Tetrahedron Letters 49 (2008) 6231–6233

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient one-step method for the synthesis of 2-(indolizin-2-yl)benzimidazoles from quinoxalinones and α-picoline via a novel rearrangement

Vakhid A. Mamedov *, Dina F. Saifina, Aidar T. Gubaidullin, Alina F. Saifina, Il'dar Kh. Rizvanov

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center of the Russian Academy of Sciences, Arbuzov Str. 8, 420088 Kazan, Russian Federation

ARTICLE INFO

Article history:
Received 25 June 2008
Revised 6 August 2008
Accepted 11 August 2008
Available online 14 August 2008

Keywords:
Quinoxalin-2-one
Benzimidazole
α-Picoline
Ring contraction
Rearrangement
Indolizinylbenzimidazoles
^{1}H NMR data
X-ray diffraction analysis

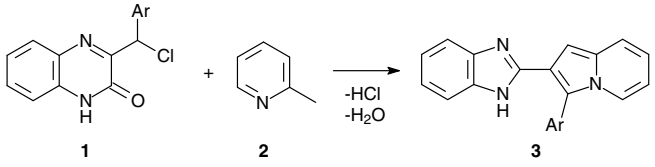
ABSTRACT

A highly efficient one-step and versatile method for the synthesis of 2-(indolizin-2-yl)benzimidazoles has been developed on the basis of the novel ring contraction of 3-arylchloromethyl- and alkylchloromethylquinoxalin-2-ones with α-picoline.

Benzimidazole-containing compounds exhibit a wide range of biological properties. This class of heterocyclic systems has found commercial applications in several therapeutic areas such as antiulcer, antihypertensive, antiviral,[1a,1b] antifungal,[1c] antitumor,[1d–h] and antihistamine agents[1i] as well as anthelmintic agents in veterinary medicine.[1j–n] Medicinal chemists consider these heterocycles to be promising compounds.

Almost all the existing methods for the synthesis of benzimidazoles[1n,2a–j] have some synthetic shortcomings, such as rigid conditions and poor yields of target products, which limit their scope. The one-step method of Fokas and co-workers[3] is the most efficient method for the synthesis of benzimidazoles, involving the $Na_2S_2O_4$ reduction of *o*-nitroanilines in the presence of aldehydes in EtOH or other appropriate solvents. However, the method is restricted by its ability to synthesize a limited number of benzimidazole derivatives.

In this Letter, a direct, efficient, and convenient approach to the synthesis of 2-(indolizinyl)benzimidazoles is presented. The method is based on a new quinoxaline-benzimidazole rearrangement of 3-arylchloromethyl- **1a–d** and alkylchloromethyl- **1e** quinoxalin-2-ones[4] under the action of α-picoline **2**. Thus, the reaction of quinoxalin-2-one **1** with α-picoline **2** at reflux results in high yields of the corresponding (indolizinyl)benzimidazoles **3**[5] (Scheme 1). As is evident from the structure of compounds **3**, the C(2)–C(3)–C(Cl)Ar and N=C–Me fragments of quinoxaline **1** and α-picoline **2** are involved in constructing the two new heterocyclic rings.



1 **2** **3**

Entry	Ar	Substrates		Product (yield)	M.p., °C
1	4-$NO_2C_6H_4$	**1a**	**2**	**3a** (72%)	>300
2	Ph	**1b**	**2**	**3b** (78%)	246-248
3	2,4-$Cl_2C_6H_3$	**1c**	**2**	**3c** (76%)	160-162
4	3,5-$Cl_2C_6H_3$	**1d**	**2**	**3d** (65%)	170-172
5	CH_2Ph	**1e**	**2**	**3e** (70%)	155-157

Scheme 1.

The structures of compounds **3a–e** were deduced from their elemental analyses and ^{1}H NMR data.[5] The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. Initial fragmentation involved scission of the benzimidazole and indolizine ring systems.[5]

The molecular structure of compound **3a** was confirmed by a single-crystal X-ray analysis (Fig. 1).[6]

Initially, complete dissolution of compounds **1** is observed in refluxing α-picoline solution, then an abundant precipitation of

* Corresponding author. Tel.: +7 843 2727304; fax: +7 843 2732253.
E-mail address: mamedov@iopc.kcn.ru (V. A. Mamedov).

0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.08.032

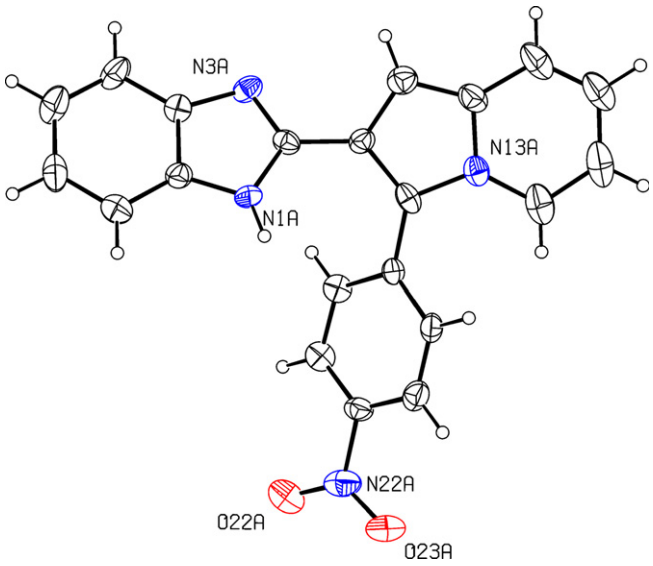
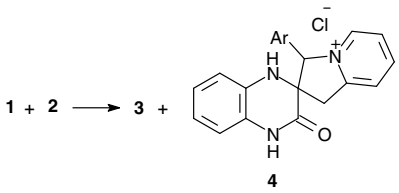


Figure 1. ORTEP drawing of one of the two independent molecules in the asymmetric part of the unit cell of **3a**. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented by circles of arbitrary size.



4	Ar	Yield	M.p., °C
a	4-$NO_2C_6H_4$	10%	272-274
b	Ph	37%	271-273
c	2,4-$Cl_2C_6H_3$	41%	263-265
d	3,5-$Cl_2C_6H_3$	16%	274-276

Scheme 2. Isolated and characterized spiro compounds, formed after reflux of the reaction mixture for 1 h.

crystals occurs rapidly which gradually dissolve during the course of the reaction. The yield of crystalline products with a precise melting point, obtained, for example, after refluxing quinoxalin-2(1*H*)-one **1c** in α-picoline **2** for 1 h, is 41%[7] (Scheme 2). The ^{1}H NMR spectrum of the product **4c** showed signals for pyridinium, phenyl, and phenylene rings at 7.98–8.67, 7.32–7.48 and 6.26–6.69 ppm, respectively, three singlet signals at 6.73, 7.53, and

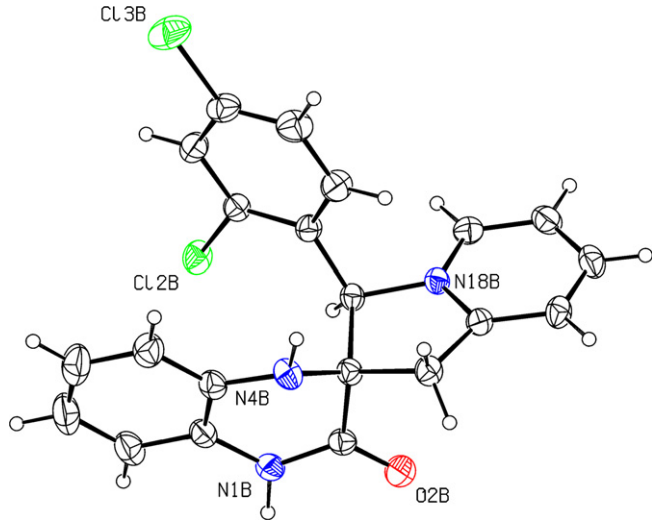
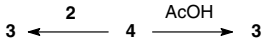


Figure 2. ORTEP drawing of one of the independent molecules of compound **4c** (the compound crystallized in salt form with two independent molecules, two chlorine anions, and acetic acid in the asymmetric part of the unit cell).

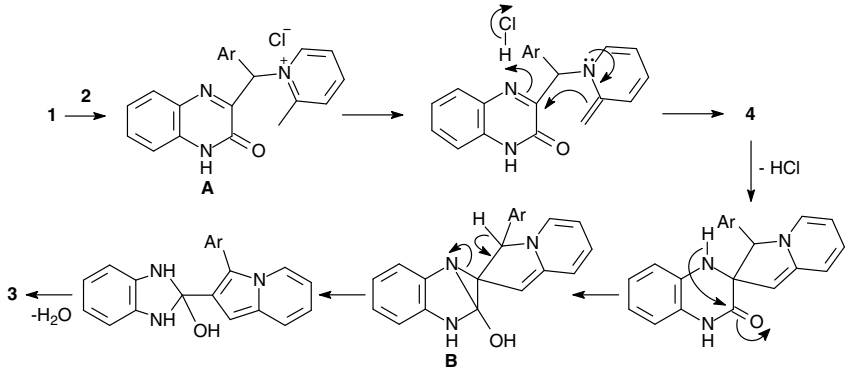


Scheme 3.

10.97 ppm and two doublets at 3.91 and 4.67 ppm with ^2J 18.5 Hz. The signals of the phenylene protons are shifted to stronger fields as compared with the shifts of the protons of the phenylene ring (7.33–7.82 ppm) of the quinoxalin-2(1*H*)-one **1**.[4] This demonstrates the imine carbon atom involvement in the reaction, the nitrogen becoming an electron-donating amine atom. These data along with those already available to our group[8] proved to be sufficient to assign the structure of the spiro compound **4** to the product formed at the first stage of the reaction (Scheme 2). IR spectroscopy and mass spectrometric data also confirm this structure. The formation of spiro compound **4** was unambiguously confirmed by a single-crystal X-ray analysis of **4c** (Fig. 2).[9]

It should be noted that spiro compound **4** is quantitatively transformed into 2-(3-arylindolizin-2-yl)benzimidazole **3** not only in boiling α-picoline, but also in acetic acid (Scheme 3).

On the basis of the known chemistry of α-picoline,[10a–i] α-haloimines,[11a–j] and quinoxalinones,[12a,b] it is reasonable to assume that the first stage involves nucleophilic substitution of the halogen atom of the α-haloimine fragment by the nitrogen atom of the pyridine ring with the formation of intermediate **A**. This is followed by



Scheme 4.

a cascade reaction involving (a) elimination of a proton from the methyl group of α-picoline, (b) nucleophilic attack of the methylene group on the C(3) atom of the quinoxalinone to form the spiro-quinoxaline derivative **4**, (c) intramolecular nucleophilic attack by the N(4) nitrogen atom on the carbamoyl carbonyl group with the formation of intermediate pentacyclic system **B**, (d) ring contraction with cleavage of the C(3)–N(4) bond, and (e) elimination of water leading to the formation of the final product **3** (Scheme 4). It was shown that the reaction does not proceed in neutral or aprotic solvents.

To summarize, we have found an efficient and versatile one-step method for the preparation of a series of benzimidazoles as well as other imidazole-containing ring systems. This was accomplished by a novel quinoxalinone-benzimidazole rearrangement of 3-chloroarylmethyl- and 3-chloroalkylmethyl-quinoxalin-2-ones on exposure to α-picoline. The reaction is readily applicable to large scale synthesis. Application of this methodology to the synthesis of other heterocyclic ring systems is currently under investigation and the results will be published in due course.

Acknowledgment

We thank the Russian Foundation for Basic Research (Grant No. 07-03-00613-a) for financial support.

References and notes

1. (a) Salluja, S.; Zou, R.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1996**, *39*, 881; (b) Zarrinmayeh, H.; Zimmerman, D. M.; Cantrell, B. E.; Schober, D. A.; Bruns, R. F.; Gackenheimer, S. L.; Oznstein, P. L.; Hipskind, P. A.; Britton, T. C.; Gehlert, D. R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 647; (c) Taggart, P. J.; Cooke, L. R.; Mercer, P. C.; Shaw, M. W. *Crop Protection* **1998**, *17*, 727; (d) Antonini, I.; Claudi, F.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *J. Med. Chem.* **1988**, *31*, 260; (e) Skibo, E. B.; Schulz, W. G. *J. Med. Chem.* **1993**, *36*, 3050; (f) Skibo, E. B. *Curr. Med. Chem.* **1996**, *2*, 900; (g) Zhou, R.; Skibo, E. B. *J. Med. Chem.* **1996**, *39*, 4321; (h) Craigo, W. A.; LeSueur, B. W.; Skibo, E. B. *J. Med. Chem.* **1999**, *42*, 3324; (i) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1925; (j) Cedillo-Rivera, R.; Muñoz, O. *J. Med. Microbiol.* **1992**, 37; (k) Chavez, B.; Cedillo-Rivera, R.; Martinez-Palomo, A. *J. Protozool.* **1992**, *39*, 510; (l) Fears, S. D.; O'Jare *J. Antimicrob. Agents Chemother.* **1998**, *32*, 144; (m) Spasov, A. A.; Yoshitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharm. Chem. J.* **1999**, *33*, 232; (n) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II. Five-Membered Rings with Two Heteroatoms and Fused Carbocyclic Derivatives*; Elsevier, 1996. Vol. 3, Chapter 2.
2. (a) Wright, J. B. *Chem. Rev.* **1951**, *48*, 397; (b) Preston, P. N. *Chem. Rev.* **1974**, *74*, 279; (c) Gray, D. N. *J. Heterocycl. Chem.* **1970**, *7*, 947; (d) Hudkins, R. L. *Heterocycles* **1995**, *41*, 1045; (e) Balasubramaniyan, V.; Balasubramaniyan, P.; Patil, S. V. *Indian J. Chem., Sect. B* **1990**, *29*, 124; (f) Salakhov, M. S.; Umaeva, V. S.; Salakhova, Y. S.; Idrisova, S. S. *Russ. J. Org. Chem.* **1999**, *35*, 397; (g) Hölljes, E. L.; Wagner, E. C. *J. Org. Chem.* **1944**, *9*, 31; (h) King, F. E.; Acheson, R. M. *J. Chem. Soc.* **1949**, 1396; (i) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893; (j) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814.
3. Yang, D.; Fokas, D.; Li, J.; Yu, L.; Boldino, C. M. *Synthesis* **2005**, 47.
4. Method for the synthesis of **1b**: Mamedov, V. A.; Nuretdinov, I. A.; Sibgatullina, F. G. *Bull. Acad. Sci. USSR* **1989**, *38*, 1294. Quinoxalinones **1a** and **1c–e** were prepared by the method for **1b**. Mp 235–238 °C (**1c**); 264–266 °C (**1d**), 199–200 °C (**1e**).
5. *Typical procedure for the preparation of* **3**: A solution of 0.30 g (1.0 mmol) of 3-(α-chloro-4-nitrophenylmethyl)quinoxalin-2(1*H*)-one **1a** in 4 mL of α-picoline was heated while complete dissolution of compounds **1a** was first observed in the boiling solution. After ca. an hour an abundant precipitation of crystals occurred which gradually dissolved in the course of the reaction over 8 h. The reaction solution was evaporated in vacuo. The resulting crude brown oil was washed with water (2 × 5 mL), dried air, and after crystallization from AcOH gave 0.24 g (72%) of an analytically pure sample of 2-[3-(4-nitrophenyl)]benzimidazole **3a**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.75 (1H, dd, H(7′), J = 7.0; 6.7 Hz); 6.97 (1 H, dd, H(6′), J = 8.6; 7.0 Hz); 7.17–7.21 (3H, m, H(1′), H(5), H(6)); 7.50–7.54 (2H, m, H(4), H(7)); 7.69 (1H, d, H(8′), J = 9.2 Hz); 7.91 (2H, d, H(Ph^2), H(Ph^6), J = 8.9 Hz); 8.22 (1H, d, H(5′), J = 7.3 Hz); 8.37 (2H, d, H(Ph^3), H(Ph^5), J = 8.6 Hz). MS (EI$^+$), *m/z* (*I* (%): 355(19), 354(81) M$^{+\cdot}$, 353(100), 309(5), 308(27), 307(74), 306(49), 305(21), 304(6), 295(7), 279(5), 265(13), 264(12), 262(8), 216(8), 203(6), 191(5), 190(5), 154(49), 153(54), 152(9), 140(10), 139(5), 126 (5), 112(5), 109(6), 98(6), 95(9)). * (The peaks of ions with relative intensity less then 5% are not specified.) Anal. Calcd for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81. Found: C, 70.80; H, 3.78; N, 16.00.
6. The X-ray diffraction data for crystals of **3a** were collected on a Smart Apex II CCD diffractometer at 293 K. *Crystallographic data* for **3a**. $C_{21}H_{14}N_4O_2$, two independent molecules, dark pink prism crystal, formula weight 354.36, monoclinic, $P2_1$, a = 10.8916(16), b = 15.042(2), c = 11.751(2) Å, β = 117.483(2)°, V = 1707.9(5) Å^3, Z = 4, ρ_{calc} = 1.378 g cm^{-3}, μ(λMo K$_\alpha$) = 0.092 mm^{-1}. F(000) = 736, reflections collected = 28,590, unique = 8025, $R_{(int)}$ = 0.0388, full-matrix least-squares on F^2, parameters = 487, restraints = 1. Final indices R_1 = 0.0884, wR_2 = 0.2048 for 5660 reflections with $I > 2\sigma(I)$; R_1 = 0.1252, wR_2 = 0.2240 for all data, goodness-of-fit on F^2 = 1.058, largest difference in peak and hole (0.291 and −0.299 e Å^{-3}).
7. *Typical procedure for the preparation of* **4**. A solution of 0.50 g (1.5 mmol) of 3-(α-chloro-2,4-dichlorophenylmethyl)quinoxalin-2(1*H*)-one **1c** in 4 mL of α-picoline was heated while complete dissolution of compound **1c** was observed in the boiling α-picoline solution. After ca. an hour an abundant precipitation of crystals occurred rapidly which were collected by suction filtration. Thus, 0.26 g (41%) of an analytically pure sample of 3-(2,4-dichloro)phenyl-1,2,3,1,2-pentahydrospiro[quinoxalin-2,2′-indolizin]-3(4*H*)-one **4c** was obtained: ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.91 (1H, d, CH$_A$H$_B$, J_{ab} = 18.5 Hz); 4.67 (1H, d, CH$_A$H$_B$, J_{ab} = 18.5 Hz); 6.26 (1H, d, H(8), J = 7.7 Hz); 6.50 (1H, ddd, H(6), J = 7.7; 7.3; 1.5 Hz); 6.59 (1H, ddd, H(7), J = 7.7; 7.3; 1.5 Hz); 6.69 (1H, dd, H(5), J = 7.7; 1.1 Hz); 6.73 (1H, s, CH); 7.32–7.48 (3H, m, H(Ph^3), H(Ph^5), H(Ph^6)); 7.53 (1H, br s, N(1)H); 7.98 (1H, dd, H(5′), J = 7.3; 6.6 Hz); 8.32 (1H, d, H(3′), J = 8.1 Hz); 8.61 (1H, d, H(6′), J = 6.2 Hz); 8.67 (1H, dd, H(4′), J = 8.1; J = 7.7 Hz), 10.97 (1H, br s, N(4)H). MS (EI$^+$), *m/z* (*I* (%): 398(5), 397(18), 396(8) M$^+$, 395(28), 367(7), 362(10), 361(8), 360(32), 344(20), 343(19), 342(61), 341(15), 334(5), 332(18), 307(9), 306(7), 305(6), 292(9), 291(11), 290(50), 289(18), 288(79), 281(5), 268(6), 261(7), 255(28), 254(20), 253(99), 252(13), 250(14), 240(5), 237(15), 236(28), 227(11), 226(9), 225(32), 224(6), 218(7), 216(16), 215(8), 214(39), 209(18), 208(100), 207(16), 206(5), 201(5), 197(9), 191(21), 190(28), 189(15), 188(6), 180(5), 179(6), 178(5), 172(11), 171(27), 163(8), 162(7), 161(13), 158(23), 153(7), 153(10), 148(6), 140(7), 123(5), 118(7), 104(6), 102(5), 94(5), 93(92), 92(35), 91(6), 90(9), 89(7), 80(10), 79(7), 78(29), 77(6), 66(28), 65(23) 38(17), 36(35) [HCl]). * (The peaks of ions with relative intensity less then 5% are not specified.). Anal. Calcd for $C_{21}H_{16}Cl_3N_3O$: C, 58.29; H, 3.73; Cl, 24.58; N, 9.71. Found: C, 58.34; H, 3.97; Cl, 24.28; N, 9.52.
8. Mamedov, V. A.; Kalinin, A. A.; Gubaidullin, A. T.; Litvinov, I. A. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 2386.
9. The X-ray diffraction data for crystal **4c** (acceptable crystals for X-ray analysis were obtained after crystallization from acetic acid) were collected on a Smart Apex II CCD diffractometer at 293 K. *Crystallographic data* for **4c**. $2(C_{21}H_{16}Cl_2N_3O^+)\cdot 2(Cl^-)\cdot C_2H_4O_2$, green plate crystal, formula weight 925.49, triclinic, $P\bar{1}$, a = 7.4352(13), b = 17.032(3), c = 17.361(3) Å, α = 102.775(2)°, β = 93.238(2)°, γ = 98.979(2)°, V = 2108.4(6) Å^3, Z = 2, ρ_{calc} = 1.458 g cm^{-3}, μ(λMo K$_\alpha$) = 0.460 mm^{-1}. F(000) = 952, reflections collected = 23,090, unique = 9116, $R_{(int)}$ = 0.0241, full-matrix least-squares on F^2, parameters = 557, restraints = 4. Final indices R_1 = 0.0459, wR_2 = 0.1190 for 6422 reflections with $I > 2\sigma(I)$; R_1 = 0.0716, wR_2 = 0.1327 for all data, goodness-of-fit on F^2 = 1.018, largest difference in peak and hole (0.714 and −0.397 e Å^{-3}). Crystallographic data (excluding structure factors) for the structures **3a** and **4c** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 692009, 692010. 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).
10. (a) Fuks, L.; Gniazdowska, E.; Mieczkowski, J.; Narbutt, J.; Starosta, W.; Zasepa, M. *J. Organomet. Chem.* **2004**, 4751; (b) Carran, J.; Waschbuesch, R.; Savignac, P. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, 209; (c) Arai, S.; Arai, H.; Tabuchi, K.; Yamagishi, T.; Hida, M. *J. Heterocycl. Chem.* **1992**, 215; (d) Hisano, T.; Yabuta, Y. *Chem. Pharm. Bull.* **1973**, 511; (e) Mamane, V.; Aubert, E.; Fort, Y. *J. Organomet. Chem.* **2007**, 7294; (f) Jiang, Y.; Zhou, G.-Ch.; He, G.-L.; He, L.; Li, J.-L.; Zheng, Sh.-L. *Synthesis* **2007**, 1459; (g) Natarajan, S. R.; Chen, M.-H.; Heller, S.-T.; Tynebor, R. M.; Crawford, E. M.; Minxiang, C.; Kaizheng, H.; Dong, J.; Hu, B.; Hao, W.; Chen, S.-H. *Tetrahedron Lett.* **2006**, 5063; (h) Mohr, F.; Binfield, S. A.; Fettinger, J. C.; Vedernikov, A. N. *J. Org. Chem.* **2005**, 4833; (i) Goel, Sh.; Parkash, S.; Goel, V. K. *J. Indian Chem. Soc.* **2004**, 344.
11. (a) Jones, G. B.; Moody, C. J.; Padwa, A.; Kassir, J. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1721; (b) Biresaw, G.; Bunton, C. A. *J. Phys. Chem.* **1986**, 5849; (c) Ishida, M.; Ichikawa, K.; Asano, H.; Nakanishi, H.; Kato, Sh. *Synthesis* **1987**, 349; (d) Curran, W. V.; Sassiver, M. L.; Boothe, J. H.; Jacob, L. *J. Heterocycl. Chem.* **1985**, 479; (e) Aszodi, J.; Bonnet, A.; Teutsch, G. *Tetrahedron* **1990**, 1579; (f) Bosch, J.; Salas, M.; Amat, M.; Alvarez, M.; Morgo, I.; Adrover, B. *Tetrahedron* **1991**, 5269; (g) Sakaizumi, T.; Nichikawa, M.; Ohashi, A. *J. Mol. Spectrosc.* **1995**, 518; (h) Miyabe, H.; Kanehiro, S.; Kume, K.; Kandori, H.; Naito, T. *Tetrahedron* **1998**, 5883; (i) Grimmins, M. T.; Shamsad, M. *Org. Lett.* **2007**, 149; (j) Korapala, Ch. S.; Qin, J.; Friestad, G. K. *Org. Lett.* **2007**, 4243.
12. (a) Cheeseman, G. W. H.; Cookson, R. F. *Condensed Pyrazines* **1979**, *35*; (b) Mamedov, V. A.; Kalinin, A. A.; Yanilkin, V. V.; Gubaidullin, A. T.; Latypov, Sh. K.; Balandina, A. A.; Isaikina, O. G.; Toropchina, A. V.; Nastapova, N. V.; Iglamova, N. A.; Litvinov, I. A. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 2616.