HETEROCYCLES, Vol. 86, No. 1, 2012, pp. 719 - 725. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 1st June, 2012, Accepted, 13th July, 2012, Published online, 18th July, 2012
DOI: 10.3987/COM-12-S(N)25

RING-OPENING REACTIONS OF 2-PHENYL-1'*H*,5*H*-SPIRO-[OXAZOLE-4,2'-QUINOXALIN]-3'(4'*H*)-ONES[#]

Irena Mušič and Bojan Verček*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia. E-mail: bojan.vercek@fkkt.uni-lj.si

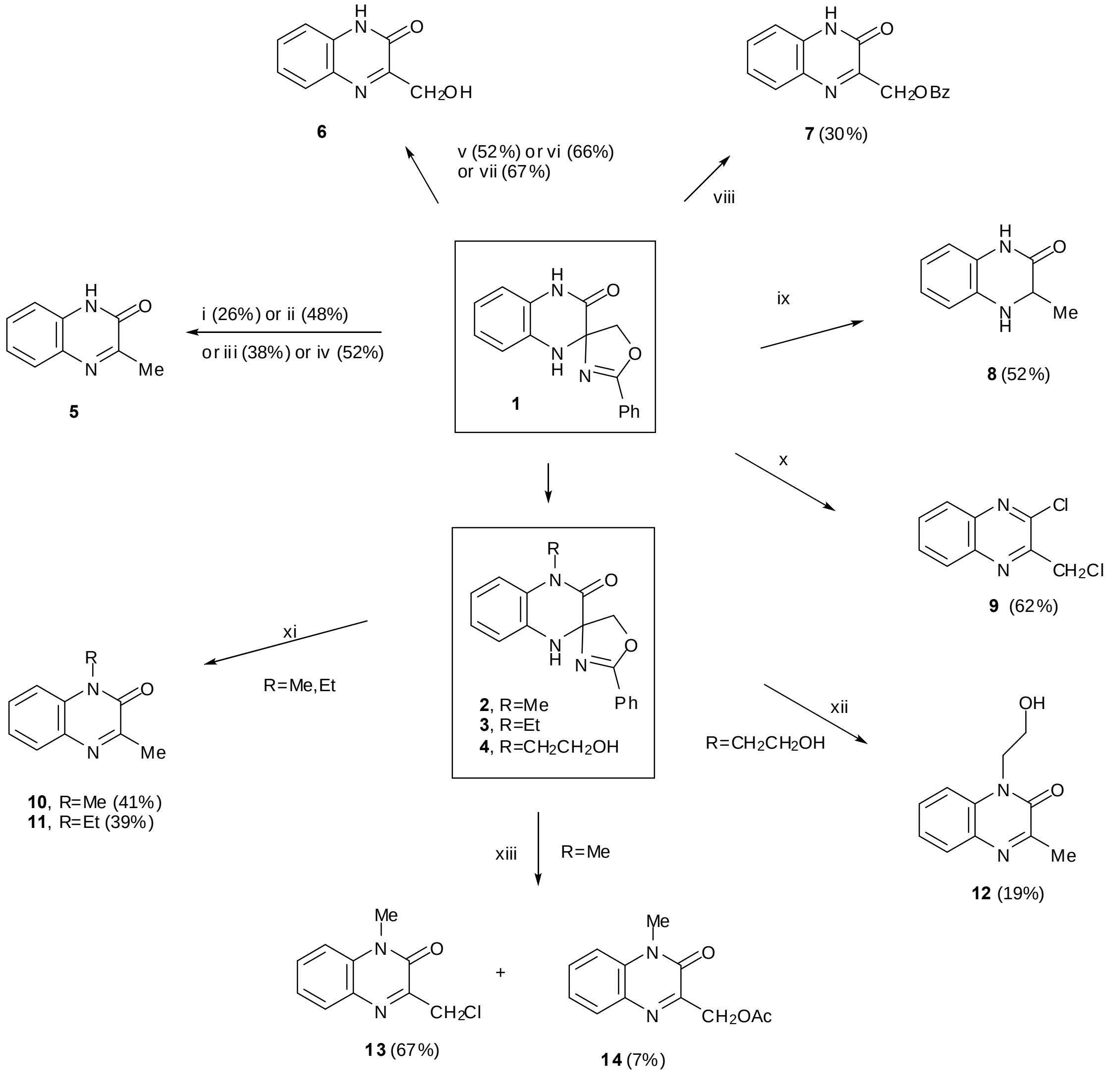
Abstract – Several simple quinoxaline derivatives were prepared by ring-opening reactions of 2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one and its *N*-alkyl derivatives under various reaction conditions.

Quinoxaline is an important heterocyclic system which constitutes the scaffold of many biologically active compounds.[1] Therefore, the development of novel approaches to quinoxalines still remains an important task in heterocyclic synthesis. The most common synthetic routes to quinoxaline are the condensation reactions between *o*-phenylenediamines and various 1,2-bifunctional electrophiles such as, for example, diketones, ketoesters, haloketones, and haloesters.[2] As part of our studies on the synthesis of heterocyclic compounds utilizing simple amino acid derivatives,[3] we described the synthesis of several 1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-ones and their alkylation which resulted in the introduction of an alkyl group or a substituted alkyl group on the lactam nitrogen atom.[3a,3h] Since the oxazoline system can undergo ring-opening reactions,[4] our further research focused on reactions leading towards the formation of simple quinoxaline derivatives starting from 2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-ones (**1-4**) as shown in Scheme 1.

First, we investigated the reactions of 2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (**1**). The most often isolated product of these reactions was 3-methylquinoxalin-2(1*H*)-one (**5**). It was formed by refluxing compound **1** in hydrochloric acid as well as by treatment of **1** with hot hydrazine hydrate. Interestingly, compound **5** was also formed in an unsuccessful attempt of the *N*-methylation of **1** with methyl iodide in methanol in an autoclave at 80 °C, and in an unsuccessful attempt of the exchange of the oxo with thioxo group in the pyrazinone part of **1** using phosphorus pentasulfide in hot xylene.

[#] Dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday

When **1** was heated with hydrazine hydrate, sodium ethoxide or free hydroxylamine in ethanol, 3-(hydroxymethyl)quinoxalin-2(1*H*)-one (**6**) was formed. On the other hand, heating **1** in concentrated sulphuric acid gave its *O*-benzoyl derivative, 3-(benzoyloxymethyl)quinoxalin-2(1*H*)-one (**7**). Catalytic hydrogenation of **1** with H_2 in the presence of Pd/C resulted in the formation of 3,4-dihydro-3-methylquinoxalin-2(1*H*)-one (**8**). Treatment of **1** with hot phosphorus oxychloride gave 2-chloro-3-(chloromethyl)quinoxaline (**9**).



Scheme 1. *Reagents and conditions*: i) 18% HCl, reflux; ii) $NH_2NH_2{\cdot}H_2O$, 110 °C; iii) MeI, MeOH, autoclave, 80 °C; iv) P_4S_{10}, xylene, reflux; v) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; vi) NaOEt, EtOH, reflux; vii) $NH_2OH{\cdot}HCl$, NaOEt, EtOH, reflux; viii) conc. H_2SO_4, 80-90 °C; ix) H_2, Pd/C, EtOH, rt; x) $POCl_3$, 80–85 °C; xi) 18% HCl, EtOH, reflux; xii) PPA, 90 °C; xiii) AcCl, CH_2Cl_2, reflux.

Other reactions were carried out with spiro compounds **2-4**. Refluxing of 4’-methyl-2-phenyl-1’*H*,5*H*-spiro[oxazole-4,2’-quinoxalin]-3’(4’*H*)-one (**2**) in a mixture of aqueous HCl and ethanol gave

1,3-dimethylquinoxalin-2(1*H*)-one (**10**). Under similar reaction conditions, 1-ethyl-3-methylquinoxalin-2(1*H*)-one (**11**) was formed from 4’-ethyl-2-phenyl-1’*H*,5*H*-spiro[oxazole-4,2’-quinoxalin]-3’(4’*H*)-one (**3**). Furthermore, an unsuccessful attempt of the dehydration reaction of the *N*-hydroxyethyl derivative **4** using hot polyphosphoric acid (PPA) led to the formation of 1-(2-hydroxyethyl)-3-methylquinoxalin-2(1*H*)-one (**12**). Finally, the reaction between **2** and acetyl chloride in hot dichloromethane gave a mixture of 3-(chloromethyl)-1-methylquinoxalin-2(1*H*)-one (**13**) and 3-(acetyloxymethyl)-1-methylquinoxalin-2(1*H*)-one (**14**).

In summary, we have demonstrated that several quinoxaline derivatives can be produced by ring-opening reactions of 2-phenyl-1’*H*,5*H*-spiro[oxazole-4,2’-quinoxalin]-3’(4’*H*)-ones **1-4**. Although the formation of simple quinoxalines was achieved under various reaction conditions, the reactions usually gave complex mixtures of products and moderate yields of mostly known quinoxalines.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (300 MHz for ^{1}H) in DMSO-d_6 with TMS as an internal standard. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. Elemental analyses were performed on a Perkin-Elmer CHN Analyzer 2400. TLC was carried out on Fluka silica gel TLC-cards. Radial chromatography was performed on Merck Kieselgel PF$_{254}$ silica gel. Starting compounds **1-4** were prepared as described in the literature.[3a,3h] Side products, benzamide and benzamidoxime,[5] were identified by comparison with authentic samples. All other compounds were used without purification as obtained from commercial sources.

3-Methylquinoxalin-2(1*H*)-one (5). a) A mixture of **1** (320 mg, 1.15 mmol) and aqueous HCl (18%, 4 mL) was heated under reflux for 3.5 h. After cooling and addition of cold water (4 mL), the precipitated benzoic acid was filtered off and washed with water (128 mg, 91%). The filtrate was neutralized with $NaHCO_3$ and extracted with AcOEt (3x20 mL). After drying with Na_2SO_4, AcOEt was evaporated under reduced pressure and the solid residue was purified with radial chromatography ($CHCl_3$/MeOH, 50:1) to afford compound **5**[6] (47 mg, 26%). mp 242–244 °C (AcOEt). ^{1}H NMR δ: 2.40 (s, 3H, CH_3), 7.26 (m, 2H, H6, H8), 7.47 (m, 1H, H7), 7.69 (m, 1H, H5), 12.28 (bs, 1H, NH). MS (EI, *m/z*, %): 160 (M^+, 100). *Anal.* Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.21; H, 5.11; N, 17.43.

b) A mixture of **1** (558 mg, 2 mmol) and hydrazine hydrate (99%, 6 mL) was heated on an oil bath at 110 °C for 2 h. After cooling, the reaction mixture was filtered, the filtrate was evaporated and the residue was suspended in water (4 mL). The solid was filtered off and crystallized from EtOH to give **5** (154 mg, 48%).

c) A mixture of **1** (279 mg, 1 mmol), MeOH (12 mL) and MeI (0.13 mL, 2 mmol) was heated in an autoclave at 80 °C for 22 h. After cooling, the volatile components were evaporated under reduced pressure and the residue was purified by radial chromatography ($CHCl_3$/MeOH, 50:1) to give **5** (60 mg, 38%) and benzamide (58 mg, 48%).

d) A mixture of **1** (140 mg, 0.5 mmol), P_4S_{10} (120 mg, 0.54 mmol) and xylene (2 mL) was heated under reflux for 3.5 h. The reaction mixture was decanted and the solid residue was extracted with AcOEt (3 x 50 mL). The solvent was evaporated under reduced pressure and the solid residue was separated by radial chromatography ($CHCl_3$/MeOH, 50:1) to give **5** (42 mg, 52%) and benzamide (26 mg, 43%).

3-(Hydroxymethyl)quinoxalin-2(1*H*)-one (6). a) A mixture of **1** (140 mg, 0.5 mmol), EtOH (2 mL) and hydrazine hydrate (50 mg, 1 mmol) was heated under reflux for 13 h. After cooling to rt, the solid product was filtered off, washed with EtOH and crystallized from water to give **6**[7] (46 mg, 52%). mp 200–205 °C. ^{1}H NMR δ: 4.61 (d, 2H, *J* = 6.0 Hz, CH_2), 4.99 (t, 1H, *J* = 6.0 Hz, OH), 7.31 (m, 2H, H6, H8), 7.51 (m, 1H, H7), 7.78 (m, 1H, H5), 12.38 (bs, 1H, NH). MS (EI, *m/z*, %): 176 (M^+, 81). *Anal.* Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.18; H, 4.34; N, 15.97.

b) To a solution of EtONa, prepared from Na (60 mg, 2.6 mmol) and EtOH (5 mL), compound **1** (300 mg, 1.07 mmol) was added. The mixture was heated under reflux for 1.5 h and then cooled to rt. The solid product was filtered off, washed with EtOH and crystallized from EtOH to give **6** (124 mg, 66%).

c) To a solution of hydroxylamine hydrochloride (104 mg, 1.5 mmol) in EtOH (4.3 mL), a solution of EtONa, prepared from Na (34.8 mg, 1.5 mmol) and EtOH (2.9 mL), was added, followed by an addition of **1** (209 mg, 0.75 mmol). The reaction mixture was heated under reflux for 6.5 h. After cooling to rt, the separated solid was filtered off, washed with EtOH and crystallized from EtOH to afford product **6** (89 mg, 67%). The collected filtrate was evaporated and the remaining residue was purified by radial chromatography (AcOEt/$CHCl_3$, 2:1) to give benzamidoxime[5] (75 mg, 74 %).

3-(Benzoyloxymethyl)quinoxalin-2(1*H*)-one (7). A mixture of **1** (200 mg, 0.72 mmol) and concd H_2SO_4 (1 mL) was heated on an oil bath at 80–90 °C for 3.5 h. The hot reaction mixture was then diluted with cold water (10 mL), the precipitated solid was filtered off, washed with water and purified by radial chromatography ($CHCl_3$/MeOH, 25:1) to give **7** (36 mg, 18%). First filtrate was neutralized with $NaHCO_3$ and extracted with AcOEt (3 x 20 mL). After drying with Na_2SO_4, AcOEt was evaporated. The residue was suspended in EtOH (1 mL), filtered off and washed with EtOH to give **7** (25 mg, 12%). mp 190–192 °C. ^{1}H NMR δ: 5.49 (s, 2H, CH_2), 7.30 (m, 2H, H6, H8), 7.55 (m, 3H, 2H of Ph, H7), 7.69 (m, 2H, 1H of Ph, H5), 8.05 (m, 2H, Ph), 12.75 (bs, 1H, NH). MS (EI, *m/z*, %): 280 (M^+, 7). *Anal.* Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found: C, 68.38; H, 4.65; N, 9.97.

3,4-Dihydro-3-methylquinoxalin-2(1*H*)-one (8). To a suspension of **1** (100 mg, 0.36 mmol) in EtOH (20 mL), a suspension of Pd/C (20%, 20 mg) in EtOH was added. The resulting mixture was shaken under H_2 at rt for 20 h. After hydrogenation, the reaction mixture was filtered through celite, the solvent was evaporated under reduced pressure and the crude product was separated by radial chromatography ($CHCl_3$/MeOH, 25:1) to give benzamide (40 mg, 92%) and **8**[2b,8] (30 mg, 52%). mp 130–133 °C. ^1H NMR δ: 1.24 (d, 3H, J = 6.6 Hz, CH_3), 3.75 (dq, 1H, J = 1.7 and 6.6 Hz, H3), 5.97 (s, 1H, NH), 6.56–6.78 (m, 4H, H5, H6, H7, H8), 10.13 (s, 1H, NH). MS (EI, *m/z*, %): 162 (M^+, 87). *Anal.* Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.48; H, 6.33; N, 17.11.

2-Chloro-3-(chloromethyl)quinoxaline (9). A mixture of **1** (300 mg, 1.07 mmol) and $POCl_3$ (3 mL) was heated on an oil bath at 80–85 °C for 2 h. The volatile components were evaporated under reduced pressure and the residue was suspended in ice-cooled saturated aqueous NH_3 (17 mL). The precipitated solid was filtered off, washed with water and purified by radial chromatography (petroleum ether/AcOEt, 25:1) to give **9**[9] (142 mg, 62%). mp 150–151 °C. ^1H NMR δ: 5.09 (s, 2H, CH_2), 7.94–8.19 (m, 4H, H5, H6, H7, H8). MS (EI, *m/z*, %): 212 (M^+, 76). *Anal.* Calcd for $C_9H_6Cl_2N_2$: C, 50.73; H, 2.84; N, 13.15. Found: C, 50.86; H, 2.57; N, 13.17.

1,3-Dimethylquinoxalin-2(1*H*)-one (10). A mixture of **2** (155 mg, 0.53 mmol), EtOH (1 mL) and aqueous HCl (18%, 2 mL) was heated under reflux for 2 h. After cooling to rt, the reaction mixture was neutralized with 1M HCl and extracted with AcOEt (3x20 mL). After drying with Na_2SO_4, AcOEt was evaporated under reduced pressure and the solid residue was purified by radial chromatography ($CHCl_3$/MeOH, 50:1) to afford compound **10**[6a] (38 mg, 41%). mp 84–85 °C. ^1H NMR δ: 2.44 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 7.36 (ddd, 1H, J = 1.5, 7.9, 7.9 Hz, H6), 7.53 (dd, 1H, J = 1.5, 8.5 Hz, H8), 7.59 (ddd, 1H, J = 1.5, 7.9, 8.5 Hz, H7), 7.75 (dd, 1H, J = 1.5, 7.9 Hz, H5). MS (EI, *m/z*, %): 174 (M^+, 100). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.06; H, 6.09; N, 15.88.

1-Ethyl-3-methylquinoxalin-2(1*H*)-one (11). A mixture of **3** (163 mg, 0.53 mmol), EtOH (1 mL) and aqueous HCl (18%, 2 mL) was heated under reflux for 2 h. After cooling to rt, the reaction mixture was neutralized with 1M HCl and extracted with AcOEt (3x20 mL). After drying with Na_2SO_4, AcOEt was evaporated under reduced pressure and the solid residue was purified by radial chromatography ($CHCl_3$/MeOH, 50:1) to afford compound **11**[6a] (39 mg, 39%). mp 93–95 °C. ^1H NMR δ: 1.24 (t, 3H, J = 7.1 Hz, CH_2CH_3), 2.44 (s, 3H, CH_3), 4.26 (q, 2H, J = 7.1 Hz, CH_2CH_3), 7.32–7.77 (m, 4H, H5, H6, H7, H8). MS (EI, *m/z*, %): 188 (M^+, 100). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.20; H, 6.72; N, 15.17.

1-(2-Hydroxyethyl)-3-methylquinoxalin-2(1*H*)-one (12). A mixture of **4** (100 mg, 0.3 mmol) and PPA (1.1 g) was heated on an oil bath at 90 °C or 3 h. After cooling to rt, ice-cooled water was added (10 mL) and the suspension was extracted with AcOEt (3x20 mL). After drying with Na_2SO_4, AcOEt was evaporated under reduced pressure and the solid residue was purified by radial chromatography (AcOEt) to afford benzamide (27 mg, 72%) and **12**[11] (12 mg, 19%). mp 152-155 °C. ^{1}H NMR δ: 2.44 (s, 3H, CH_3), 3.69 (m, 2H, CH_2CH_2OH), 4.31 (t, 2H, *J* = 6.1 Hz, CH_2CH_2OH), 4.88 (t, 1H, *J* = 5.9 Hz, OH), 7.33 (m, 1H, H6), 7.55 (m, 1H, H7), 7.65 (m, 1H, H8), 7.74 (m, 1H, H5). MS (EI, *m/z*, %): 204 (M^+, 41). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.91; H, 6.19; N, 13.42.

Formation of 3-(chloromethyl)-1-methylquinoxalin-2(1*H*)-one (13) and 3-(acetyloxymethyl)-1-methylquinoxalin-2(1*H*)-one (14). A mixture of **2** (293 mg, 1 mmol), CH_2Cl_2 (17 mL) and AcCl (0.14 mL, 2 mmol) was heated under reflux for 4 h. The volatile components were evaporated under reduced pressure and the solid residue was purified by radial chromatography (petroleum ether/AcOEt, 5:1) to give **13**[11] (143 mg, 67%), followed by radial chromatography (petroleum ether/AcOEt, 1:1) to give **14** (17 mg, 7%) and benzamide (103 mg, 85%). Compound **13**: mp 165–169 °C (MeOH). ^{1}H NMR δ: 3.66 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 7.43 (m, 1H, H6), 7.61 (m, 1H, H8), 7.70 (m, 1H, H7), 7.85 (m, 1H, H5). MS (EI, *m/z*, %): 208 (M^+, 100). *Anal.* Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.46; H, 4.30; N, 13.27. Compound **14**: mp 49–50 °C. ^{1}H NMR δ: 2.16 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 5.23 (s, 3H, CH_2), 7.41 (ddd, 1H, *J* = 1.5, 6.8, 8.3 Hz, H6), 7.60 (dd, 1H, *J* = 1.5, 8.3 Hz, H8), 7.67 (ddd, 1H, *J* = 1.5, 6.8, 8.3 Hz, H7), 7.81 (dd, 1H, *J* = 1.5, 8.3 Hz, H5). MS (EI, *m/z*, %): 232 (M^+, 29). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.29; H, 5.62; N, 11.62.

ACKNOWLEDGEMENTS

We thank the Slovenian Research Agency for financial support (P1-0230-0103).

REFERENCES

1. For reviews, see: (a) A. E. A. Porter, *Pyrazines and their Benzo Derivatives* in *Comprehensive Heterocyclic Chemistry*, Vol. 3, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, 1984, p. 173; (b) N. Sato, *Pyrazines and their Benzo Derivatives* in *Comprehensive Heterocyclic Chemistry II*, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Vol. 6, ed. by A. J. Boulton, Pergamon Press, 1996, p. 244; (c) A. Husain and D. Madhesia, *Journal of Pharmacy Research*, 2011, **4** , 924.
2. For examples, see: (a) S. Kamila and E.R. Biehl, *Heterocycles*, 2006, **68**, 1931; (b) F.-W. Wu, R.-S. Hou, H.-M. Wang, I.-J. Kang, and L.-C. Chen, *Heterocycles*, 2011, **83**, 2313; (c) M. A. Ibrahim, *Heterocycles*, 2011, **83**, 2689.
3. For examples, see: (a) I. Mušič, A. Golobič, and B. Verček, *Synlett*, 1998, 983; (b) K. Čuček and B. Verček, *Synlett*, 1999, 120; (c) T. Trček, A. Meden, and B. Verček, *Synlett*, 2000, 1458; (d) T. Jug, M. Polak, T. Trček, and B. Verček, *Heterocycles*, 2002, **56**, 353; (e) T. Trček and B. Verček, *Synthesis*, 2006, 3437; (f) K. Čuček, A. Golobič, and B. Verček, *Heterocycles*, 2007, **73**, 555; (g) K. Čuček and B. Verček, *Synthesis*, 2008, 1741; (h) I. Mušič and B. Verček, *Heterocycles*, 2011, **83**,

2353.

4. For reviews, see: (a) J. F. Frump, *Chem. Rev.*, 1971, **71**, 483; (b) T. G. Gant and A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297.
5. F. Tiemann and P. Kruger, *Chem. Ber.*, 1884, **17**, 1685.
6. (a) T. Nishio, *J. Org. Chem.*, 1984, **49**, 827; (b) O. Hinsberg, *Liebigs Ann. Chem.*, 1896, **292**, 245.
7. Y. Kurasawa, Y. Moritaki, and A. Takada, *Heterocycles*, 1982, **19**, 1619.
8. Y.-Z. Li and A. Townshend, *Anal. Chim. Acta*, 1997, **340**, 159.
9. J. J. Krajewski, P. J. Kotz, J. T. Traxler, S. S. Ristich, and C. W. Huffman, *J. Agr. Food Chem.*, 1971, **19**, 298.
10. G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1948, 519.
11. M. Yaso, Y. Suzuki, S. Saito, and D. Mochizuki, Jpn. Kokai Tokkyo Koho JP 06009622 (1994).