Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2006, 16(2), 82–83
Mendeleev Communications

Stereoselective synthesis of spirofused 3-substituted 2,3,4,4a,5,6-hexahydro-6*H*-benzo[*c*]quinolizine using the *tert*-amino effect

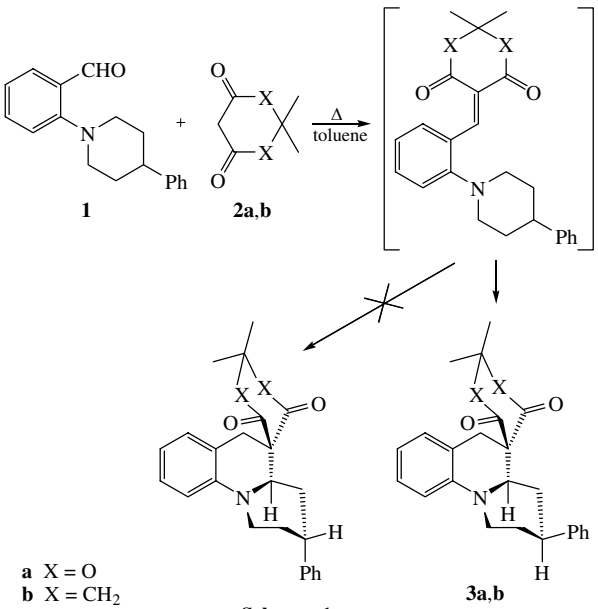
Elisaveta V. Deeva,[a] Tatiana V. Glukhareva,[a] Alexey V. Tkachev[b] and Yury Yu. Morzherin*[a]

[a] *Department of Technology of Organic Synthesis, Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 343 374 5483; e-mail: morjerine@htf.ustu.ru*
[b] *N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. E-mail: atkachev@nioch.nsc.ru*

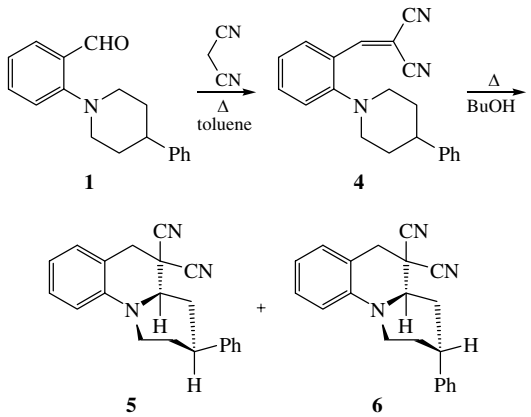
DOI: 10.1070/MC2006v016n02ABEH002247

The interaction of 2-(4-R-piperidino)benzaldehyde and cyclic CH-active compounds occurred as a tandem of Knövenagel condensation and cyclization by *tert*-amino effect and led to spiro-fused 3-substituted 2,3,4,4a,5,6-hexahydro-6*H*-benzo[*c*]quinolizine.

New strategies for the stereoselective synthesis of nitrogen-containing heterocycles are of interest in organic chemistry, and various methods have been proposed.[1–3] The α-cyclization of



Scheme 1



Scheme 2

tertiary amines is a mechanistically intriguing and synthetically useful cyclization.[4] Meth-Cohn and Suschitzky[5] have coined the term 'tertiary amine effect' to describe such processes, which have been further developed by Verboom and Reinhoudt.[6] The use of the *tert*-amino effect for preparation of pyrido-fused ring systems has been well documented.[7,8] The stereochemical studies on the cyclization of derivatives of type **1** substituted at the atom adjacent to the nitrogen of *tert*-amine moieties revealed high regio- and stereoselectivity of the reaction.[9] We found that in the case when substituted at the β-carbon of cyclic amino group

the reaction is also stereoselective.[10] Here, we report a stereoselective reaction of 2-(4-phenylpiperidino)benzaldehyde **1**† and cyclic CH-active compounds **2a**,**b**, which led to a single isomer‡ with an axiality hydrogen in the 3- and 4a-positions of benzo[*c*]quinolizine (Scheme 1). The structures of **3a**,**b** were determined by 2D correlation NMR spectroscopy (DEPT, COSY, HETCOR) and ax-eq coupling constants.

In contrast to the cyclization of **1** with **2a**,**b**, the reaction of **1** and malononitrile led to benzylidene malononitrile **5**, similarly to published data.[9] The cyclization of **4**§ led to a mixture¶ of two isomers **5** and **6** in a ratio of 1:1 (Scheme 2).

Our present results indicate that the cyclization of benzaldehyde **1** and CH-active compounds occurred stereoselectively for reaction with cyclic CH-active compounds but not for one of malononitrile.

† 4-Phenylpiperidine (0.160 mg, 0.988 mmol) and potassium carbonate (0.138 g, 0.988 mmol) were added to a solution of 2-fluorobenzaldehyde (0.118 g, 0.949 mmol) in DMF (1.0 ml). The reaction mixture was refluxed in a glycerol bath at 150 °C for 20 h. The completion of the reaction was judged from TLC. The reaction mixture was cooled to ~20 °C, water (15 ml) was added, and the product was extracted with ethyl acetate (3×20 ml). The combined organic extract was washed with a solution of ammonium chloride. The organic layer was dried with Na_2SO_4, and the solvent was removed *in vacuo*. Data for **1**: 2-(4-phenylpiperidino)-benzaldehyde. Yield, 75%; mp 122 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 10.26 (s, 1H, CHO), 7.70 (dd, 1H, H_{Ar}, *J* 7.7 and 1.7 Hz), 7.61 (ddd, 1H, H_{Ar}, *J* 8.3, 8.5 and 1.7 Hz), 7.30–7.33 (m, 4H, H_{Ar}), 7.25 (d, 1H, H_{Ar}, *J* 8.3 Hz), 7.21 (ddd, 1H, H_{Ar}, *J* 7.7, 7.0 and 4.7 Hz), 7.14 (dd, 1H, H_{Ar}, *J* 7.7 and 8.5 Hz), 3.32–3.38 (m, 2H, 2NCH), 3.01 (ddd, 2H, 2NCH, *J* 11.9, 11.8 and 2.9 Hz), 2.64–2.74 (m, 1H, CH), 1.87–1.99 (m, 4H, $2CH_2$). ^{13}C NMR ([$^2H_6$]DMSO) δ: 33.09 (CH_2), 41.28 (CH_2Ph), 54.64 (NCH_2), 119.33 (ArH), 121.90 (ArH), 126.10 (Ph), 126.74 (Ph), 127.86 (Ph), 128.34 (Ph), 128.97 (ArH), 135.07 (ArH), 145.82 (Ar), 155.86 (Ar), 190.80 (CHO). MS, *m*/*z*: 265 (M^+). Found (%): N, 5.15. Calc. for $C_{18}H_{19}NO$ (%): N, 5.28.

‡ Meldrum's acid (or dimedone) (2.3 mmol) was added to a solution of benzaldehyde **1** (0.608 g, 2.3 mmol) in toluene (20 ml). The reaction mixture was refluxed for 3 h. The completion of the reaction was determined by TLC. The reaction mixture was cooled to ~20 °C and concentrated *in vacuo*. The residue was triturated with ethanol.

*3-Phenyl-2′,2′-dimethyl-2,3,4,4a,5,6-hexahydro-6*H-*spiro(benzo[*c*]-quinolizine-5,5′-[1,3]dioxane)-4′,6′-dione* **3a**. Yield, 80%; mp 240 °C. ^{1}H NMR ($CDCl_3$) δ: 7.27 (dd, 2H, H_{Ph}, *J* 7.4 and 7.4 Hz), 7.19 (tt, 1H, H_{Ph}, *J* 7.4 and 1.9 Hz), 7.15 (ddd, 1H, H_{Ar}, *J* 8.2, 6.9 and 1.3 Hz), 7.09–7.12 (m, 2H, H_{Ar}), 6.97 (d, 1H, H_{Ar}, *J* 7.3 Hz), 6.93 (d, 1H, H_{Ar}, *J* 8.3 Hz), 6.74 (ddd, 1H, H_{Ar}, *J* 7.4, 7.4 and 1.0 Hz), 4.10 [ddd, 1H, CH(1), *J* 12.8, 4.6 and 2.6 Hz], 3.52 [d, 1H, CH(6), *J* 16.4 Hz], 3.43 [dd, 1H, CH(4a), *J* 11.8 and 2.4 Hz], 3.11 [d, 1H, CH(6), *J* 16.4 Hz], 2.72 [ddd, 1H, CH(1), *J* 12.8, 12.8 and 2.6 Hz], 2.60 [dd, 1H, CH(4), *J* 13.7 and 6.0 Hz], 2.50 [dd, 1H, CH(3), *J* 13.7 and 7.8 Hz], 1.76 (s, 3H, Me), 1.75 (s, 3H, Me), 1.72–1.78 [m, 1H, CH(4)], 1.36 [ddd, 1H, CH(2), *J* 12.8, 12.8 and 4.6 Hz], 1.15 [ddd, 1H, H(2), *J* 12.8, 12.8 and 12.8 Hz]. ^{13}C NMR ($CDCl_3$) δ: 169.28 (CO), 164.78 (CO), 144.60 (Ar), 139.46 (Ar), 129.06 (ArH), 128.71 (ArH), 128.37 (ArH), 127.67 (ArH), 126.23 (ArH), 119.50 (Ar), 118.49 (ArH), 113.52 (ArH), 61.24 (C^{4a}), 52.21 (OCO), 48.27 (C^1), 43.00 (C^5), 37.63 (C^3), 34.72 (C^6), 34.56 (C^4), 30.62 (C^2), 30.28 (Me), 28.20 (Me). MS, *m*/*z*: 391 (M^+). Found (%): N, 3.58. Calc. for $C_{24}H_{25}NO_4$ (%): N, 3.58.

*3-Phenyl-5′,5′-dimethyl-2,3,4,4a,5,6-hexahydro-6*H-*spiro(benzo[*c*]-quinolizine-5,2′-cyclohexane)-1′,3′-dione* **3b**. Yield, 68%; mp 230 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.23 (dd, 2H, H_{Ph}, *J* 7.6 and 7.6 Hz), 7.16 (tt, 1H, H_{Ph}, *J* 7.6 and 1.3 Hz), 7.07 (d, 1H, H_{Ar}, *J* 7.6 Hz), 7.05–7.10 (m, 2H, H_{Ar}), 7.00 (ddd, 1H, H_{Ar}, *J* 7.9, 7.2 and 1.3 Hz), 6.86 (d, 1H, H_{Ar}, *J* 7.9 Hz), 6.66 (ddd, 1H, H_{Ar}, *J* 7.3, 7.4 and 1.0 Hz), 4.59 [dd, 1H, CH(1), *J* 12.2 and 3.1 Hz], 4.13 [d, 1H, CH(4a), *J* 14.5 Hz], 3.48 [d, 1H, CH(6), *J* 13.3 Hz], 3.11–3.32 (m, 3H, 3CH), 3.11 [d, 1H, CH(6), *J* 13.3 Hz], 2.64 [d, 1H, CH(4′), *J* 16.9 Hz], 2.27 (dd, 1H, CH, *J* 13.8 and 2.1 Hz), 2.14 (dd, 1H, CH, *J* 13.8 and 2.1 Hz), 1.47–1.59 (m, 2H, 2CH), 1.18–1.23 (m, 2H, 2CH), 1.23 (s, 3H, Me), 0.68 (s, 3H, Me). ^{13}C NMR ([$^2H_6$]DMSO) δ: 205.99 (CO), 205.01 (CO), 145.22 (Ar), 141.67 (Ar), 129.32 (ArH), 128.37 (ArH), 126.45 (ArH), 125.37 (ArH), 126.15 (ArH), 122.32 (Ar), 117.66 (ArH), 113.22 (ArH), 67.32 (C^{4a}), 60.09 (C^1), 50.83 (C^5), 49.09 ($C^{4'}$), 48.09 ($C^{6'}$), 42.11 ($C^{5'}$), 31.14 (C^3), 30.69 (C^6), 29.46 (C^4), 27.91 (C^5), 26.18 (Me), 23.56 (Me). MS, *m*/*z*: 387 (M^+). Found (%): N, 3.47. Calc. for $C_{26}H_{29}NO_2$ (%): N, 3.61.

References

1 A. Domling, *Chem. Rev.*, 2006, **106**, 17.
2 E. Garcia, S. Arrasate, E. Lete and N. Sotomayor, *J. Org. Chem.*, 2005, **70**, 10368.
3 K. Tatsuta and S. Hosokawa, *Chem. Rev.*, 2005, **105**, 4707.
4 N. Kaval, B. Halasz-Dajka, G. Vo-Thanh, W. Dehaen, J. Van der Eycken, P. Mátyus, A. Loupyc and E. Van der Eycken, *Tetrahedron*, 2005, **61**, 9052.
5 O. Melh-Cohn and H. Suschitzky, *Adv. Heterocycl. Chem.*, 1972, **14**, 211.
6 W. Verboom and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas*, 1990, **109**, 311.
7 O. Elias, L. Karolyhazy, G. Horvath, V. Harmat and P. Mtyus, *J. Molecular Structure (Theochem)*, 2003, **666–667**, 625.
8 A. V. Tverdokhlebov, A. P. Gorulya, A. A. Tolmachev, A. N. Kostyuk, A. N. Chernega and E. B. Rusanov, *Synthesis*, 2005, **37**, 2161.
9 W. H. N. Nijhuis, W. Verboom, D. N. Reinhoudt and S. Harkema, *J. Am. Chem. Soc.*, 1987, **109**, 3136.
10 E. V. Deeva, T. V. Glukhareva, N. A. Zybina and Yu. Yu. Morzherin, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 1492 (*Russ. Chem Bull., Int. Ed.*, 2005, **54**, 1537).

Received: 3rd October 2005; Com. 05/2585

§ *2-[2-(4-Phenylpiperidino)benzylidene]malononitrile* **4**. Yield, 85%; mp 116 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.26 (s, 1H, CH=), 7.98 (dd, 1H, H_{Ar}, *J* 8.1 and 1.2 Hz), 7.58 (ddd, 1H, H_{Ar}, *J* 8.4, 7.4 and 1.2 Hz), 7.00–7.30 (m, 7H, H_{Ar}), 3.20–3.26 (m, 2H, 2NCH), 2.94–3.06 (m, 2H, 2NCH), 2.60–2.70 (m, 1H, CH), 1.90–2.08 (m, 4H, $2CH_2$). ^{13}C NMR ([$^2H_6$]DMSO) δ: 33.07 (CH_2), 41.26 (CH_2Ph), 54.22 (NCH_2), 81.10 (C=), 113.32 (CN), 114.51 (CN), 119.58 (ArH), 122.18 (ArH), 124.37 (Ph), 126.13 (Ph), 126.76 (Ph), 128.34 (Ph), 129.00 (ArH), 134.84 (ArH), 145.75 (Ar), 154.59 (Ar), 158.34 (C=). MS, *m*/*z*: 313 (M^+). Found (%): N, 13.51. Calc. for $C_{21}H_{19}N_3$ (%): N, 13.41.

¶ A solution of vinyl compound **4** (0.225 g, 0.72 mmol) in BuOH (10 ml) was heated at 100 °C for 3 h and then filtered with charcoal. The solvent was evaporated, and the residue was recrystallised from ethyl acetate.

*A mixture of 3-phenyl-2,3,4,4a,5,6-hexahydro-6*H-*benzo[*c*]quinolizine-5,5-dicarbonitriles* **5**, **6**: Yield, 91%; mp 115 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: two isomers 6.90–7.40 (m, 7H, H_{Ar}), 6.78 (d, 1H, H_{Ar}, *J* 7.0 Hz), 6.74 (dd, 1H, H_{Ar}, *J* 7.0 and 7.0 Hz), 4.18 (d, 0.5H, CH, *J* 12.5 Hz), 3.50–3.90 (m, 3.5H, CH), 3.35–3.40 (m, 1H, CH), 2.80–3.12 (m, 1H, CH), 2.58–2.65 (m, 1H, CH), 2.10–2.38 (m, 3H, CH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 144.37, 142.39, 129.13, 128.58, 127.37, 126.62, 126.12, 118.75, 116.59, 115.21, 114.69, 113.89, 54.44, 43.52, 36.41, 35.34, 33.71, 32.99, 28.49, isomer 144.47, 143.78, 129.35, 129.12, 128.62, 128.40, 126.55, 118.89, 116.59, 115.18, 114.46, 114.03, 58.10, 47.45, 36.51, 35.78, 34.78, 34.13, 31.24. MS, *m*/*z*: 313 (M^+). Found (%): N, 13.19. Calc. for $C_{21}H_{19}N_3$ (%): N, 13.41.