Synthesis of 6-aryl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*]-1,7- and -1,8-phenanthrolines

A. G. Tolstikov, R. G. Savchenko, E. S. Lukina, R. M. Limantseva, and V. N. Odinokov★

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences,
141 prosp. Oktyabrya, 450075 Ufa, Russian Federation.
Fax: +7 (347) 284 2750. E-mail: odinokov@anrb.ru

A three-component acid-catalyzed cyclocondensation of 5-aminoquinoline and 5-aminoisoquinoline with aromatic aldehydes and cyclopentadiene leads to (6*S**,6a*R**,9a*S**)-6-aryl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*]-1,7- and (6*S**,6a*R**,9a*S**)-6-aryl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*]-1,8-phenanthrolines.

Key words: three-component condensation, Povarov reaction, 5-aminoquinoline, 5-aminoisoquinoline, aromatic aldehydes, cyclopentadiene, tetrahydro-1,7-phenanthrolines, tetrahydro-1,8-phenanthrolines.

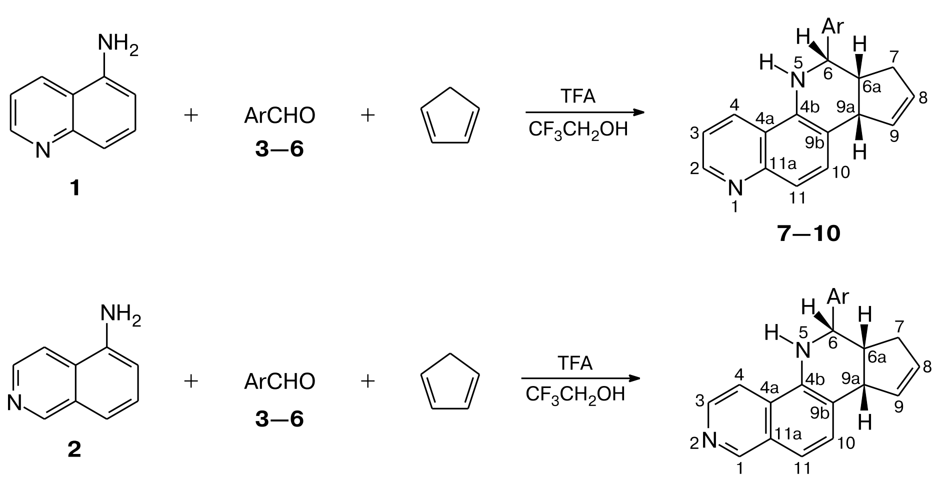
Phenanthroline tetrahydro derivatives, being analogues of alkaloids and diazasteroids, possess a high potential of biological activity.[1,2] Commonly, they are synthesized by the reaction of aminoquinolines with carbonyl compounds.[3] There is another very promising approach to the synthesis of diazasteroids, which is based on a three-component condensation of aminoquinolines with formaldehyde and cyclopentadiene.[4,5]

We were the first to study an acid-catalyzed one-step cyclocondensation of aminoquinolines with aromatic aldehydes and cyclopentadiene.

The reaction of 5-aminoquinoline (**1**) and 5-aminoisoquinoline (**2**) with aromatic aldehydes (benzaldehyde (**3**), *m*-chloro- (**4**), *o*-fluoro- (**5**), and *p*-trifluoromethylbenzaldehydes (**6**)) and cyclopentadiene gave earlier unknown tetrahydro-1,7- and tetrahydro-1,8-phenanthrolines annulated to cyclopentene, which belong to the class of 4,11-diazasteroids.[5]

The reaction went smoothly when 2,2,2-trifluoroethanol was used as a solvent (room temperature, 2—3 h, catalyst trifluoroacetic acid (TFA)) and led to the target 6-aryl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*]-1,7- (**7—10**) and 6-aryl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*]-1,8-phenanthrolines (**11—14**) (Scheme 1). Running the reaction in acetonitrile[6—8] commonly used for such processes led only to the corresponding Schiff bases. It should be

Scheme 1



Ar = Ph (**3**, **7**, **11**), *m*-Cl-C_6H_4 (**4**, **8**, **12**), *o*-F-C_6H_4 (**5**, **9**, **13**), *p*-CF_3-C_6H_4 (**6**, **10**, **14**)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 2077—2080, September, 2014.

noted that in the cases when an amino group was located on the pyridine ring of quinolines (3- and 4-aminoquinolines), the corresponding tetrahydrophenanthrolines were not obtain even in trifluoroethanol.

The formation of 6-aryltetrahydrophenanthrolines annulated with cyclopentene occurred with high diastereoselectivity. The ^{1}H NMR data (from the ratio of intensities of major and minor signals of vinyl protons H(8) or H(9) in the region δ 5.7—6.1) showed that the diastereomeric purity (*de*) of compounds **7—14** was no less than 90%. The spin-spin coupling constants for vicinal protons H(6) and H(6a) equal to 2.4 or 2.8 Hz, as well as that for protons H(6a) and H(9a) equal to 8.4 Hz (Tables 1 and 2) indicate a mutual *cis*-orientation of protons H(6), H(6a),

Table 1. ^{1}H and ^{13}C NMR spectra (δ, *J*/Hz) of compounds **7—10**

Group or atom	**7**		**8**		**9**		**10**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
C(2)H	149.30	8.83 d, *J* = 3.2	149.36	8.89 d, *J* = 3.2	149.28	8.83 d, *J* = 3.2	149.32	8.84 d, *J* = 3.2
C(3)H	119.63	7.32 dd, *J* = 8.0, 3.2	119.72	7.21 dd, *J* = 8.0, 3.2	119.66	7.32 dd, *J* = 8.0, 3.2	119.77	7.35 dd, *J* = 8.0, 3.2
C(4)H	128.27	8.12 d, *J* = 8.0	128.26	8.07 d, *J* = 8.0	128.21	8.13 d, *J* = 8.0	128.28	8.16 d, *J* = 8.0
C(4a)	118.62	—	118.67	—	118.70	—	118.69	—
C(4b)	147.57	—	147.55	—	147.51	—	147.46	—
C(6)H	58.20	4.77 d, *J* = 2.4	57.71	4.70 d, *J* = 2.4	57.04	5.12 d, *J* = 2.4	57.91	4.84 d, *J* = 2.4
C(6a)H	46.07	3.27 td, *J* = 8.4, 2.4	45.83	3.08 td, *J* = 8.4, 2.4	43.46	3.27 td, *J* = 8.4, 2.4	45.79	3.14 td, *J* = 8.4, 2.4
C(7)H_2	31.38	1.92 dd, *J* = 15.6, 8.4; 2.74 m	31.27	1.89 dd, *J* = 15.6, 8.4; 2.66 m	31.56	1.91 dd, *J* = 15.6, 8.4; 2.68 m	31.23	1.88 dd, *J* = 15.6, 8.4; 2.69 m
C(8)H	130.90	5.70 m (5.77 m)*	131.47	5.68 m (5.76 m)*	130.71	5.68 m (5.75 m)*	130.73	5.70 m (5.75 m)*
C(9)H	133.72	5.98 m (6.08 br.s)*	133.66	5.95 m (6.06 br.s)*	133.80	5.96 m (6.09 br.s)*	133.64	5.99 m (6.07 br.s)*
C(9a)H	46.82	4.29 d, *J* = 8.4	46.64	4.25 d, *J* = 8.4	46.53	4.30 d, *J* = 8.4	46.67	4.31 d, *J* = 8.4
C(9b)	120.81	—	120.76	—	120.99	—	120.85	—
C(10)H	131.13	7.47 d, *J* = 8.8	131.01	7.36 d, *J* = 8.8	131.11	7.45 d, *J* = 8.8	131.06	7.46 d, *J* = 8.8
C(11)H	119.96	7.58 d, *J* = 8.8	120.28	7.53 d, *J* = 8.8	120.21	7.58 d, *J* = 8.8	120.34	7.59 d, *J* = 8.8
C(11a)	139.89	—	139.41	—	139.72	—	139.31	—
C(1´)	142.59	—	144.74	—	129.67 d, $^2J_{CF}$ = 12.0	—	146.63	—
C(2´)	—	—	—		160.17 d, $^1J_{CF}$ = 245.0	—	—	—
C(2´)H	128.72	7.56 d, *J* = 4.8	129.78	7.44 s	—	—	125.67	7.69 dd, *J* = 8.8, 2.8
C(3´)	—	—	135.93	—	—	—	—	—
C(3´)H	126.68	7.46 m	—	—	115.45 d, $^2J_{CF}$ = 21	7.78 dd, J_{CF} = 8.0, $J_{H,H}$ = 8.0	127.01	7.69 dd, *J* = 8.8, 2.8
C(4´)	—	—	—	—	—	—	122.79	—
C(4´)H	127.59	7.38 m	127.71	7.30 m	127.34 d, $^3J_{CF}$ = 4	7.12 dd, *J* = 8.0	—	—
C(5´)H	126.68	7.46 m	124.87	7.30 m	124.38 d, $^4J_{CF}$ = 3	7.26 m	127.01	7.69 dd, *J* = 8.8, 2.8
C(6´)H	128.72	7.56 d, *J* = 4.8	126.73	7.30 m	129.42 d, $^3J_{CF}$ = 8	7.36 m	125.64	7.69 dd, *J* = 8.8, 2.8
CF_3	—	—	—	—	—	—	125.50 q $^1J_{CF}$ = 270	—
NH	—	4.49 br.s	—	4.45 br.s	—	4.35 br.s	—	4.49 br.s

* Chemical shifts δ_H C(8)H and C(9)H for minor 6*R**-diastereomers are given in parentheses.

Table 2. ^{1}H and ^{13}C NMR spectra (δ, *J*/Hz) of compounds **11—14**

Group or atom	**11**		**12**		**13**		**14**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
C(1)H	152.72	9.11 s	152.67	9.22 s	152.74	9.12 s	152.76	9.12 s
C(3)H	142.35	8.45 d, *J* = 6.0	142.39	8.42 d, *J* = 6.0	142.38	8.46 d, *J* = 6.0	142.51	8.47 d, *J* = 6.0
C(4)H	113.17	7.53 d, *J* = 6.0	113.24	7.54 d, *J* = 6.0	113.08	7.54 d, *J* = 6.0	113.05	7.55 d, *J* = 6.0
C(4a)	126.30	—	126.35	—	126.38	—	126.37	—
C(4b)	139.11	—	138.68	—	138.95	—	138.53	—
C(6)H	58.04	4.77 d, *J* = 2.8	57.51	4.50 s	50.91	5.11 d, *J* = 2.8	57.74	4.83 d, *J* = 2.8
C(6a)H	46.12	3.15, td, *J* = 8.4, 2.8	45.88	3.06 td, *J* = 8.4, 2.8	43.48	3.28 td, *J* = 8.4, 2.8	45.84	3.15 td, *J* = 8.4, 2.8
$C(7)H_2$	31.39	1.92 dd, *J* =15.6, 8.4; 2.73 m	31.29	1.86 dd *J* =15.6, 8.4; 2.63 m	31.57	1.91 td, *J* =15.6, 8.4; 2.68 m	31.24	1.87 dd, *J* =15.6, 8.4; 2.68 m
C(8)H	131.22	5.71 m (5.79 br.s)*	131.07	5.67 br.s (5.75 br.s)*	131.02	5.69 m (5.79 br.s)*	131.03	5.70 m (5.78 m)*
C(9)H	133.34	5.96 m (6.06 br.s)*	133.30	5.93 br.s (6.08 br.s)*	133.42	5.94 m (6.05 br.s)*	133.28	5.96 m (6.06 m)*
C(9a)H	47.09	4.30 d, *J* = 8.4	46.89	4.23 d, *J* = 8.4	46.81	4.30 d, *J* = 8.4	47.61	4.31 d, *J* = 8.4
C(9b)	124.36	—	124.29	—	124.50	—	124.37	—
C(10)H	128.74	7.46 d, *J* = 8.0	128.67	7.29 d, *J* = 8.0	128.77	7.39 d, *J* = 8.0	128.64	7.32 d, *J* = 8.0
C(11)H	117.83	7.43 d, *J* = 8.0	118.10	7.39 d, *J* = 8.0	118.11	7.41 d, *J* = 8.0	118.29	7.41 d, *J* = 8.0
C(11a)	127.72	—	127.63	—	128.04	—	127.69	—
C(1´)	142.35	—	134.62	—	129.61	—	143.23	—
C(2´)	—	—	—	—	160.15 q, $^1J_{CF}$ = 245.0	—	—	—
C(2´)H	126.65	7.42 m	130.01	7.35 m	—	—	127.00	7.70 dd, *J* = 8.8, 2.8
C(3´)H	127.62	7.42 m	—	—	115.44 d, $^2J_{CF}$ = 21	7.12 dd, J_{CF} = 8.0, $J_{H,H}$ = 8.0	125.69	7.70 dd, *J* = 8.8, 2.8
C(3´)	—	—	144.64	—	—	—	—	—
C(4´)H	128.74	7.42 m	126.75	7.35 m	127.33 d, $^3J_{CF}$ = 4.0	7.28	—	—
C(4´)	—	—	—	—	—	—	146.52	—
C(5´)H	128.74	7.42 m	127.74	7.35 m	124.42 d, $^4J_{CF}$ = 3.0	7.37	125.69	7.70 dd, *J* = 8.8, 2.8
C(6´)H	126.65	7.42 m	124.84	7.35 m	128.98 d, $^3J_{CF}$ = 27.0	7.79 t, *J* = 8.0	127.00	7.70 dd, *J* = 8.8, 2.8
CF_3	—	—	—	—	—	—	125.50 q $^1J_{CF}$ = 270	—
NH	—	4.51 br.s	—	4.66 br.s	—	4.37 br.s	—	4.50 br.s

* Chemical shifts δ_H C(8)H and C(9)H for minor 6*R**-diastereomers are given in parentheses.

and H(9a) and the *S**, *R**, and *S** relative configuration of asymmetric atoms C(6), C(6a), and C(9a), respectively. According to the data of the work,[9] the minor diastereomers differ from the major ones in the configuration of carbon atom C(6) bearing the aryl substituent, *i.e.*, the minor diastereomers have the 6*R**, 6a*R**, and 9a*S** relative configuration of the chiral centers.

The signals in the ^{1}H and ^{13}C NMR spectra of synthesized compounds (see Tables 1 and 2) were assigned using 1D and 2D ^{1}H and ^{13}C NMR procedures (JMOD, HSQC, HMBC, COSY, NOESY). The mass spectra MALDI TOF of compounds **7—14** showed the presence of the corresponding molecular ions.

In conclusion, a three-component condensation in CF_3CH_2OH of aminoquinolines, aromatic aldehydes, and cyclopentadiene in the presence of TFA as a catalyst gives rise to (6*S**,6a*R**,9a*S**)-6-aryl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*]-1,7- and -1,8-phenanthrolines, which are structural analogues of alkaloids and diazasteroids.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400.13 MHz (^{1}H) and 100.62 (^{13}C) MHz) in $CDCl_3$, using $SiMe_4$ as an internal standard. Homo- and heteronuclear procedures COSY, HSQC, and HMBC were carried out according to the Bruker standard procedures. Mass spectra were obtained on a Bruker-Autoflex III instrument in the MALDI TOF regime with registration of positive ions and using α-cyano-4-hydroxycinnamic acid as a matrix. Melting points were measured on a Boetius heating microstage. Elemental analysis was performed on a Carlo Erba EA-1108 CHNS-O-analyzer. Column chromatography was carried out on KSKG silica gel, 100/200. Silufol plates covered with SiO_2 was used for TLC monitoring, visualizing with a solution of vanillin in ethanol acidified with sulfuric acid.

The starting compounds **1**—**6** were purchased from Acros Organics. ^1H and ^{13}C NMR spectra of compounds **7**—**10** and **11**—**14** are given in Tables 1 and 2, respectively.

Synthesis of 6-aryl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*]-1,7- (7—10) and 6-aryl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*]-1,8-phenanthrolines (11—14) (general procedure). The compound CF_3COOH (0.08 mL, 1 mmol), a freshly distilled cyclopentadiene (0.33 mL, 4 mmol), and the corresponding aldehyde **3**—**6** (1 mmol) were sequentially added to a solution of aminoquinoline **1** or **2** (144 mg, 1 mmol) in anhydrous CF_3CH_2OH (15 mL) (Ar, ~25 °C). The reaction mixture was stirred at room temperature until the amine disappeared (2—3 h, TLC monitoring, eluent ethyl acetate). The solvent was evaporated, a saturated solution of $NaHSO_3$—$NaHCO_3$ was added to the residue until neutrality (~5 mL), followed by extraction with ethyl acetate (3×10 mL). The organic layer was concentrated, the residue was subjected to chromatography (SiO_2, *n*-hexane/ethyl acetate, 4 : 1) to isolate the corresponding 1,7- (**7**—**10**) or 1,8-phenanthrolines (**11**—**14**).

(6*S,6a*R**,9a*S**)-6-Phenyl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,7]phenanthroline (7).** The yield was 51%, *de* 92% (from the ratio of signal intensities at δ 5.98 and 6.08), R_f 0.49 (ethyl acetate), m.p. 102—104 °C (*n*-hexane). MS (MALDI TOF), *m/z*: 299 $[M + H]^+$. Found (%): C, 84.60; H, 6.12; N, 9.28. $C_{21}H_{18}N_2$. Calculated (%): C, 84.56; H, 6.04; N, 9.40.

(6*S,6a*R**,9a*S**)-6-(*m*-Chlorophenyl)-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,7]phenanthroline (8).** The yield was 68%, *de* 90% (from the ratio of signal intensities at δ 5.95 and 6.06), R_f 0.40 (ethyl acetate), m.p. 97—99 °C (*n*-hexane). MS (MALDI TOF), *m/z*: 333 $[M + H]^+$. Found (%): C, 75.93; H, 5.18; Cl, 10.61; N, 8.50. $C_{21}H_{17}ClN_2$. Calculated (%): C, 75.90; H, 5.12; Cl, 10.69; N, 8.43.

(6*S,6a*R**,9a*S**)-6-(*o*-Fluorophenyl)-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,7]phenanthroline (9).** The yield was 70%, *de* 94% (from the ratio of signal intensities at δ 5.96 and 6.09), R_f 0.43 (ethyl acetate), m.p. 90—92 °C (*n*-hexane). MS (MALDI TOF), *m/z*: 317 $[M + H]^+$. Found (%): C, 79.64; H, 5.28; N, 8.69. $C_{21}H_{17}FN_2$. Calculated (%): C, 79.75; H, 5.40; N, 8.86.

(6*S,6a*R**,9a*S**)-6-[*p*-(Trifluoromethyl)phenyl]-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,7]phenanthroline (10).** The yield was 51%, *de* 97% (from the ratio of signal intensities at δ 5.99 and 6.07), R_f 0.48 (ethyl acetate), m.p. 120—122 °C (*n*-hexane). MS (MALDI TOF), *m/z*: 367 $[M + H]^+$. Found (%): C, 72.01; H, 4.58; N, 7.51. $C_{22}H_{17}F_3N_2$. Calculated (%): C, 72.13; H, 4.64; N, 7.65.

(6*S,6a*R**,9a*S**)-6-Phenyl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,8]phenanthroline (11).** The yield was 56%, *de* 90% (from the ratio of signal intensities at δ 5.96 and 6.06), R_f 0.47 (ethyl acetate), m.p. 60—62 °C (*n*-hexane). MS (MALDI TOF), *m/z*: 299 $[M + H]^+$. Found (%): C, 84.67; H, 6.15; N, 9.32. $C_{21}H_{18}N_2$. Calculated (%): C, 84.56; H, 6.04; N, 9.40.

(6*S,6a*R**,9a*S**)-6-(*m*-Chlorophenyl)-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,8]phenanthroline (12).** The yield was 70%, *de* 90% (from the ratio of signal intensities at δ 5.93 and 6.08), R_f 0.40 (ethyl acetate), m.p. 89—91 °C (*n*-hexane). MS (MALDI TOF), *m/z*: 333 $[M + H]^+$. Found (%): C, 75.76; H, 5.23; Cl, 10.42; N, 8.29. $C_{21}H_{17}ClN_2$. Calculated (%): C, 75.90; H, 5.12; Cl, 10.69; N, 8.43.

(6*S,6a*R**,9a*S**)-6-(*o*-Fluorophenyl)-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,8]phenanthroline (13).** The yield was 70%, *de* 94% (from the ratio of signal intensities at δ 5.94 and 6.05), R_f 0.42 (ethyl acetate), m.p. 58—60 °C (*n*-hexane). MS (MALDI TOF), *m/z*: 317 $[M + H]^+$. Found (%): C, 79.87; H, 5.64; N, 8.73. $C_{21}H_{17}FN_2$. Calculated (%): C, 79.75; H, 5.40; N, 8.86.

(6*S,6a*R**,9a*S**)-6-[*p*-(Trifluoromethyl)phenyl]-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[c][1,8]phenanthroline (14).** The yield was 62%, *de* 94% (from the ratio of signal intensities at δ 5.96 and 6.06), R_f 0.50 (ethyl acetate), m.p. 52—54 °C (*n*-hexane). MS (MALDI TOF), *m/z*: 367 $[M + H]^+$. Found (%): C, 72.23; H, 4.60; N, 7.58. $C_{22}H_{17}F_3N_2$. Calculated (%): C, 72.13; H, 4.64; N, 7.65.

The authors are grateful to Prof. L. M. Khalilov for discussion of ^1H and ^{13}C NMR spectra.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 14-03-00286) and the Presidium of the Russian Academy of Sciences (Program "Fundamental Science to Medicine").

References

1. K. Saeki, T. Matsuda, T. Kato, S. Matsui, K. Fukuhara, N. Miyata, *Biolog. Pharm. Bull.*, 2003, **26**, 448.
2. M. Duszyk, L. Mac Vinish, A. W. Guthbert, *Brit. J. Pharm.*, 2001, **134**, 853.
3. N. G. Kozlov, A. B. Tereshko, *Russ. J. Org. Chem.* (*Engl. Transl.*), 2010, **46**, 1223 [*Zh. Org. Khim.*, 2010, **46**, 1221].
4. P. J. Gregoire, J. M. Mellor, G. D. Merriman, *Tetrahedron Lett.*, 1991, **32**, 7099.
5. J. M. Mellor, G. D. Merriman, *Steroids*, 1995, **60**, 693.
6. A. G. Tolstikov, L. M. Khalilov, R. G. Savchenko, D. V. Nedopekin, V. A. Glushkov, G. F. Krainova, I. V. Glukhov, M. Yu. Antipin, V. N. Odinokov, *Russ. Chem. Bull.* (*Int. Ed.*), 2009, **58**, 1991 [*Izv. Akad. Nauk, Ser. Khim.*, 2009, 1929].
7. A. G. Tolstikov, R. G. Savchenko, D. V. Nedopekin, S. R. Afon´kina, E. S. Lukina, V. N. Odinokov, *Russ. Chem. Bull.* (*Int. Ed.*), 2011, **60**, 160 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2011, 153].
8. A. G. Tolstikov, R. G. Savchenko, E. S. Lukina, D. V. Nedopekin, V. N. Odinokov, *Russ. Chem. Bull.* (*Int. Ed.*), 2013, **62**, 203 [*Izv. Akad. Nauk, Ser. Khim.*, 2013, 203].
9. V. A. Glushkov, A. G. Tolstikov, *Russ. Chem. Rev.* (*Engl. Transl.*), 2008, **77**, 137.

Received December 12, 2013;
in revised form March 25, 2014