Synthesis of Benzimidazoles Condensed with, or Linked to, Nitroxides or Heterocyclic *N*-Oxides

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Received 3 April 2008

Dedicated to Professor Antal Rockenbauer on the occasion of his 70th birthday

Abstract: Pyrazino[1,2-*a*]benzimidazoles were synthesized starting from 2-acetyl-1*H*-benzimidazole. Benzimidazoles were linked to nitroxides by lithiation and ring-closure and cross-coupling reactions leading to pH-sensitive EPR probes and a paramagnetic analogue of antiviral agent HBB.

Key words: cross-coupling, free radicals, heterocycles, lithiation, ring closure

The synthesis and study of benzimidazoles are of interest for several reasons.[1] Derivatives of benzimidazole possess a variety of biological actions; anthelmintic[2] and antitumor[3] agents, gastric acid secretion inhibitors,[4] and PARP inhibitors[5] to mention a few.

Due to our interest in both benzimidazoles[6] and nitroxides,[7] we have reported paramagnetically modified benzimidazoles starting from spin labeled 1,2-phenylenediamine[8] or connecting to the 2-position of benzimidazole with a heterocycle fused with a nitroxide.[9,10]

The modification of benzimidazole-containing omeprazole-like compounds with nitroxide did not alter the gastric acid secretion inhibitory effect and the new compound exhibited antioxidant properties.[11] So, it was a real challenge to synthesize paramagnetically modified benzimidazoles with C–C bond formation in the hope of finding new, biologically active compounds.

In this paper we describe two approaches to this problem; synthesis of 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazoles as a benzimidazole ring system condensed with a stable nitroxide free radical or attaching a nitroxide to 2-position of the benzimidazole ring.

The pyrazino[1,2-*a*]benzimidazole ring systems were prepared by the reaction of 1-(2-chloroethyl)-2-(chloromethyl)-1*H*-benzimidazole and a primary amine,[12] by intramolecular cyclization of *N*-(2-hydroxyethyl)-1*H*-benzimidazole-2-carboxamide,[13] or by 1,3-dipolar cycloaddition of 2-(azidomethyl)-1-propargyl-1*H*-benzimidazoles.[14] Pyrazino[1,2-*a*]benzimidazoles with anticancer activity were achieved also by cyclization of 2-(2-acyl-1*H*-benzoimidazol-1-yl)-1-arylethanones and ammonia generated in situ.[15] Construction of the pyrazino[1,2-*a*]indole skeleton by cyclization of 1-alkynyl-1*H*-indole-2-carbaldehydes[16] inspired us to apply this method to the synthesis of pyrazino[1,2-*a*]benzimidazoles.

N-Alkylation of 1-(1*H*-benzimidazol-2-yl)ethanone (**1**) with propargyl bromide in acetonitrile in the presence of potassium carbonate afforded 1-(1-propargyl-1*H*-benzimidazol-2-yl)ethanone (**2**). The treatment of **2** with hydroxylamine in aqueous ethanol yielded an oxime that underwent 6-*exo-dig* cyclization to give compound **4**. A similar reaction was carried out with compound **2** or **3** and with methanolic ammonia solution in a sealed tube. This reaction yielded two products in the case of **2**, the cyclized product **5a** and the unexpected deacetylated derivative **6a** in a ratio of ~1:1 as identified by MS and NMR studies. The deacetylation reaction of the quaternary salt of 2-acetylbenzimidazolium was described by Serafin and Glowczyk, although under more harsh conditions.[17]

This cyclization reaction could be extended to other *N*-propargyl derivatives of compound **2**. The new substrates are readily available by Sonogashira coupling, for example, compound **2** reacts with iodobenzene in the presence of palladium and copper catalysts to afforded compound **3**. The cyclization reaction of this with methanolic ammonia solution in a sealed tube furnished blue fluorescent compound **5b** and deacetylated **6b** in a 1:1 ratio (Scheme 1).

The above cyclization reactions gave fully aromatic ring systems, such as compounds **4**, **5a**, and **5b**, hence for nitroxides condensed with a benzimidazole a partially saturated ring was required. A nitro group must be introduced into compound **1** by alkylating with compound **8** in the presence of sodium hydride in tetrahydrofuran–*N*,*N*-dimethylformamide solvent. Compound **8** was obtained previously by treating 2-methyl-2-nitropropan-1-ol with methanesulfonyl chloride in dichloromethane in the presence of triethylamine. Reduction of compound **9** with zinc/ammonium chloride afforded a hydroxylamine, which cyclized in situ to give nitrone **10**. Treatment of **10** with methylmagnesium iodide followed by oxidation with activated manganese(IV) oxide gave nitroxide **11**, condensed with benzimidazole (Scheme 2).

Another challenge was the introduction of the nitroxide ring into the 2-position of benzimidazole. The treatment of 1,2-phenylenediamine with 3-carboxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl radical in aqueous hydrogen chloride solution did not furnish **13**.

SYNTHESIS 2008, No. 15, pp 2439–2445
Advanced online publication: 08.07.2008
DOI: 10.1055/s-2008-1067158; Art ID: P04808SS
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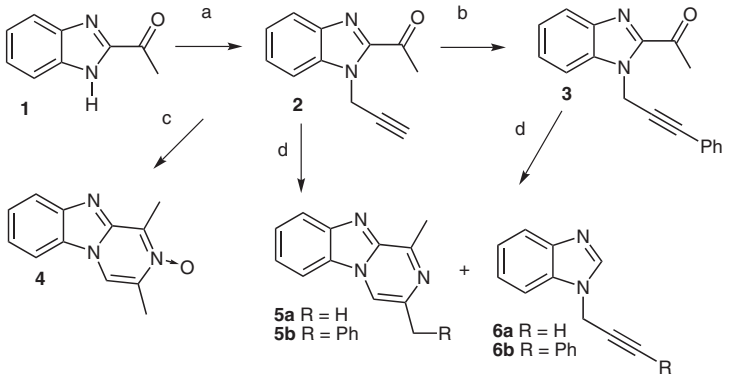
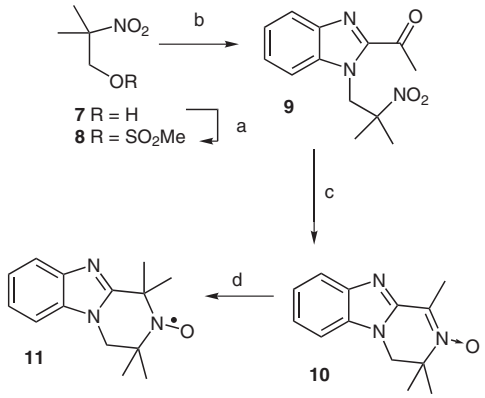
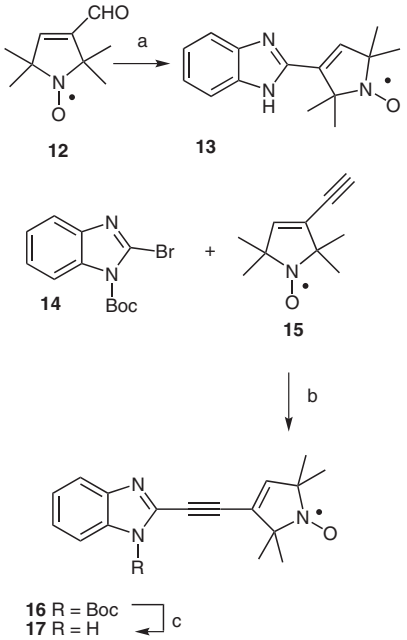


Scheme 1 *Reagents and conditions*: (a) propargyl bromide (1.1 equiv), K_2CO_3 (1.1 equiv), MeCN, reflux, 3 h, 88%; (b) PhI (1 equiv), $PdCl_2(PPh_3)_2$ (0.1 equiv), CuI (0.05 equiv), Et_3N, under N_2, r.t., 5 h, 63%; (c) $NH_2OH{\cdot}HCl$ (1.5 equiv), NaOAc (1.5 equiv), EtOH–H_2O, reflux, 3 h, 70%; (d) 7 M NH_3–MeOH (excess), 120 °C, sealed tube, 12 h, 32–45% for **5** and 35–46% for **6**.



Scheme 2 *Reagents and conditions*: (a) MsCl (1.1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C to r.t., 1 h, 88%; (b) **1** (0.5 equiv), NaH (0.5 equiv), THF–DMF, 0 °C, 30 min, then **8** (1.0 equiv), reflux, 12 h, 33%; (c) Zn powder (4.0 equiv), NH_4Cl (1.5 equiv), THF–H_2O >10 °C, 2 h, 48%; (d) (i) MeMgI (2.0 equiv), THF–Et_2O, reflux 1 h (ii) aq NH_4Cl (iii) MnO_2, O_2, 15 min, 28%.



Scheme 3 *Reagents and conditions*: (a) (i) 1,2-phenylenediamine (1.0 equiv), TsOH (0.05 equiv), toluene, reflux, 4 h (ii) MnO_2 (2.0 equiv), $CHCl_3$, reflux 1 h, 46%; (b) **15** (1 equiv), $PdCl_2(PPh_3)_2$ (0.1 equiv), CuI (0.05 equiv), Et_3N, under N_2, r.t., 5 h, 59%. (c) 7 M NH_3–MeOH (excess), r.t., sealed tube, 12 h, 88%.

However, we found that acid-catalyzed Schiff base formation between aldehyde **12**[18] and 1,2-phenylenediamine followed by oxidation with manganese(IV) oxide gave the desired 2-substituted benzimidazole **13**. To achieve various 2-substituted benzimidazoles attached to the nitroxide ring, we utilized palladium-catalyzed cross-coupling reactions. Sonogashira reaction of 2-bromo-1-(*tert*-butoxycarbonyl)-1*H*-benzimidazole (**14**)[19] with nitroxide **15** yielded benzimidazole **16** bearing a nitroxide ring through an alkyne spacer. The *tert*-butoxycarbonyl (Boc) protecting group was removed by treating compound **16** with methanolic ammonia solution in a sealed tube to yield compound **17** (Scheme 3).

Another synthetic approach to 2-substituted benzimidazoles was the lithiation[20] of 1-(hydroxymethyl)-1*H*-benzimidazole[21] (**18**) and its treatment with electrophiles such as **12** and **19**[22] aldehydes. This reaction furnished 2-(hydroxymethyl)benzimidazole derivatives **20** and **21**. The latter is the paramagnetic analogue of 2-(α-hydroxybenzyl)benzimidazole (HBB), the known viral RNA synthesis blocking agent.[23] Oxidation of alcohol **20** with activated manganese(IV) oxide gave ketone **22**. Reaction of lithiated **18** with nitrones **23** and **24** furnished stable paramagnetic free radicals **25** and **26**, respectively, after the oxidation of the thus formed hydroxylamine with activated manganese(IV) oxide. We assumed that hyperfine splitting constant of compounds **11**, **25**, and **26** exhibit some pH-dependence, analogously to 2,2,5,5-tetrasubstituted 2,5-dihydro-1*H*-imidazol-1-oxyl compounds.[24] Unfortunately, compound **11** was reduced under acidic pH to hydroxylamine, resulting in EPR signal loss, however compound **25** and **26** exhibited a pH sensitivity range of pH 2 to 6 (Figure 1). The change in hyperfine splitting constant (~0.6 G) is smaller than that of 2,2,5,5-tetrasubstituted 2,5-dihydro-1*H*-imidazol-1-oxyl (~1.5 G). We also tested the pH sensitivity of a paramagnetic benzothiazole compound, synthesized by treatment of 2-lithiobenzothiazole with nitrone **23** (Scheme 4).

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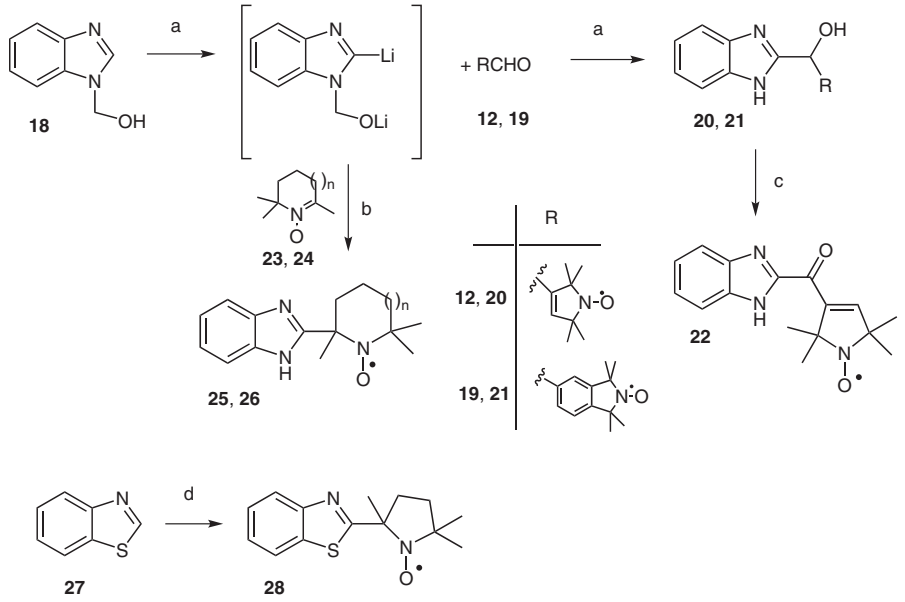

Scheme 4 *Reagents and conditions*: (a) (i) BuLi (2.0 equiv), THF, –78 °C, 30 min; –20 °C, 30 min; –78 °C (ii) **13** or **19** (1 equiv), –78 °C, 1 h; –78 °C to r.t. (iii) aq NH_4Cl soln, 55–72%; (b) (i) –78 °C to r.t. (iii) aq NH_4Cl soln (iii) MnO_2 (1.0 equiv), O_2, 15 min, 15–20%; (c) MnO_2 (5.0 equiv), $CHCl_3$, reflux, 1 h, 63%; (d) (i) BuLi (1.0 equiv), –78 °C, 30 min (ii) **23** (1.0 equiv) –78 °C, 30 min; –78 °C to r.t. (iii) aq NH_4Cl soln (iv) MnO_2 (1.0 equiv), O_2, 15 min, 77%.

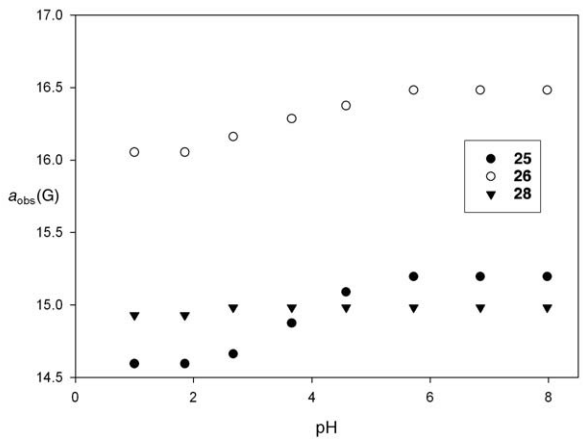

Figure 1 pH dependence of hyperfine splitting constant of the nitroxides **25**, **26**, and **28**, obtained by X-band EPR

The resulting compound **28** exhibited minimal pH dependence (Figure 1) supporting the necessity of the imidazole moiety in EPR active pH sensors.

In conclusion, we have developed a new approach for synthesis of pyrazino[1,2-*a*]benzimidazole ring system. During the cyclizations deacetylation processes were observed. Nitroxides annulated or linked to benzimidazole were synthesized by classical ring closure, lithiation, and palladium-catalyzed cross-coupling. Among the newly synthesized benzimidazoles, pH-sensitive EPR probes and a paramagnetic analogue of antiviral agent HBB were described. Further biological studies of these compounds are in progress.

Melting points were determined with a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N, S) were performed on a Fisons EA 1110 CHNS elemental analyzer. The IR (Specord 85) spectra were in each case consistent with the assigned structure. Mass spectra were recorded on a Thermoquest Automass Multi and VG TRIO-2 instruments and in the EI mode. ^{1}H NMR spectra were recorded with a Varian UNITY *INOVA* 400 WB spectrometer. Chemical shifts are referenced to TMS. Measurements were run at 298 K probe temperature in $CDCl_3$ soln. ESR spectra were taken on Miniscope MS 200 in 10^{-4} M $CHCl_3$ soln and all monoradicals gave triplet line a_N = 14.7–16.5 G. The pH measurement was performed in 10^{-4} M MeOH–Sorensen buffer (1:9) soln. Fluorescence spectra were taken with Perkin Elmer LSB 50 instrument. Flash column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Qualitative TLC was carried out on commercially prepared plates (20 × 20 × 0.02 cm) coated with Merck Kieselgel GF_{254}. Compound **7** was purchased from Fluka or prepared as published earlier.[25] All reagents were purchased from Aldrich. Compounds **1**,[26] **12**,[18] **14**,[19] **15**,[27] **18**,[21] **19**,[22] **23**,[28] and **24**[29] were prepared according to published procedures.

1-(1-Prop-2-ynyl-1*H*-benzoimidazol-2-yl)ethanone (2)

To a stirred soln of **1** (3.20 g, 20.0 mmol) and K_2CO_3 (3.03 g, 22.0 mmol) in MeCN (20 mL) was added propargyl bromide (2.61 g, 22.0 mmol) and the mixture was stirred and heated under reflux for 3 h. After cooling the mixture was filtered, the filtrate was evaporated, the residue was dissolved in EtOAc (30 mL) and washed with brine (10 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to yield a white solid; yield: 3.48 g (88%); mp 112–113 °C; R_f = 0.25 (hexane–Et_2O, 2:1).

IR (Nujol): 2105 (C≡C), 1687 (C=O), 1615, 1605 (C=C), 1580 (C=N) cm^{-1}.

^{1}H NMR: δ = 7.92 (d, *J* = 8.4 Hz, 1 H), 7.59 (d, *J* = 8.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 5.51 (s, 2 H), 2.86 (s, 3 H), 2.32 (s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 198 (71) [M^+], 169 (100), 155 (58), 43 (46).

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.65; H, 5.00; N, 14.21.

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1-[1-(3-Phenylprop-2-ynyl)-1*H*-benzimidazol-2-yl]ethanone (3)
To a soln of PhI (2.04 g, 10.0 mmol) in deoxygenated anhyd Et_3N (10 mL) were added $PdCl_2(PPh_3)_2$ (700 mg, 1.0 mmol) and CuI (95 mg, 0.5 mmol) and the mixture was stirred for 15 min under N_2. Then **2** (1.98 g, 10.0 mmol) dissolved in anhyd Et_3N (5 mL) was added dropwise causing an immediate brown precipitation from the yellow soln. Within 10 min the mixture became a thick slurry and was vigorously stirred at r.t. for 5 h. The mixture was diluted with EtOAc (20 mL), filtered through a Celite pad, and washed with EtOAc (5 mL) and then the solvents were evaporated off. The residue was partitioned between EtOAc (30 mL) and H_2O (10 mL) and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to give **3** as a white solid; yield: 1.72 g (63%); mp 84–85 °C; R_f = 0.27 (hexane–Et_2O, 2:1).

IR (Nujol): 1695 (C=O), 1610 (C=C), 1585 (C=N) cm^{-1}.

^1H NMR: δ = 7.91 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.47–7.28 (m, 7 H), 5.68 (s, 2 H), 2.85 (s, 3 H).

MS (EI, 70 eV): *m*/*z* (%) = 274 (85) [M^+], 231 (69), 115 (100), 43 (46).

Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.77; H, 5.08; N, 10.16.

1,3-Dimethylbenzimidazo[1,2-*a*]pyrazine 2-Oxide (4)
A soln of **2** (990 mg, 5.0 mmol), $NH_2OH{\cdot}HCl$ (513 mg, 7.5 mmol), NaOAc (615 mg, 7.5 mmol) in EtOH (10 mL) and H_2O (4 mL) was refluxed for 3 h. After cooling the mixture was evaporated under reduced pressure and the residue was partitioned between $CHCl_3$ (30 mL) and H_2O (10 mL). The organic phase was separated, dried, filtered, and evaporated. After chromatographic purification ($CHCl_3$–Et_2O–MeOH, 10:5:1), **4** was obtained as a yellow solid; yield: 745 mg (70%); mp 228–230 °C; R_f = 0.34 ($CHCl_3$–Et_2O–MeOH, 8:3:1), blue fluorescent spot ($\lambda_{ex}/\lambda_{em}$ = 362/422 nm in MeCN).

IR (Nujol): 1610 (C=C), 1580 (C=N) cm^{-1}.

^1H NMR: δ = 8.15 (s, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 2.86 (s, 3 H), 2.52 (s, 3 H).

MS (EI, 70 eV): *m*/*z* (%) = 213 (50) [M^+], 197 (100), 155 (35), 42 (45).

Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.62; H, 5.15; N, 19.65.

Pyrazino[1,2-*a*]benzimidazoles 5a,b; General Procedure
A 7.0 M NH_3 in MeOH soln of **2** (990 mg, 5.0 mmol) or **3** (1.37 g, 5.0 mmol) was heated overnight at 120 °C in a sealed tube. After cooling the mixture was evaporated, the residue was subjected to flash column chromatography ($CHCl_3$–Et_2O) to give the cyclized product **5a** as a first blue fluorescent spot ($\lambda_{ex}/\lambda_{em}$ = 363/425 nm in MeCN) or **5b** again as a blue fluorescent spot ($\lambda_{ex}/\lambda_{em}$ = 365/427 nm in MeCN) and followed by the deacetylated byproduct **6a** or **6b** as a second band.

1,3-Dimethylpyrazino[1,2-*a*]benzimidazole (5a)
Off-white solid; yield: 443 mg (45%); mp 102–104 °C; R_f = 0.40 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 1632 (C=C), 1585 (C=N) cm^{-1}.

^1H NMR: δ = 8.02–7.40 (m, 5 H), 2.98 (s, 3 H), 2.55 (s, 3 H).

MS (EI, 70 eV): *m*/*z* (%) = 197 (38) [M^+], 156 (100), 129 (73), 102 (29).

Anal. Calcd For $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.03. Found: C, 73.10; H, 5.55; N, 21.14.

1-Prop-2-ynyl-1*H*-benzimidazole (6a)[30]
White solid; yield: 358 mg (46%); mp 38–40 °C; R_f = 0.32 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 2105 (C≡C), 1620 (C=C), 1590 (C=N) cm^{-1}.

^1H NMR: δ = 8.17 (s, 1 H), 8.02–7.40 (m, 4 H), 4.94 (d, *J* = 2.4 Hz, 2 H), 2.48 (t, *J* = 2.4 Hz, 1 H).

Anal. Calcd For $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.83; H, 5.20; N, 17.88.

3-Benzyl-1-methylpyrazino[1,2-*a*]benzimidazole (5b)
Yellow solid; yield: 432 mg (32%); mp 55–58 °C; R_f = 0.77 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 1620, 1610 (C=C), 1580 (C=N) cm^{-1}.

^1H NMR: δ = 8.01 (d, *J* = 8.4 Hz, 1 H), 7.86 (s, 1 H), 7.78 (d, *J* = 8.4 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.38–7.25 (m, 6 H), 4.18 (s, 2 H), 2.99 (s, 3 H).

MS (EI, 70 eV): *m*/*z* (%) = 273 (73) [M^+], 272 (72), 258 (12), 77 (41), 43 (100).

Anal. Calcd For $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.08; H, 5.49; N, 15.18.

1-(3-Phenylprop-2-ynyl)-1*H*-benzimidazole (6b)
White solid; yield: 406 mg (35%); mp 102–103 °C; R_f = 0.50 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 1605 (C=C), 1580 (C=N) cm^{-1}.

^1H NMR: δ = 8.33 (s 1 H), 7.85 (d, *J* = 7.2 Hz, 1 H), 7.57 (d, *J* = 7.2 Hz, 1 H), 7.43–7.25 (m, 7 H), 5.19 (s, 2 H).

MS (EI, 70 eV): *m*/*z* (%) = 232 (65) [M^+], 115 (100).

Anal. Calcd For $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.64; H, 5.20; N, 11.99.

2-Methyl-2-nitropropyl Methanesulfonate (8)
To a soln of **7** (2.38 g, 20.0 mmol) and Et_3N (2.22 g, 22.0 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C MsCl (2.52 g, 22.0 mmol) and the mixture was stirred at r.t. for 1 h. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was crystallized (hexane–Et_2O) to give **8** as an off-white solid; yield: 3.46 g (88%); mp 40–43 °C.

IR (Nujol): 1550 (NO_2) cm^{-1}.

^1H NMR: δ = 4.47 (s, 2 H), 3.03 (s, 3 H), 1.65 (s, 6 H).

MS (EI, 70 eV): *m*/*z* (%) = 197 (1>) [M^+], 151 (26), 79 (91), 55 (100).

Anal. Calcd For $C_5H_{11}NO_5S$: C, 30.45; H, 5.62; N, 7.10; S 16.26. Found: C, 30.21; H, 5.66; N, 7.03; S 16.11.

1-[1-(2-Methyl-2-nitropropyl)-1*H*-benzimidazol-2-yl]ethanone (9)
To a suspension of NaH (240 mg, 10.0 mmol) in anhyd THF (20 mL) was added dropwise **1** (1.60 g, 10.0 mmol) in anhyd DMF (5 mL) and the mixture was stirred at 0 °C for 30 min Then **8** (3.94 g, 20.0 mmol) dissolved in anhyd DMF (5 mL) was added and the mixture was stirred and heated under reflux for 12 h. After cooling all the solvents were evaporated off and the residue was partitioned between H_2O (10 mL) and $CHCl_3$ (30 mL). The organic phase was separated, dried, filtered, and evaporated and the residue was purified by flash column chromatography (hexane–EtOAc 2:1) to yield **9** as a white solid: 861 mg (33%); mp 134 °C; R_f = 0.54 (hexane–EtOAc 2:1).

IR (Nujol): 1685 (C=O), 1605 (C=C), 1580 (C=N), 1535 (NO_2) cm^{-1}.

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^{1}H NMR: δ = 7.88 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 8.4 Hz, 1 H), 7.45 (t, *J* = 7.2 Hz, 1 H), 7.37 (t, *J* = 7.2 Hz, 1 H), 5.31 (s, 2 H), 2.85 (s, 3 H), 1.60 (s, 6 H).

MS (EI, 70 eV): *m*/*z* (%) = 261 (65) [M$^+$], 215 (100), 173 (62), 43 (42).

Anal. Calcd For $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.75; H, 5.81; N, 16.03.

1,3,3-Trimethyl-3,4-dihydropyrazino[1,2-*a*]benzimidazole 2-Oxide (10)

To a stirred soln of **9** (1.305 g, 5.0 mmol) and NH_4Cl (401 mg, 7.5 mmol) in THF (10 mL) and H_2O (5 mL) was added Zn dust (1.3 g, 20.0 mmol) in small portions over 1.5 h, such that the temperature inside the flask did not exceed 10 °C. The mixture was stirred for an additional 0.5 h and then was filtered. The filtrate was combined with MeOH washes (20 mL) of the filter cake. The solvent volume was reduced by evaporation to 10 mL. The aqueous solvent was saturated with NaCl and extracted with $CHCl_3$ (2 × 15 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated and the residue was purified by flash column chromatography ($CHCl_3$–Et_2O–MeOH, 8:3:0.5) to give **10** as a white solid; yield: 554 mg (48%); mp 126–130 °C; R_f = 0.5 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 1605 (C=C), 1580 (C=N) cm^{-1}.

^{1}H NMR: δ = 7.88 (d, *J* = 8.4 Hz, 1 H), 7.40–7.30 (m, 3 H), 4.24 (s, 2 H), 2.58 (s, 3 H), 1.60 (s, 6 H).

MS (EI, 70 eV): *m*/*z* (%) = 239 (100) [M$^+$], 213 (65), 198 (32), 42 (66).

Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.03; H, 6.62; N, 18.38.

1,1,3,3-Tetramethyl-3,4-dihydropyrazino[1,2-*a*]benzimidazol-2-yloxyl Radical (11)

To freshly made MeMgI in Et_2O (20 mL) soln [freshly made from Mg (24 0 mg) and MeI (1.42 g)] a soln of **10** (1.19 g, 5.0) mmol in anhyd THF (10 mL) was added at 0 °C under N_2 blank. The mixture was warmed to r.t. and then it was stirred and heated under reflux for 1 h. The mixture was then cooled and it was quenched with sat. aq NH_4Cl (10 mL). The organic phase was separated and the aqueous phase was extracted with $CHCl_3$ (10 mL). The combined organic phases were dried ($MgSO_4$), MnO_2 (870 mg, 10.0 mmol) was added and O_2 was bubbled through for 15 min. After filtration the solvents were evaporated and the residue was purified by flash column chromatography ($CHCl_3$–Et_2O, 2:1) to give **11** as a brownish-yellow solid; yield: 342 mg (28%); mp 62–64 °C; R_f = 0.30 ($CHCl_3$–Et_2O, 2:1).

IR (Nujol): 1600 (C=C), 1575 (C=N) cm^{-1}.

ESR: triplet, a_N = 14.9 G ($CHCl_3$).

MS (EI, 70 eV): *m*/*z* (%) = 244 (89) [M$^+$], 199 (100), 171 (90), 41 (71).

Anal. Calcd for $C_{14}H_{18}N_3O$: C, 68.83; H, 7.43; N, 17.20. Found: C, 68.77; H, 7.48; N, 17.05.

3-(1*H*-Benzimidazol-2-yl)-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-yloxyl Radical (13)

A mixture of 1,2-phenylenediamine (1.08 g, 10.0 mmol) and aldehyde **12** (1.68 g, 10.0 mmol) and $TsOH·H_2O$ (100 mg) in toluene (40 mL) was heated in a Dean–Stark apparatus for 4 h. After cooling the solvents were evaporated off, the residue was dissolved in $CHCl_3$ (30 mL), activated MnO_2 (1.74 g, 20.0 mmol) was added, and the mixture was stirred and heated under reflux for a further 1 h. After cooling the mixture was filtered through Celite, the solvents were evaporated off and the residue was purified by flash column chromatography ($CHCl_3$–Et_2O, 2:1) to give **13** as a yellow solid; yield: 1.17 g (46%); mp 203–205 °C; R_f = 0.24 ($CHCl_3$–Et_2O, 2:1).

IR (Nujol): 3300 (NH), 1615 (C=C), 1580 (C=N).

MS (EI, 70 eV): *m*/*z* (%) = 256 (30) [M$^+$], 242 (29), 226 (53), 211 (100).

Anal. Calcd for $C_{15}H_{18}N_3O$: C, 70.29; H, 7.08; N, 16.39. Found: C, 70.27; H, 7.08; N, 16.44.

3-{[1-(*tert*-Butoxycarbonyl)-1*H*-benzimidazol-2-yl]ethynyl}-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (16)

The soln of **14** (1.48 g, 5.0 mmol), $PdCl_2(PPh_3)_2$ (350 mg, 0.5 mmol), and CuI (48 mg, 0.25 mmol) in freshly distilled Et_3N (30 mL) was stirred for 15 min under N_2. Then alkyne **15** (820 mg, 5.0 mmol) dissolved in Et_3N (10 mL) was added and the mixture was stirred at r.t. for 5 h. The soln was filtered through Celite, washed with EtOAc (20 mL), and evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (20 mL). The organic phase was separated and dried ($MgSO_4$) and MnO_2 (87 mg, 1.0 mmol) was added and oxygen was bubbled through the soln for 15 min. After filtration and evaporation the residue was purified by flash chromatography ($CHCl_3$–Et_2O, 2:1) to yield **16** as a yellow solid; yield: 1.12 g (59%); mp 95–97 °C; R_f = 0.59 ($CHCl_3$–Et_2O, 2:1).

IR (Nujol): 1750 (C=O), 1600 (C=C), 1570 (C=N) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 380 (1>) [M$^+$], 279 (5), 235 (23), 149 (23), 57 (100).

Anal. Calcd for $C_{22}H_{26}N_3O_3$: C, 69.45; H, 6.89; N, 11.04. Found: C, 69.40; H, 6.83; N, 11.12.

3-(1*H*-Benzimidazol-2-ylethynyl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (17)

Compound **16** (760 mg, 2.0 mmol) was dissolved in 7 M NH_3 in MeOH soln (5 mL) and then was allowed to stand at r.t. in a sealed tube for 18 h. The soln was filtered and evaporated and the residue was dissolved in $CHCl_3$ (30 mL), washed with brine, and dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure to give **17** as a pale yellow solid; yield: 493 mg (88%); mp 176–179 °C; R_f = 0.62 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 3150 (NH), 1605, 1595 (C=C), 1575 (C=N) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 280 (14) [M$^+$], 250 (100), 235 (82), 43 (81).

Anal. Calcd for $C_{17}H_{18}N_3O$: C, 72.83; H, 6.47; N, 14.99. Found: C, 72.82; H, 6.43; N, 14.90.

Lithiation of 1-(Hydroxymethyl)-1*H*-benzimidazole (18) and Coupling with Electrophiles To Give 20, 21, 25, 26; General Procedure

To the soln 1-(hydroxymethyl)-1*H*-benzimidazole (**18**, 1.48 g, 10.0 mmol) in anhyd THF (20 mL) was added dropwise 2.5 M BuLi in hexanes (8 mL, 20.0 mmol) at –78 °C under N_2. The mixture was stirred at –20 °C for an additional 30 min. The mixture was cooled to –78 °C, and aldehyde **12** or **19** (10.0 mmol) or nitrone **23** or **24** (10.0 mmol) dissolved in THF (10 mL) was added dropwise. Then the soln was stirred for 45 min at this temperature and the soln was allowed to warm to r.t. slowly, followed by quenching with sat. aq NH_4Cl (20 mL) soln. After 10 min stirring the layers were separated and the aqueous layer was washed with $CHCl_3$ (2 × 30 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in $CHCl_3$ (30 mL), PbO_2 (2.39 g, 10.0 mmol) for compound **20** and **21** or MnO_2 (870 mg, 10.0 mmol) for compound **25** or **26** was added and O_2 was bubbled through the soln for 30 min, then the mixture was filtered and evaporated. The residue was puri-

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fied by flash chromatography ($CHCl_3$–Et_2O–MeOH, 8:3:1) to yield nitroxides **20**, **21**, **25**, **26** (15–72%) as yellow solids.

3-[(1*H*-Benzimidazol-2-yl)hydroxymethyl]-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (20)

Yellow solid; yield: 2.05 g (72%); mp 210–212 °C; R_f = 0.28 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 3200 (NH), 1620 (C=C), 1590 (C=N) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 286 (8) [M^+], 256 (20), 239 (100), 41 (49).

Anal. Calcd for $C_{16}H_{20}N_3O_2$: C, 67.11; H, 7.04; N, 14.67. Found: C, 67.10; H, 7.00; N, 14.64.

5-[(1*H*-Benzimidazol-2-yl)hydroxymethyl]-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-yloxyl Radical (21)

Yellow solid; yield: 1.84 g (55%); mp 206–209 °C; R_f = 0.23 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 3495 (OH), 3250 (NH), 1615 (C=C), 1585 (C=N) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 336 (7) [M^+], 306 (6), 273 (15), 218 (36), 118 (80), 43 (100).

Anal. Calcd for $C_{20}H_{22}N_3O_2$: C, 71.41; H, 6.59; N, 12.49. Found: C, 71.25; H, 6.44; N, 12.36.

2-(1*H*-Benzimidazol-2-yl)-2,5,5-trimethylpyrrolidin-1-yloxyl Radical (25)

Yellow solid; yield: 488 mg (20%); mp 136–139 °C; R_f = 0.63 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 3200 (NH), 1610 (C=C), 1580 (C=N) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 244 (40) [M^+], 214 (11), 190 (11), 158 (100).

Anal. Calcd for $C_{14}H_{18}N_3O$: C, 68.83; H, 7.43; N, 17.20. Found: C, 68.88; H, 7.39; N, 17.15.

2-(1*H*-Benzimidazol-2-yl)-2,6,6-trimethylpiperidin-1-yloxyl Radical (26)

Orange solid: yield: 387 mg (15%); mp 42–43 °C; R_f = 0.66 ($CHCl_3$–Et_2O–MeOH, 8:3:1).

IR (Nujol): 3200 (NH), 1605 (C=C), 1580 (C=N) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 258 (40) [M^+], 228 (31), 172 (82), 159 (100).

Anal. Calcd for $C_{15}H_{20}N_3O$: C, 69.74; H, 7.80; N, 16.27. Found: C, 69.57; H, 7.77; N, 16.20.

3-[(1*H*-Benzimidazol-2-yl)carbonyl]-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (22)

To the soln of alcohol **20** (572 mg, 2.0 mmol) in $CHCl_3$ (20 mL) was added activated MnO_2 (870 mg, 10.0 mmol) and the mixture was stirred and heated under reflux for 1 h. After filtration the mixture was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash chromatography (hexane–EtOAc, 2:1) to give ketone **22** as a yellow solid; yield: 358 mg (63%); mp 196–197 °C; R_f = 0.42 (hexane–EtOAc, 2:1).

IR (Nujol): 3305 (NH), 1640 (C=O), 1615 (C=C), 1580 (C=N) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 284 (2) [M^+], 283 (8), 268 (59), 139 (72), 41 (100).

Anal. Calcd for $C_{16}H_{18}N_3O_2$: C, 67.59; H, 6.38; N, 14.78. Found: C, 67.61; H, 6.40; N, 14.74.

2-(Benzothiazol-2-yl)-2,5,5-trimethylpyrrolidin-1-yloxyl Radical (28)

To a stirred soln of **27** (1.35 g, 10.0 mmol) in anhyd THF (20 mL), 2.5 M BuLi in hexanes (4 mL, 10.0 mmol) was added dropwise under N_2 at –78 °C. The mixture was stirred at this temperature for 30 min, then **23** (1.27 g, 10.0 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm to r.t. (~1 h) and sat. aq NH_4Cl (20 mL) soln was added. After 15 min stirring, the organic phase was separated and the aqueous phase extracted with $CHCl_3$ (2 × 30 mL). The organic phase was dried ($MgSO_4$), activated MnO_2 (870 mg, 10.0 mmol) was added and O_2 was bubbled through for 20 min. After filtration the solvent was evaporated under vacuum. The residue was purified by flash column chromatography with (hexane–EtOAc, 2:1) to give **28** as a yellow solid; yield: 1.91 g (77%); mp 102–104 °C; R_f = 0.54 (hexane–EtOAc, 2:1).

IR (Nujol): 1605 (C=C), 1585 (C=N) cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 261 (38) [M^+], 231 (10), 216 (8), 175 (100).

Anal. Calcd for $C_{14}H_{17}N_2OS$: C, 64.34; H, 6.56; N, 10.72; S: 12.27. Found: C, 64.28; H, 6.55; N, 10.74; S: 12.11.

Acknowledgment

This work was supported by a grant from Hungarian National Research Fund (OTKA-NKTH K67597, T48334 and M045190). The authors thank Krisztina Kis for elemental analysis, Gergely Gulyas for NMR measurements (Department of Biochemistry and Medical Chemistry) and Maria Balog for technical assistance.

References

(1) (a) Wright, J. B. *Chem. Rev.* **1951**, *48*, 397. (b) Preston, P. N. *Chem. Rev.* **1974**, *74*, 279. (c) *Benzimidazoles and Congeneric Tricyclic Compounds*; Preston, P. N., Ed.; Wiley: New York, **1980**. (d) Grimmett, M. S. *Imidazole and Benzimidazole Synthesis*; Academic Press: London, **1997**.
(2) Chassaing, C.; Berger, M.; Heckeroth, A.; Ilg, T.; Jaeger, M.; Kern, C.; Schmid, K.; Uphoff, M. *J. Med. Chem.* **2008**, *51*, 1111.
(3) O'Shaughnessy, J.; Aldabbagh, F. *Synthesis* **2005**, 1069.
(4) Kromer, W. *Digestion* **1995**, *56*, 443.
(5) White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. *J. Med. Chem.* **2000**, *43*, 4084.
(6) Hankovszky, H. O.; Hideg, K.; Lex, L.; Földesi, A.; Sohár, P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 699.
(7) Hideg, K.; Kálai, T.; Sár, C. P. *J. Heterocycl. Chem.* **2005**, *42*, 437.
(8) Hankovszky, H. O.; Hideg, K.; Lovas, J.; Jerkovich, G.; Rockenbauer, A.; Győr, M.; Sohár, P. *Can. J. Chem.* **1989**, *67*, 1392.
(9) Kálai, T.; Jekő, J.; Hideg, K. *Synthesis* **2000**, 831.
(10) Kulcsár, G.; Kálai, T.; Jekő, J.; Hideg, K. *Synthesis* **2003**, 1361.
(11) Mózsik, G.; Peidl, Z.; Szolcsányi, J.; Dömötör, A.; Hideg, K.; Szekeres, G.; Karádi, O.; Hunyady, B. *Inflammopharmacology* **2005**, *13*, 139.
(12) Matrick, H.; Day, A. R. *J. Org. Chem.* **1961**, *26*, 1511.
(13) Edwards, W. B.; Day, A. R. *J. Org. Chem.* **1974**, *39*, 1519.
(14) Hideg, K.; Hankovszky, H. O. *Synthesis* **1978**, 313.
(15) Demoirayak, S.; Mohsen, A. U.; Karaburun, A. C. *Eur. J. Med. Chem.* **2002**, *37*, 255.
(16) Abbiati, G.; Arcadi, A.; Billinazzi, A.; Beccalli, E.; Rossi, E.; Zanzola, S. *J. Org. Chem.* **2005**, *70*, 4088.

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(17) Serafin, B.; Glowczyk, J. *Rocz. Chem.* **1976**, *50*, 1211; *Chem. Abstr.* **1977**, *86*, 43618.
(18) Hideg, K.; Hankovszky, H. O.; Lex, L.; Kulcsár, G. *Synthesis* **1980**, 911.
(19) Nadipuram, A. K.; David, W. M.; Kumar, D.; Kerwin, S. M. *Org. Lett.* **2002**, *4*, 4543.
(20) Katritzky, A. R.; Akutagawa, K. *J. Org. Chem.* **1989**, *54*, 2949.
(21) Hideg, K.; Hankovszky, H. O. *Acta Chim. Acad. Sci. Hung.* **1966**, *49*, 303*; Chem. Abstr.* **1968**, *69*, 51956.
(22) Bottle, S. E.; Gillies, D. G.; Hughes, D. L.; Micallef, A. S.; Smirnov, A. I.; Sutcliffe, L. H. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1285.
(23) Eggers, H. J.; Tamm, I. *Nature* **1963**, *197*, 1327.
(24) Potapenko, D. I.; Foster, M. A.; Lurie, D. J.; Kirilyuk, I. A.; Hutchison, J. M. S.; Grigor'ev, I. A.; Bagryanskaya, E. G.; Khramtsov, V. V. *J. Magn. Reson.* **2006**, *182*, 1.
(25) Dornow, A.; Muller, A. *Chem. Ber.* **1960**, *93*, 41.
(26) Dubey, P. K.; Kumar, C. R.; Babu, B. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2003**, *42*, 3128.
(27) Kálai, T.; Balog, M.; Jekő, J.; Hideg, K. *Synthesis* **1999**, 973.
(28) Delpierre, G. R.; Lamchen, M. *J. Chem. Soc.* **1963**, 4693.
(29) Tasz, M. K.; Plenat, F.; Cristau, H. J.; Skowronski, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *57*, 143.
(30) Popov, I. I.; Tkachenko, P. V.; Simonov, A. M. *Khim. Geterotsikl. Soedin.* **1973**, 551; *Chem. Abstr.* **1973**, *79*, 31984.

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