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Tetrahedron Letters 47 (2006) 51–54
Tetrahedron Letters

Novel approach to the synthesis of perhydropyrazino[1,2-*a*]pyrazine derivatives from amino alcohols

Tatyana V. Lukina,[a] Sergey I. Sviridov,[b,*] Sergey V. Shorshnev,[b] Grigory G. Aleksandrov[b] and Aleksandr E. Stepanov[a]

[a]*M. V. Lomonosov Moscow State Academy of Fine Chemical Technology, Malaya Pirogovskaya 1, 119435 Moscow, Russian Federation*
[b]*ChemBridge Corporation, Malaya Pirogovskaya 1, 119435 Moscow, Russian Federation*

Received 16 August 2005; revised 12 October 2005; accepted 25 October 2005
Available online 11 November 2005

Abstract—2,4,7-Trisubstituted hydrogenated pyrazino[1,2-*a*]pyrazines as potential β-turn mimetics were prepared for the first time in a stereoselective synthesis from hexahydro[1,2,3]triazolo[1,5-*a*]pyrazines.
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The synthesis of new types of β-turn mimetics is of great interest in medicinal chemistry, as potential agonists/antagonists of various protein receptors. In the series of hydrogenated bicyclic heterocycles the derivatives of tetrahydro-2*H*-pyrazino[1,2-*a*]pyrimidine-4,7-diones[1] and bicyclic diketopiperazines[2] are known as such mimetics. Moreover, the related perhydropyrazino[1,2-*a*]pyrazines proved to have interesting biological activity.[3]

We report here, a novel stereoselective approach to 2,4,7-trisubstituted hexahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3(4*H*)-ones as a new class of such compounds. The method allows for the modification of the substituents R^1, R^2, and R^3 and, therefore, could lead to a great variety of products.

We used hexahydro[1,2,3]triazolo[1,5-*a*]pyrazines **1** as starting compounds, the synthesis of which from amino alcohols was developed recently in our laboratory (Scheme 1).[4] We showed that the cyclization is characterized by a high degree of diastereoselectivity and affords single stereoisomers.[4] Triazolines **1** readily undergo ring opening with various electrophiles.[4] Thus, they reacted effectively with bromoacetic ester to form esters **2**.[5] We found that the rate of this reaction depended on substituent R^1. More bulky substituents, for example, $R^1 = i$-Pr, accelerated the reaction. An exceptional case was the unsubstituted triazoline (**1**, $R^1 = H$) which reacted rather rapidly. The yield of products **2** increased when $CaCO_3$ was added to reaction mixtures. Evidently, this substance suppresses a number of side processes without participating in the reaction. The standard procedure for the substitution of a halogen atom with the azide group resulted in product **3**.[6]

Our attempts to cyclize of the Ns-protected intermediates **3** (e.g., using PPh_3 for reduction of the N_3-function) were unsuccessful. Therefore, we were forced to exchange the endocyclic amino protecting group with Boc, and obtained the compounds **4**.[7] These products were readily cyclized to form the desired bicyclic compounds **5** under catalytic hydrogenation conditions. Subsequent N-alkylation under standard conditions resulted in piperazines **6** (Table 1).[8,9] To our surprise,

Table 1. Preparation of compounds **6a–g**

Entry	R^1	R^2	$[\alpha]_D^{20}$ (*c*, MeOH)	Yield[a] **6a–g** (%)
6a	Et	Me	Racemic	28
6b	Et	*i*-Bu	Racemic	42
6c	Et	$MeOCH_2CH_2$	Racemic	45
6d	Et	$Et_2NCH_2CH_2$	Racemic	15
6e	Et	4-$FC_6H_4CH_2$	Racemic	22
6f	*i*-Pr	Me	−85 (*c* 1)	34
6g	Bn	Me	+375 (*c* 1)	19

[a] From **1a–c**.

Keywords: β-Turn mimetics; Piperazines; Pyrazino[1,2-*a*]pyrazines.
* Corresponding author. Fax: +7 095 956 49 48; e-mail: sviridov@chembridge.ru

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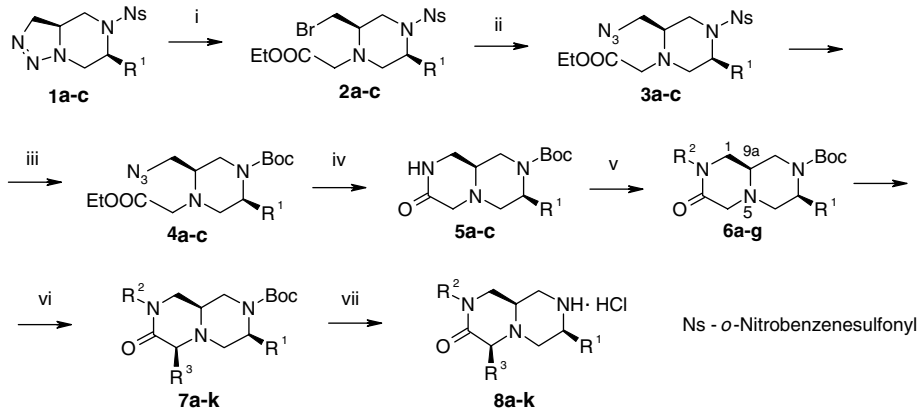
doi:10.1016/j.tetlet.2005.10.130



Scheme 1. Reagents and conditions: (i) $BrCH_2COOEt$, $CaCO_3$/MeCN; (ii) NaN_3/DMF; (iii) $HOCH_2CH_2SH$, DBU/MeCN then Boc_2O/CH_2Cl_2; (iv) H_2/Pd–C/MeOH; (v) R^2Hal, NaH/DMF; (vi) LDA, HMPA, R^3Hal/THF, −78 °C; (vii) HCl/dioxane.

there are many examples of 3-*C*-alkylation of 4-*N*-acylated piperazin-2-ones (mostly 4-*N*-Boc derivatives),[10] but no examples of such alkylation for 4-*N*-alkylated derivatives. We found that piperazinones **6** (as well as simple derivatives that we used as model compounds) formed Li-enolates in the presence of LDA/HMPA, which reacted with alkyl halides affording products **7** in good yields.[11] If an excess of the alkylating agent was used, it was possible to obtain a *C*,*C*-bisalkylated product. It should be noted that the alkylation occurred with a high degree of diastereoselectivity yielding single products. The electrophilic attack occurs in all probability from the least hindered side of the enolate and is determined by the presence of two axial hydrogen atoms at positions 6 and 9a.

The target products **8** containing a free amino group and thus useful for the construction of β-turn mimetic libraries (Table 2). The structures of compounds **8** were confirmed by ^1H NMR spectroscopic analysis.[12] The assignment of the ^1H and ^{13}C NMR spectra involved ^1H–^1H COSY, ^1H–^{13}C HMBC, and ^1H–^{13}C HSQC experiments. However, the conclusions based on the NMR data did not enable us to assign unambiguously the stereochemistry of the new chiral center. Therefore, we used X-ray crystallographic analysis that unequivocally confirmed the structure of **8b**. Since the NMR spectra of **8a** and **8c**–**k** are similar to that of **8b**, and a single product formed in the reaction, we attributed the stereochemistry identical to that of **8b** (Fig. 1).[13]

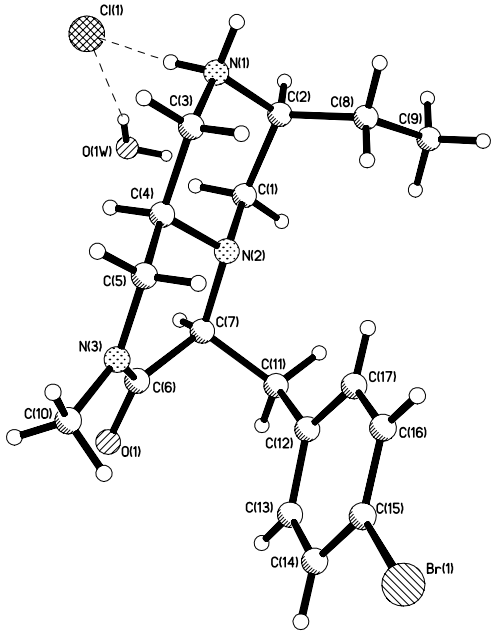


Figure 1. X-ray crystal structure of compound **8b**.

Table 2. Preparation of the hexahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3(4*H*)-one, hydrochlorides **8a**–**k**

Entry	R^1	R^2	R^3	$[\alpha]_D^{20}$ (*c*, MeOH)	Yield[a] **8a**–**k** (%)
8a	Et	Me	*i*-$PrCH_2CH_2$	Racemic	36
8b	Et	Me	4-$BrC_6H_4CH_2$	Racemic	45
8c	Et	*i*-Bu	4-$ClC_6H_4CH_2$	Racemic	34
8d	Et	$MeOCH_2CH_2$	3-$CH_3OC_6H_4CH_2$	Racemic	42
8e	Et	$Et_2NCH_2CH_2$	3-$CH_3OC_6H_4CH_2$	Racemic	20
8f	Et	4-$FC_6H_4CH_2$	4-$ClC_6H_4CH_2$	Racemic	27
8g	Et	Me	3-$CH_3OC_6H_4CH_2$	Racemic	42
8h	*i*-Pr	Me	3-$CH_3OC_6H_4CH_2$	+110 (*c* 1)	47
8i	*i*-Pr	$MeOCH_2CH_2$	4-$ClC_6H_4CH_2$	+100 (*c* 1)	45
8j	Bn	Me	*i*-$PrCH_2CH_2$	−120 (*c* 1)	23
8k	Bn	Me	3-$CH_3OC_6H_4CH_2$	−70 (*c* 1)	25

[a] From **6a**–**c**.

We have described a novel approach to 2,4,7-trisubstituted hexahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3(4*H*)-ones, which enables the synthesis of a wide variety of these compounds in relatively good yields. Due to the high diastereoselectivity, this method is appropriate for the synthesis of optically pure products starting from readily available chiral amino alcohols.

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5. *Triazoline ring opening*: $CaCO_3$ (3.5 g, 30 mmol) was added to a solution of compound **1a** (9.5 g, 30 mmol) and ethyl bromoacetate (5.14 g, 35 mmol) in anhydrous acetonitrile (1000 mL). The reaction mixture was stirred at room temperature for 2 days and evaporated. The residue was dissolved in MeOH, and the solution was passed through Celite. The product was purified by column chromatography (silica gel, hexane/dichloromethane 2:1) to afford compound **2a** (6.7 g, 50%) as an oil. **2a** (R^1 = Et): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.83 (3H, t, J = 7.2 Hz), 1.23 (3H, t, J = 7.2 Hz), 1.70–1.94 (2H, m), 2.78 (1H, dd, J = 11.9, 1.5 Hz), 2.92–2.98 (1H, m), 3.00 (1H, dd, J = 11.9, 3.7 Hz), 3.28 (1H, dd, J = 10.8, 13.5 Hz), 3.30 (1H, d, J = 17.4 Hz), 3.44 (1H, dd, J = 11.6, 2.2 Hz), 3.51 (1H, dd, J = 11.6, 4.6 Hz), 3.58 (1H, d, J = 17.4 Hz), 3.71 (1H, dd, J = 13.7, 3.7 Hz), 3.77–3.84 (1H, m), 4.12 (2H, q, J = 7.2 Hz), 7.62–7.73 (3H, m), 8.03–8.09 (1H, m).
6. *Substitution of the halogen atom with the azide group*: Sodium azide (1.85 g, 28 mmol) was added to a solution of compound **2a** (6.7 g, 14 mmol) in DMF (150 mL). The reaction mixture was stirred for 24 h at room temperature and then extracted with ether. The extract was washed with a 30% solution of Na_2CO_3 then brine, dried over Na_2SO_4, and evaporated to furnish an oil **3a** (5.97 g, 97%). Compound **3a** (R^1 = Et): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.83 (3H, t, J = 7.2 Hz), 1.24 (3H, t, J = 7.2 Hz), 1.71–1.92 (2H, m), 2.79 (1H, dd, J = 11.9, 1.5 Hz), 2.94–2.99 (1H, m), 3.10 (1H, dd, J = 11.9, 3.7 Hz), 3.30 (1H, dd, J = 10.8, 13.5 Hz), 3.32 (1H, d, J = 17.4 Hz), 3.46 (1H, dd, J = 11.6, 2.2 Hz), 3.52 (1H, dd, J = 11.6, 4.6 Hz), 3.58 (1H, d, J = 17.4 Hz), 3.71 (1H, dd, J = 13.7, 3.7 Hz), 3.77–3.85 (1H, m), 4.14 (2H, q, J = 7.2 Hz), 7.60–7.72 (3H, m), 8.04–8.08 (1H, m).
7. *Replacement of the protective group*: Azide **3a** (8.56 g, 20 mmol) was dissolved in anhydrous acetonitrile. DBU (2.98 g, 20 mmol) and 2-mercaptoethanol (1.52 g, 20 mmol) were added to the reaction mixture which was stirred at room temperature for 8 h and evaporated. Ether (150 mL) and 30% aqueous solution of citric acid (60 mL) were added to the residue. The aqueous layer was separated and neutralized with a 30% aqueous solution of $NaHCO_3$. The product was extracted with ethyl acetate (3×50 mL). The extract was dried with Na_2SO_4 and evaporated to give the free amine (2.98 g, 60%). This substance was dissolved in dichloromethane (100 mL), and a solution of di-*tert*-butyl dicarbonate (2.56 g, 12 mmol) in dichloromethane (30 mL) was added dropwise under stirring for 30 min. The reaction mixture was washed with a saturated solution of Na_2CO_3 (3×50 mL). The organic layer was dried with Na_2SO_4 and evaporated to afford compound **4a** as an oil (3.78 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.3 Hz), 1.46 (9H, s), 1.60–1.70 (1H, m), 1.72–1.86 (1H, m), 2.69–2.91 (4H, m), 3.30–3.55 (4H, m), 3.83–4.02 (2H, m), 4.17 (2H, q, J = 7.3 Hz).
8. *Cyclization*: Compound **4a** (3.78 g, 1 mol) was dissolved in methanol (40 mL), and 10% Pd/C (150 mg) was added to the solution under argon. The reaction was carried out in a Parr apparatus (hydrogen pressure 40 psi, 40 °C) for 8 h, after which the reaction mixture was passed through Celite and evaporated. The residue was purified by column chromatography (silica gel, dichloromethane/ethyl acetate 1:1) to give compound **5a** as a white powder (2.38 g, 63%), mp 149–151 °C (ethyl acetate/hexane, 1:1).^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (3H, t, J = 7.3 Hz), 1.46 (9H, s), 1.56–1.94 (2H, m), 2.22 (1H, dd, J = 11.3, 3.7 Hz), 2.26–2.35 (1H, m), 2.58–2.65 (1H, m), 2.67–2.70 (1H, m), 2.76 (1H, d, J = 16.6 Hz), 3.11 (1H, dd, J = 11.0, 10.8 Hz), 3.23 (1H, dt, J = 11.5, 3.7 Hz), 3.39 (1H, d, J = 16.6 Hz), 3.81–4.18 (2H, m), 6.12–6.26 (1H, m). $C_{14}H_{25}N_3O_3$, found: C, 59.37; H, 8.94; N, 14.80. Calcd: C, 59.34; H, 8.89; N, 14.83.
9. *N-Alkylation*: Sodium hydride (0.23 g, 9 mmol, 60% w/w dispersion in mineral oil) was added to a solution of compound **5a** (1.6 g, 6 mmol) in DMF (5 mL). The reaction mixture was stirred for 30 min at room temperature. Methyl iodide (0.88 g, 6 mmol) was then added under stirring. After 2 h, the product was extracted with ether. The extract was washed with a 30% solution of Na_2CO_3 then brine, dried with Na_2SO_4, and evaporated to afford white powder **6a** (0.5 g, 89%), mp 144–146 °C (ethyl acetate/hexane, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (3H, t, J = 7.3 Hz), 1.46 (9H, s), 1.55–1.91 (2H, m), 2.20 (1H, dd, J = 11.3, 3.7 Hz), 2.32–2.42 (1H, m), 2.60–2.71 (2H, m), 2.76 (1H, d, J = 16.6 Hz), 2.94 (3H, s), 3.09–3.15 (2H, m), 3.42 (1H, d, J = 16.6 Hz), 3.82–4.18 (2H, m). $C_{15}H_{27}N_3O_3$, found: C, 60.57; H, 9.17; N, 14.10. Calcd: C, 60.58; H, 9.15; N, 14.13.
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11. *C-alkylation*: *N*-butyllithium (1.2 mL, 20 mmol, 15% solution in *n*-hexane) and HMPA (345 mg, 20 mmol) were added under argon, at −78 °C, to a solution of diisopropylamine (227 mg, 22 mmol) in anhydrous THF (3 mL). After 30 min, a solution of compound **6a** (R^2 = Me, 500 mg, 16 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was warmed to −40 °C over 1 h, and a solution of *p*-bromobenzyl bromide (240 mg, 16 mmol) in anhydrous THF (5 mL) was added dropwise. When the reaction mixture reached 5 °C, it was treated with a 30% aqueous solution of citric acid (30 mL). The product was extracted with ethyl acetate (3×5 mL). The extract was dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, hexane/dichloromethane 1:1) to afford the oil **7b** (450 mg, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (3H, t, J = 7.4 Hz), 1.45 (9H, s), 1.65–1.93 (2H, m), 2.29 (1H, dd, J = 11.3, 3.9 Hz), 2.41–2.54 (2H, m), 2.81 (3H, s), 2.80 (1H, d,

$J = 11.3$ Hz), 2.97 (1H, d, $J = 11.3$ Hz), 3.02–3.09 (1H, m), 3.14–3.21 (2H, m), 3.22–3.30 (1H, m), 3.67–4.19 (2H, m), 7.10 (2H, d, $J = 8.31$ Hz), 7.36 (2H, d, $J = 8.31$ Hz).

12. *Removal of the Boc-group*: A 4.0 M solution of HCl in 1,4-dioxane (1 mL) was added dropwise to a solution of compound **7g** (450 mg, 10 mmol) in 1,4-dioxane (1 mL) at room temperature. The precipitate formed was separated by filtration and dried to give compound **8g** as white powder (345 mg, 98%), mp 127–130 °C (ethyl ester). ^{1}H NMR (D_2O, 400 MHz): δ 1.05 (3H, t, $J = 7.4$ Hz, CH_2CH_3), 1.73–1.86 and 1.99–2.13 (each 1H, m, CH_2CH_3), 2.66 (1H, dd, $J = 13.5$, 3.2 Hz, 6-CH_2), 2.75–2.82 (1H, m, 1-CH_2), 2.84 (3H, s, NCH_3), 2.97 (1H, d, $J = 7.6$ Hz, 9-CH_2), 3.06 (1H, d, $J = 2.9$ Hz, 1-CH_2), 3.11 (2H, dd, $J = 9.3$, 3.9 Hz, 10-CH_2), 3.21 (1H, d, $J = 9.7$ Hz, 9-CH_2), 3.29 (1H, dd, $J = 13.2$, 1.7 Hz, 6-CH_2), 3.44 (1H, t, $J = 3.9$ Hz, 4-CH), 3.49–3.56 (1H, m, 7-CH), 3.83 (3H, s, OCH_3), 6.81–6.96 (3H, m, Ph), 7.31 (1H, t, $J = 8.1$ Hz, Ph). $C_{18}H_{27}N_3O_2 \cdot HCl \cdot H_2O$, found: C, 68.09; H, 8.62; N, 13.23. Calcd: C, 68.11; H, 8.57; N, 13.24.

13. Crystallographic data for compound **8b**: $C_{17}H_{24}BrN_3O \cdot HCl \cdot H_2O$, $M_r = 420.78$, orthorhombic space group *Pbca*, $a = 8.5880(10)$, $b = 13.007(3)$, $c = 35.007(5)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 3910.4(12)$ Å^3, $Z = 8$, $T = 293(2)$ K, $F(000) = 1744$, $\mu = 2.253$ mm^{-1}, $\theta_{max} = 25.17°$, 3622 reflections measured and 3517 unique ($R_{int} = 0.0357$) reflections, full matrix least-squares refinement on F^2, R_1 (obs) = 0.2082, and wR_2 (all data) = 0.1728. Supplementary data in the form of CIFs have been deposited with the Cambridge Crystallographic Data Centre (CCDC 279331). 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].