
7ba	Me	CH ₂ Ph	Br	78	6
7ca	<i>i</i> Pr	CH ₂ Ph	Br	93	7
7da	Bn	CH ₂ Ph	Br	89	11
7ab	H	COOCH ₂ Ph	Cl	89	11
7bb	Me	COOCH ₂ Ph	Cl	76	14
7cb	<i>i</i> Pr	COOCH ₂ Ph	Cl	95	0
7db	Bn	COOCH ₂ Ph	Cl	88	0
7ac	H	COPh	Cl	57	10
7bc	Me	COPh	Cl	45	13
7cc	<i>i</i> Pr	COPh	Cl	87	0
7dc	Bn	COPh	Cl	62	0

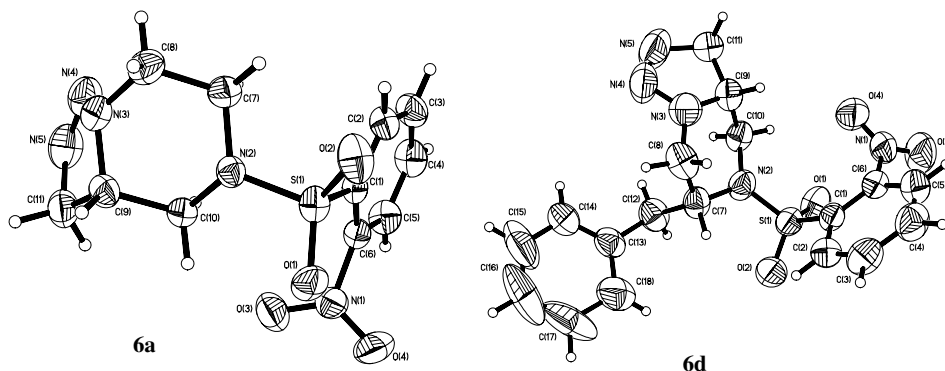


Figure 1. ORTEP drawings of triazolines **6a** and **6d**.

can be obtained from halides **7** by exposure to various bases) were obtained as side products along with the target compounds **7**.

Thus, quite stable triazolopiperazines **6** can be obtained by intramolecular [2+3] cycloaddition of the azide group in **5** to the C=C bond. The reaction proceeds stereoselectively in acceptable yields. We showed that the halogenomethyl derivatives **7** as precursors for the hydrogenated pyrazino[1,2-*a*]pyrazines can be obtained by a previously unknown reaction of triazolines **6** with alkyl and acyl halides.

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- Typical procedure for **6b**: Azide **4d** (3.0 g, 8 mmol) was dissolved in acetonitrile (50 mL) and K_2CO_3 (2.3 g, 16 mmol), allyl bromide (1.4 g, 10 mmol) and then 18-crown-6 (0.4 g, 2 mmol) were added to the mixture, which was then stirred for 3 h at room temperature. The solvent was evaporated, and the residue was purified by chromatography (alumina, hexane/dichloromethane 1:1). Compound **5d** was obtained and kept as a solution in acetonitrile (200 mL) until complete cyclization to triazoline **6d**, which was crystallized from hexane/ethyl acetate mixture (2:1) to afford **6d** (1.1 g, 34%). 1H NMR ($CDCl_3$, 400 MHz): δ 2.73 (1H, dd, $J = 13.3$ Hz, $J = 5.6$ Hz, 6- CH_2 Ph), 2.83 (1H, dd, $J = 13.3$ Hz, $J = 9.6$ Hz, 6- CH_2 Ph), 3.05 (1H, dd, $J = 14.1$ Hz, $J = 11.6$ Hz, 4H_{ax}), 3.52 (1H, dd, $J = 14.1$ Hz, $J = 5.0$ Hz, 4-H_{eq}), 3.65 (1H, m, 7-H_{ax}), 3.77 (1H, m, 3a-H), 4.01 (1H, dd, $J = 16.1$ Hz, $J = 9.8$ Hz, 3-H_A), 4.08 (1H, m, 6-H), 4.17 (1H, dd, $J = 16.1$ Hz, $J = 3.2$ Hz, 3-H_B), 4.25 (1H, d, $J = 14.4$ Hz, 7-H_{eq}), 7.10–7.22 (5H, m, 6- CH_2 Ph), 7.60–7.70 and 7.92–7.94 (3H and 1H, m, 5-Ns). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.48 (6- CH_2 Ph), 40.81 (C-4), 46.42 (C-7), 52.44 (C-3a), 56.45 (C-6), 67.88 (C-3), 124.66, 130.95, 132.07, 133.74, 136.71, 147.42 (carbons of Ns), 126.88, 128.58, 129.47, 133.35 (Ph).
- Crystallographic data for compound **6a**: $C_{11}H_{13}N_5O_4S$, $M_r = 311.32$, monoclinic space group $P2(1)/n$, $a = 8.4690(17)$, $b = 8.4690(17)$, $c = 9.806(2)$ Å, $\alpha = 90^\circ$, $\beta = 110.56(3)^\circ$, $\gamma = 90^\circ$, $V = 1339.3(5)$ Å³, $Z = 4$, $T = 293(2)$ K, $F(000) = 648$, $\mu = 0.267$ mm⁻¹, $\theta_{max} = 27.79^\circ$, 2588 reflections measured and 2362 unique ($R_{int} = 0.0171$) reflections, full matrix least-squares refinement on F^2 , R_1 (obsd) = 0.0930, and wR_2 (all data) = 0.1090. Crystallographic data for compound **6d**: $C_{18}H_{19}N_5O_4S$, $M_r = 401.44$, monoclinic space group $P2(1)/n$, $a = 8.026(2)$, $b = 11.449(4)$, $c = 10.376(4)$ Å, $\alpha = 90^\circ$, $\beta = 97.08(2)^\circ$, $\gamma = 90^\circ$, $V = 946.2(5)$ Å³, $Z = 2$, $T = 293(2)$ K, $F(000) = 420$, $\mu = 0.207$ mm⁻¹, $\theta_{max} = 29.97^\circ$, 3066 reflections measured and 2856 unique ($R_{int} = 0.0171$) reflections, full matrix least-squares refinement on F^2 , R_1 (obsd) = 0.0932, and wR_2 (all data) = 0.1804. Supplementary data in the form of CIFs have been deposited with the Cambridge Crystallographic Data Centre (CCDC 249283 and 249284). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
- If dissolved in MeOH, the triazolines **6** transform within 3–4 h into complicated mixtures, from which compounds **7** ($X = OMe$, $R^2 = H$) can be isolated sometimes in ~15% yield.
- Iodomethylates **7** ($R^2 = Me$; $X = I$) were isolated when an excess of methyl iodide was used. In other cases, no quaternization was observed.
- Preparation of **7da** ($R^2 = Bn$; $X = Br$): A solution of benzyl bromide (0.2 g, 1.1 mmol) in acetonitrile (10 mL) was added dropwise to a solution of **6d** (0.5 g, 1 mmol) in acetonitrile (7 mL) under argon. After standing overnight, the acetonitrile was evaporated, and the residue was purified by chromatography on silica gel (hexane/dichloromethane in gradient 95:5 to 0:100 then dichloromethane/chloroform in gradient 95:5 to 0:100) to afford **7da** (0.6 g, 89%). 1H NMR ($CDCl_3$, 400 MHz): δ 2.15 (1H, dd, $J = 11.8$ Hz, $J = 3.6$ Hz, 6-H_A), 2.54 (1H, m, 2-H), 2.69 (1H, dd, $J = 11.8$ Hz, $J = 1.8$ Hz, 6-H_B), 2.87 (1H, dd, $J = 12.9$ Hz, $J = 5.2$ Hz, 5- CH_2 Ph), 2.90 (1H, d, $J = 12.5$ Hz, 1- CH_2 Ph), 3.10 (1H, dd, $J = 12.9$ Hz, $J = 9.4$ Hz, 5- CH_2 Ph), 3.54 (1H, m, 3-H_A), 3.56 (1H, m, 2- CH_2 Br), 3.76 (1H, m, 2- CH_2 Br), 3.80 (1H, m, 3-H_B), 3.94 (1H, m, 5-H), 4.16 (1H, d, $J = 12.5$ Hz, 1- CH_2 Ph), 6.79–6.82 and 6.97–7.00 (2H and 3H, m, 1- CH_2 Ph), 7.30–7.40 (5H, m, 5- CH_2 Ph), 7.60–7.65 and 7.88–7.91 (3H and 1H, m, 4-Ns). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.85 (2- CH_2 Br), 36.04 (5- CH_2 Ph), 45.27 (C-3), 52.16 (C-6), 56.40 (C-5), 56.87 (1- CH_2 Ph), 59.23 (C-2), 124.41, 130.91, 131.86, 133.36, 133.77, 147.54 (carbons of Ns), 126.24, 128.36, 129.24, 137.99 (1- CH_2 Ph), 127.39, 128.20, 129.59, 137.67 (5- CH_2 Ph).