Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2012, **22**, 114–116
Mendeleev Communications

Synthesis of 2-amino-5,5-dialkyl-4-arylmethylidene-2-oxazolines from 2-alkyl-4-arylbut-3-yn-2-ols and guanidine

Denis S. Baranov,[a] Aleksey A. Ryabichev,[a] Victor I. Mamatyuk,[b] Yurii V. Gatilov,[b] Victor G. Kartsev[c] and Sergei F. Vasilevsky*[a]

[a] *Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 383 330 7350; e-mail: vasilev@ns.kinetics.nsc.ru*
[b] *N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation*
[c] *InterBioScreen Ltd., 119019 Moscow, Russian Federation*

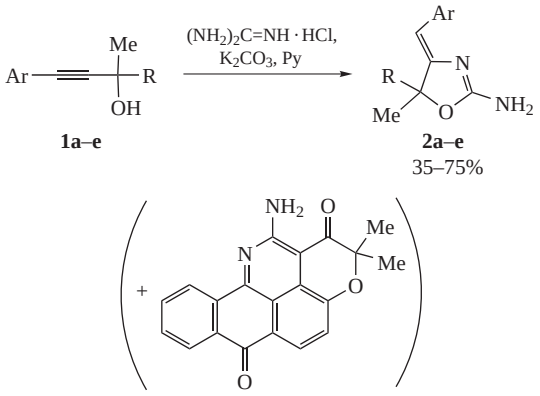
DOI: 10.1016/j.mencom.2012.03.022

Reaction between 2-alkyl-4-arylbut-3-yn-2-ols and guanidine in refluxing pyridine affords 2-amino-5,5-dialkyl-4-arylmethylidene-2-oxazolines.

Alkynes are convenient substrates for formation of diverse organic systems, and widely used in search of promising materials and medications.[1] For instance, new analogues of natural aporphinoid family alkaloids, possessing anti-cancer activity,[2] were obtained by reactions of 1-alkynyl-9,10-anthraquinones with guanidine[3] and urea.[4]

To extend this chemistry, we have studied the reaction of guanidine with 1- and 2-R-9,10-anthraquinones, and also 4-R-nitrobenzenes, where R is substituent, having tertiary acetylenic alcohol moiety. Electron-deficient alkynes, bearing additional OH group in α-position to acetylenic carbon, may be of synthetic potential.

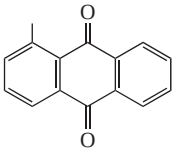
Indeed, the reaction of alkynols **1a**–**e**† with guanidine in refluxing pyridine led to heterocycles **2a**–**e** in 35–75% yields‡ (Scheme 1). In case of **1a**, along with predominant **2a** (75%) the minor product **3** was formed (7%).



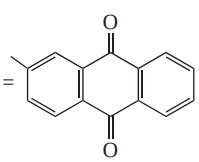
1a–e → **2a–e** 35–75%

3 (from **1a**)

a R = Me, Ar =

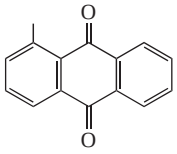


b R = Me, Ar =



c R = Me, Ar = 4-$O_2NC_6H_4$
d R = Me, Ar = 4-(4-$O_2NC_6H_4$)C_6H_4

e R = $Me_2C{=}CH(CH_2)_2$, Ar =



Scheme 1

† Combustion analysis was performed with CHN-analyzer (Model 1106, Carlo Erba, Italy). The NMR spectra were recorded on a Bruker AV 400 spectrometer (400.13 MHz) in $CDCl_3$ and Bruker-BioSpin AVANCE 600 spectrometer (600 MHz) in DMSO-d_6. Melting points were determined with a Kofler apparatus. The IR spectra were recorded in KBr pellets on a Bruker Vector 22 instrument. Column chromatography was performed on Merck 60 silica gel and the Silufol UV-254 plates were used for TLC analysis.

Synthesis of 2-alkyl-4-arylbut-3-yn-2-ols **1** *(general procedure).* A mixture of iodoarene (9 mmol), 2-methylbut-3-yn-2-ol (0.8 g, 9 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.028 mmol), CuI (10 mg, 0.052 mmol) and Et_3N (7 ml, 38.6 mmol) in 50 ml of toluene was stirred in argon atmosphere for 1.5–6 h at 65 °C. The reaction mixture was cooled and filtered through Al_2O_3 (25×20 mm), eluting with toluene. The solvents were evaporated at reduced pressure, and the residue was recrystallized.

2-Methyl-4-(9,10-anthraquinon-1-yl)but-3-yn-2-ol **1a**: yield 2.2 g (82%), mp 157–158 °C (toluene) (lit.,[10] 157.5–158.5 °C).

2-Methyl-4-(9,10-anthraquinon-2-yl)but-3-yn-2-ol **1b**: yield 2.4 g (92%), mp 133–134 °C (toluene–hexane) (lit.,[10] 134–135 °C).

2-Methyl-4-(4-nitrophenyl)but-3-yn-2-ol **1c**: yield 1.78 g (97%), mp 104.5–105.5 °C (toluene–hexane) (lit.,[11] 104.5–105 °C).

2-Methyl-4-(4′-nitrobiphenyl-4-yl)but-3-yn-2-ol **1d**: yield 1.5 g (60%), mp 117–118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.65 (s, 6H, Me), 2.10 (br. s, 1H, OH), 7.55 (m, 4H, *o*-C_6H_4-, *m*-$C_6H_4NO_2$), 7.72 (d, 2H, *m*-C_6H_4-, *J* 8.56 Hz), 8.29 (d, 2H, *o*-$C_6H_4NO_2$, *J* 8.80 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.59 (2Me), 65.82 (C–OH), 81.65, 95.68 (C≡C), 123.66, 124.31, 127.33, 127.81, 132.51, 138.47, 146.78, 147.35 (C_{Ar}). IR (ν/cm^{-1}): 3375 (OH), 2221 (C≡C), 1516, 1342 (NO_2). Found (%): C, 72.27; H, 5.22; N, 4.81. Calc. for $C_{17}H_{15}NO_3$ (%): C, 72.58; H, 5.37; N, 4.98.

3,7-Dimethyl-1-(9,10-anthraquinon-1-yl)oct-6-en-1-yn-3-ol **1e**: yield 1.418 g (44%), mp 90–91 °C (hexane–toluene). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.68 (s, 3H, Me), 1.70 (s, 6H, 2Me), 1.90 (t, 2H, CH_2, *J* 8.2 Hz), 2.43 (m, 2H, CH_2) 2.89 (s, 1H, OH), 5.24 [m, 1H, $(CH_2)_2CH$=], 7.69 (t, 1H, H_{Ar}, *J* 7.8 Hz), 7.79 (m, 2H, H_{Ar}), 7.83 (dd, 1H, H_{Ar}, *J* 1.3 and 7.5 Hz), 8.28 (m, 3H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.91, 25.91, 29.81 (3Me), 23.94, 43.51 [$(CH_2)_2$], 69.24 (C–OH), 83.27, 99.76 (C≡C), 123.44, 124.17, 127.00, 127.51, 127.66, 132.50, 132.81, 132.93, 133.53, 133.92, 134.21, 134.48, 134.58, 140.30 (C_{Ar}, C=C_{Alk}), 181.93, 182.69 (2C=O). IR (ν/cm^{-1}): 3463 (OH), 2216 (C≡C), 1676 (C=O). Found (%): C, 81.24; H, 6.02. Calc. for $C_{24}H_{22}O_3$ (%): C, 80.42; H, 6.19.

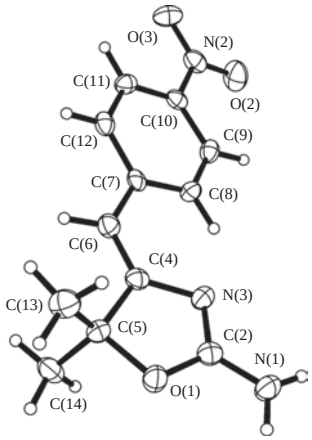
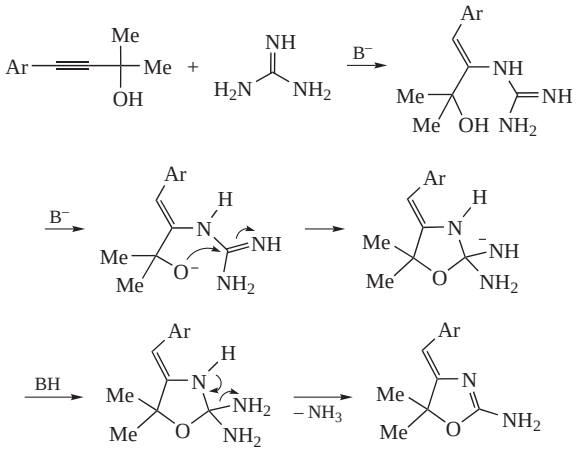


Figure 1 Crystal structure of compound **2c**.

Combination of analytical and spectral (IR, ^{1}H and ^{13}C NMR and mass spectra) data provided elucidation of the structure of products **2a**–**e** as 2-amino-5,5-dialkyl-4-arylmethylidene-2-oxazolines. Structure of **2c** was additionally proved by X-ray diffraction analysis§ (Figure 1).

The formation of an oxazole ring can be represented as consequent stages of the guanidine addition to the triple bond of **1**, the generation of the alkoxide anion under the action of base (guanidine or potassium carbonate) and cyclization with the following elimination of the ammonia molecule (Scheme 2).



Scheme 2

These transformations have analogy with cyclizations described in literature,[5,6] because the structure of the enamine intermediate is similar to those of 1-(2-hydroxyethyl)guanidine and 1-(2-hydroxyethyl)-3-nitroguanidine.

Detailed comparison of the physico-chemical properties of compounds **2a**–**e** shows, that main product of the reaction of alcohol **1a** with guanidine in 1-butanol is 2-amino-5,5-dimethyl-4-[(9,10-anthraquinon-1-yl)methylidene]-2-oxazoline **2a** rather than its isomer 3*H*-4-(2-hydroxyprop-2-yl)anthra[9,1-*de*][1,3]-diazocine-2,9-dione **A,** as it was reported earlier[3] (Scheme 3).

‡ *Reaction of 2-alkyl-4-arylbut-3-yn-2-ols* **1** *with guanidine*. A mixture of 2-methyl-4-arylbut-3-yn-2-ol **1** (3.4 mmol), guanidine hydrochloride (1.95 g, 20.4 mmol) and K_2CO_3 (2.81 g, 20.4 mmol) in 40 ml of pyridine was boiled for 16–60 h. Then CH_2Cl_2 (250 ml) and water (250 ml) were added, the organic layer was separated, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on Al_2O_3 (elution with toluene and mixture toluene–ethyl acetate). Subsequent recrystallization gave pure compounds.

2-Amino-5,5-dimethyl-4-[(9,10-anthraquinon-1-yl)methylidene]-2-oxazoline **2a**: yield 847 mg (75%), mp 290–291 °C (1,4-dioxane) (lit.,[3(b)] 290–290.4 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.67 (s, 6H, Me), 4.94 (br.s, 2H, NH_2), 6.91 (s, 1H, CH=), 7.68 (t, 1H, H_{Ar}, *J* 7.8 Hz), 7.75 (m, 2H, H_{Ar}), 8.15 (m, 1H, H_{Ar}), 8.26 (m, 2H, H_{Ar}), 8.76 (dd, 1H, H_{Ar}, *J* 1.5 and 8.1 Hz). ^{1}H NMR (DMSO-d_6, 600 MHz, 320 K) δ: 1.54 (s, 6H, Me), 6.95 (s, 1H, CH=), 7.67 (m, 1H, H_{Ar}), 7.68 (br.s, 2H, NH_2), 7.83 (m, 1H, H_{Ar}), 7.88 (m, 1H, H_{Ar}), 7.89 (m, 1H, H_{Ar}), 8.11 (m, 1H, H_{Ar}), 8.16 (m, 1H, H_{Ar}), 9.16 (m, 1H, H_{Ar}). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 27.39 (2Me), 88.84 (*C*Me$_2$), 94.80 (CH=), 122.81, 125.60, 125.91, 126.93, 132.00, 132.23, 133.46, 134.33, 134.45, 134.92, 135.55, 141.51 (C_{Ar}), 166.48 (=C<), 166.98 (CNH_2), 183.22, 184.44 (2C=O). ^{15}N NMR (DMSO-d_6, 60 MHz) δ: 72.34 (t, NH_2, *J* 90.3 Hz), 179.21 (s, N). Found (%): C, 72.25; H, 4.70; N, 8.44. Calc. for $C_{20}H_{16}N_2O_3$ (%): C, 72.28; H, 4.85; N, 8.43.

2-Amino-5,5-dimethyl-4-[(9,10-anthraquinon-2-yl)methylidene]-2-oxazoline **2b**: yield 847 mg (75%), mp 277–278 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.60 (s, 6H, Me), 5.37 (s, 1H, CH=), 6.20 (br.s, 2H, NH_2), 7.79 (m, 2H, H_{Ar}), 8.03 (m, 1H, H_{Ar}), 8.22 (d, 1H, H_{Ar}, *J* 8.06 Hz), 8.32 (m, 2H, H_{Ar}), 8.53 (d, 1H, H_{Ar}, *J* 1.61 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.63 (2Me), 90.66 (CH=), 99.63 (*C*Me$_2$), 125.25, 127.20, 127.36, 127.61, 129.54, 132.79, 133.69, 133.70, 133.92, 134.16, 134.21, 144.80 (C_{Ar}), 164.19 (=C<), 166.74 (CNH_2), 182.79, 184.57 (2C=O). IR (ν/cm^{-1}): 3330, 3380 (NH_2), 1695, 1666 (C=O), 1568 (C=N). Found (%): C, 72.56; H, 4.79; N, 8.51. Calc. for $C_{20}H_{16}N_2O_3$ (%): C, 72.28; H, 4.85; N, 8.43.

2-Amino-5,5-dimethyl-4-(4-nitrobenzylidene)-2-oxazoline **2c**: yield 560 mg (66%), mp 198–199 °C (toluene). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.56 (s, 6H, Me), 5.00 (br.s, 2H, NH_2), 5.29 (s, 1H, CH=), 7.88 (dt, 2H, *m*-$C_6H_4NO_2$, *J* 1.96, 2.45 and 9.05 Hz), 8.13 (dt, 2H, *o*-$C_6H_4NO_2$, *J* 1.96, 2.45 and 9.05 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.50 (2Me), 91.10 (*C*Me$_2$), 99.77 (CH=), 123.91 (*m*-$C_6H_4NO_2$), 127.55 (*o*-$C_6H_4NO_2$), 144.25, 145.28 (C_{Ar}), 164.04 (=C<), 166.05 (CNH_2). IR (ν/cm^{-1}): 3365, 3497 (NH_2), 1540 (C=N), 1323, 1371 (NO_2). Found (%): C, 58.47; H, 5.21; N, 16.73. Calc. for $C_{12}H_{13}N_3O_3$ (%): C, 58.29; H, 5.30; N, 16.99.

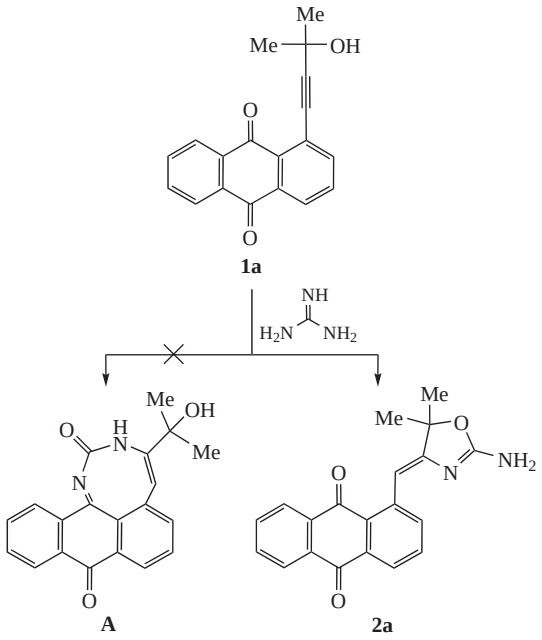
2-Amino-5,5-dimethyl-4-[(4'-nitrobiphenyl-4-yl)methylidene]-2-oxazoline **2d**: yield 385 mg (35%), mp 269–270 °C (ethyl acetate–toluene). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.56 (s, 6H, Me), 4.91 (br.s, 2H, NH_2), 5.30 (s, 1H, CH=), 7.58 (dt, 2H, *o*-C_6H_4-, *J* 1.88, 2.15 and 8.33 Hz), 7.74 (dt, 2H, *m*-$C_6H_4NO_2$, *J* 2.15, 2.42 and 9.13 Hz), 7.87 (dt, 2H, *m*-C_6H_4-, *J* 1.88, 2.15 and 8.33 Hz), 8.27 (dt, 2H, *o*-$C_6H_4NO_2$, *J* 2.15, 2.42 and 9.13 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.77 (2Me), 90.33 (*C*Me$_2$), 100.78 (HC=), 124.25, 127.25, 127.29, 128.27, 134.60, 139.05, 146.70, 147.87 (C_{Ar}), 160.14 (=C<), 165.07 (CNH_2). IR (ν/cm^{-1}): 3383, 3502 (NH_2), 1547 (C=N), 1338, 1375 (NO_2). Found (%): C, 66.59; H, 5.11; N, 12.92. Calc. for $C_{18}H_{17}N_3O_3$ (%): C, 66.86; H, 5.30; N, 13.00.

2-Amino-5-methyl-5-(4-methylpent-3-en-1-yl)-4-[(9,10-anthraquinon-1-yl)methylidene]-2-oxazoline **2e**: yield 717 mg (53%), mp 173–174 °C (toluene–hexane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.57 (s, 3H, Me), 1.62 (s, 3H, Me), 1.65 (s, 3H, Me), 1.91 (m, 2H, CH_2), 2.06 (m, 2H, CH_2), 5.13 [m, 1H, $(CH_2)_2CH$=], 5.60 (br.s, 2H, NH_2), 6.76 (s, 1H, Aq-CH=), 7.67 (t, 1H, H_{Ar}, *J* 7.8 Hz), 7.75 (qd, 2H, H_{Ar}, *J* 1.6 and 7.5 Hz), 8.15 (dd, 1H, H_{Ar}, *J* 1.3 and 7.5 Hz), 8.25 (dd, 2H, H_{Ar}, *J* 1.9 and 6.7 Hz), 8.61 (dd, 1H, H_{Ar}, *J* 1.3 and 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.79, 25.87, 26.71 (3Me), 22.39, 40.62 [$(CH_2)_2$], 92.81 (R_3C–O), 100.39 (–CH=), 123.47, 124.99, 126.67, 127.34, 128.14, 132.33, 132.57, 132.83, 133.32, 134.15, 134.91, 135.36, 137.02, 140.95 (C_{Ar}, C=C_{Alk}), 160.65 (=C–N), 166.20 (CNH_2), 184.15, 185.13 (2C=O). IR (ν/cm^{-1}): 3398 (NH_2), 1663 (C=O), 1560 (C=N). Found (%): C, 74.84; H, 5.78; N, 6.89. Calc. for $C_{25}H_{24}N_2O_3$ (%): C, 74.98; H, 6.04; N, 7.00.

*12-Amino-2,2-dimethyl-2*H*-chromeno[4,5,6-*cde*]benzo[*h*]quinoline-1,6-dione* **3**: yield 78 mg (7%), mp 259–260 °C (toluene–ethyl acetate) (lit.,[3(b)] 259.6–260 °C).

§ *Crystal data for compound* **2c**. $C_{12}H_{14}N_3O_3$, M_r = 248.26, orthorhombic, $P2_12_12_1$, a = 6.3532(9), b = 7.3907(12) and c = 24.559(4) Å, V = 1153.1(3) Å^3, Z = 4, d_{calc} = 1.430 g cm^{-3}, μ(MoKα) = 0.105 mm^{-1}, T = 150(2) K. All measurements were performed with a Bruker KAPPA APEX2 CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, crystal size 0.01×0.22×0.24 mm]. 11805 reflections were measured ($2\theta < 52°$), from which 2152 are independent (R_{int} = 0.1004), wR_2 = 0.1319 and GOF = 0.982 for all independent reflections [R_1 = 0.0537 for 1443 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELX-97.[12]

CCDC 867605 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.



Scheme 3

This mistake is connected with the fact, that the structures of **A** and **2a** have the same elemental composition and molecular ion in mass spectra, and similar IR and NMR spectra. In addition, earlier,[3(*b*)] NMR spectra were recorded in DMSO-d_6 at 297 K. Under these conditions the signal of NH_2 group was not observed. In the spectra of **2b**–**e** recorded in $CDCl_3$ solutions (due to higher solubility of compounds **2b**–**e**) broad signals of two protons of NH_2 group appear at 4.91–6.20 ppm. Therefore, we carried out prolonged accumulation of signals for sample **A** in $CDCl_3$ under normal conditions and recorded spectra in DMSO-d_6 at 320 K, which allowed us to detect signals of NH_2 protons at 4.94 ppm in $CDCl_3$ and at 7.68 ppm in DMSO-d_6. Thus, the correct structure **2a** was assigned.

As stretching vibrations of NH_2 group of **2a** and presumable signals of OH and NH groups of **A** in the IR spectra should be close, their identification was difficult. Moreover, attempted preparation of monocrystal of **2a** for X-ray analysis was unsuccessful. The authors apologize for making mistake in earlier paper.[3(*b*)]

The starting compounds were obtained under the standard Sonogashira reaction conditions[7] in the system $PdCl_2(PPh_3)_2$–CuI–Et_3N from 2-alkylbut-3-yn-2-ols and the corresponding iodoarenes.[†]

In summary, heterocyclization of 2-alkyl-4-arylbut-3-yn-2-ols with guanidine leads to 2-amino-5,5-dialkyl-4-arylmethylidene-2-oxazolines in 35–75% yields. The products synthesized may be useful for medicinal chemistry, since their structural analogues possess high psychoactive properties (aminorex, 4-methylaminorex)[8] and hypotensive activity (rilmenidine based preparations).[9]

This work was supported by the Russian Foundation for Basic Research (grant no. 10-03-00257a) and the Chemical Service Centre of the Siberian Branch of the Russian Academy of Sciences.

References

1 *Acetylene Chemistry: Chemistry, Biology and Material Science*, eds. F. Diederich, P. J. Stang and R. R. Tykwinski, Wiley-VCH, Weinheim, 2005.
2 (*a*) B.-W. Yu, L.-H. Meng, J.-Y. Chen, T.-X. Zhou, K.-F. Cheng, J. Ding and G.-W. Qin, *J. Nat. Prod.*, 2001, **64**, 968; (*b*) H. Tang, X.-D. Wang, Y.-B. Wei, S.-L. Huang, Z.-S. Huang, J.-H. Tan, L.-K. An, J.-Y. Wu, A. S.-C. Chan and L.-Q. Gu, *Eur. J. Med. Chem.*, 2008, **43**, 973; (*c*) Y. D. Min, S. U. Choi and K. R. Lee, *Arch. Pharm. Res.*, 2006, **29**, 627.
3 (*a*) S. F. Vasilevsky, D. S. Baranov, V. I. Mamatyuk, Y. V. Gatilov and I. V. Alabugin, *J. Org. Chem.*, 2009, **16**, 6143; (*b*) D. S. Baranov, S. F. Vasilevsky, V. I. Mamatyuk and Yu. V. Gatilov, *Mendeleev Commun.*, 2009, **19**, 326; (*c*) D. S. Baranov and S. F. Vasilevsky, *Izv. Akad. Nauk, Ser. Khim.*, 2010, 1008 (*Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 1031).
4 D. S. Baranov, S. F. Vasilevsky, B. Gold and I. V. Alabugin, *RSC Adv.*, 2011, **1**, 1745.
5 L. Fishbein and J. A. Gallaghan, *J. Org. Chem.*, 1956, **21**, 434.
6 B. Adcock and A. Lawson, *J. Chem. Soc.*, 1965, 474.
7 K. Sonogashira, Y. Tohda and N. A. Hagihara, *Tetrahedron Lett.*, 1975, **50**, 4457.
8 (*a*) G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszowski, N. M. Kelley and J. McGowin, *J. Med. Chem.*, 1963, **6**, 266; (*b*) E. Merirınne, S. Ellermaa, A. Kankaanpää, A. Bardy and T. Seppäla, *J. Pharmacol. Exp. Ther.*, 2004, **309**, 1198.
9 A. Remkova and H. Kratochvil'ova, *J. Human Hypertens.*, 2002, **16**, 549.
10 A. V. Piskunov, A. A. Moroz and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 828 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 755).
11 M. S. Shvartsberg, A. A. Moroz and I. L. Kotlyarevsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1971, 1306 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1971, **20**, 1306).
12 G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112.

Received: 8th November 2011; Com. 11/3834