Tetrahedron 64 (2008) 5541–5544

Contents lists available at ScienceDirect

Tetrahedron

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

Reactions of 2-phenylpyrrole with bromobenzoylacetylene on metal oxides active surfaces

Boris A. Trofimov [a,*], Lyubov' N. Sobenina [a], Zinaida V. Stepanova [a], Tamara I. Vakul'skaya [a], Ol'ga N. Kazheva [b], Grigorii G. Aleksandrov [c], Oleg A. Dyachenko [b], Al'bina I. Mikhaleva [a]

[a] A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Street, 664033 Irkutsk, Russian Federation
[b] Institute of Problems of Chemical Physics, Russian Academy of Sciences, 1 Academician Semenov Street, 142432 Chernogolovka, Russian Federation
[c] NS Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 31 Leninskii Prosp., 119991 Moscow, Russian Federation

ARTICLE INFO

Article history:
Received 22 November 2007
Received in revised form 11 March 2008
Accepted 27 March 2008
Available online 3 April 2008

ABSTRACT

The solvent-free interaction of 2-phenylpyrrole with bromobenzoylacetylene (room temperature) upon their grinding with solid metal oxides (MgO, CaO, ZnO, BaO, Al_2O_3, TiO_2, ZrO_2) and salts ($CaCO_3$, $ZrSiO_4$) leads to either the cross-coupling product or the adduct of pyrrole addition to the ripple bond of acetylene. The ethynylation is accompanied by the formation of intermediate and side products: *E*-2-(1-bromo-2-benzoylethenyl)-5-phenylpyrrole and 1,1-di(5-phenylpyrrol-2-yl)-2-benzoylethene. The activity of the metal oxides in the ethynylation reaction falls in the order (in the brackets, the content of 2-benzoylethynyl-5-phenylpyrrole in the reaction mixture is given): ZnO (81%), BaO (73%), Al_2O_3 (71%), MgO (69%), CaO (50%). The oxides, SiO_2, TiO_2, ZrO_2, and the salts, $CaCO_3$ and $ZrSiO_4$, are inactive in the ethynylation reaction affording only the intermediate adduct, with ZrO_2 the isolated yield of the bromoethenylpyrrole reaching 60%. ESR monitoring shows the reaction to start from one electron transfer from pyrrole to acetylene mediated by the oxide surface. The adduct is readily converted on Al_2O_3 to 2-(benzoylethynyl)-5-phenylpyrrole crystallized mostly as cis-rotamer (X-ray data).

1. Introduction

Recently, we have reported the direct ethynylation of pyrroles and indoles with electron deficient haloacetylenes on the Al_2O_3 active surface. This reactions proceed rapidly at room temperature with no transition-metal catalyst and base under solvent-free conditions, and require no preliminary functionalization of the pyrrole and indole nuclei.[1] The reaction paves the way to earlier inaccessible pyrroles and indoles with functionalized acetylenic substituents, useful building blocks to design drugs, and new materials for molecular electronics.

This paper aims to elucidate whether alumina is the unique metal oxide to affect the ethynylation and whether other active surfaces for this reaction can be found.

Today, the active surfaces such as metal oxides play an ever-growing role in organic synthesis and are widely employed not only for preparative organic reactions but also in industry. Such reactions normally proceed under mild conditions, with high chemo-, regio-, and stereoselectivity, securing simpler isolation procedures compared to similar reactions in solution.[2] The scope of application of the active surfaces including their modifications is steadily spreading, a testimony to their unfolding potential.[3]

2. Results and discussion

Herein, we have investigated the room temperature interaction of 2-phenylpyrrole with bromobenzoylacetylene upon their grinding with diverse metal oxides and salts (10-fold amount) as active surfaces (Table 1). The reaction course (conversion of reactants **1** and **2** and the ratio of products) was determined from the ^1H NMR spectra of the $CDCl_3$ extracts from the reaction mixture. This reaction has been chosen as a standard of the pyrrole ethynylation with haloacetylenes.

As reported,[1] this reaction when carried out on Al_2O_3 gave ethynylpyrrole **3** as a major product and small amounts of the intermediate **4** and the side product **5** (Scheme 1).

Apart from signals of these compounds, in the ^1H NMR spectra of the samples taken from the reaction mixtures appear two broad singlets at 5.70 and 12.44 ppm. According to ^1H and ^{13}C NMR spectroscopic data, these signals are assigned to unstable dipyrrolylbromoethane **6**, which was not possible to isolate. This product likely results from nucleophilic addition of pyrrole **1** onto the intermediate bromoethenylpyrrole **4** (Scheme 2).

---

* Corresponding author. Tel.: +7 3952 461411/511431; fax: +7 3952 419346.
E-mail address: boris_trofimov@irioch.irk.ru (B.A. Trofimov).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.03.104

Table 1
^{1}H NMR spectroscopic monitoring of reaction of 2-phenylpyrrole **1** with bromobenzoylacetylene **2** (room temperature)

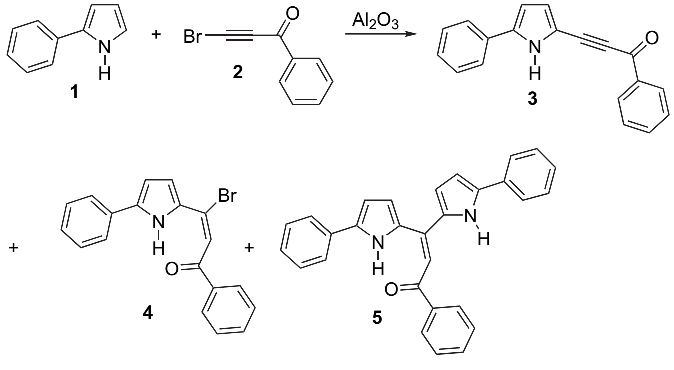
Active surface	Time of reaction, min									
	10					60				
	Composition[a] of reaction mixture, %									
	1	**3**	**4**	**5**	**6**	**1**	**3**	**4**	**5**	**6**
MgO	54	41	5	0	0	25	69	6	0	0
CaO	71	19	7	3	0	39	50	9	2	0
ZnO	0	78	18	4	0	0	81	15	4	0
BaO	7	69	20	4	0	0	73	20	6	0
Al_2O_3 (pH 7.5)	17	62	21	0	0	5	71	23	0	0
Al_2O_3 (pH 9.3)	17	62	21	0	0	6	68	26	0	0
Al_2O_3[b] (pH 9.3)	14	61	20	5	0	12	68	20	0	0
SiO_2	4	0	80	0	16	0	0	88	0	12
TiO_2	9	0	70	0	21	0	0	87	13	0
ZrO_2	0	0	73	0	27	0	0	83	0	17
$CaCO_3$	0	0	59	0	41	0	0	81	19	0
$ZrSiO_4$	7	0	61	0	32	0	0	85	0	15

[a] The percentage of acetylene **2** in the reaction mixture corresponds to the content of pyrrole **1**.
[b] K_2CO_3 (5% relative to alumina) was used.

We have also observed the formation of adduct **6** in the $CDCl_3$ solution (^{1}H NMR spectroscopy) directly from pyrrole **1** and acetylene **2**. However, evaporation of the solvent gives a solid residue of a complex unidentifiable structure.

For the first time it is shown (Table 1) that certain metal oxides are active media for the interaction studied, particularly ZnO and BaO, the activity of which surpasses that of Al_2O_3. The content of the ethynylation product in the reaction mixture is 81% (ZnO), 73% (BaO), and 71% (Al_2O_3).

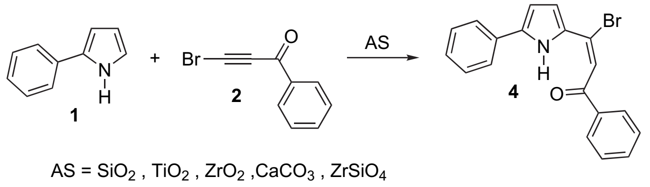
No direct dependence of the oxide efficiency in the cross-coupling on the basicity is observed as follows from Table 1 (i.e., ZnO is a weaker base than CaO but shows much higher activity in the cross-coupling). Moreover, alumina of different basicity, even with K_2CO_3 additive, gives practically the same results. One may suppose that transition-metal contaminations of the above metal oxides and salts influence the reaction studied. However, this does not agree with the practically similar results obtained with different metal oxides (MgO, CaO, ZnO, BaO, Al_2O_3, Table 1). It is improbable that all the active surfaces are equally contaminated with the same transition metals.



Scheme 1.

As the case of Al_2O_3,[1] the cross-coupling is accompanied by the formation of bromoethenylpyrrole **4** and dipyrrolylethene **5**, the former being an intermediate and the latter a side product (Scheme 1).

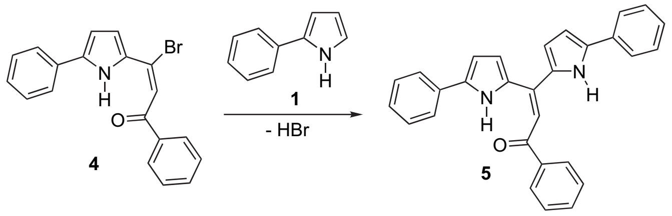
The metal oxides (TiO_2, ZrO_2) as well as SiO_2 and the salts ($CaCO_3$, $ZrSiO_4$) are found inactive in the cross-coupling. Instead, they happen to be highly active in the nucleophilic addition of pyrrole **1** to the triple bond of bromobenzoylacetylene **2** to afford the adduct **4** (the content of which in the reaction mixture ranges from 81% up to 88%) (Scheme 3).



Scheme 3.

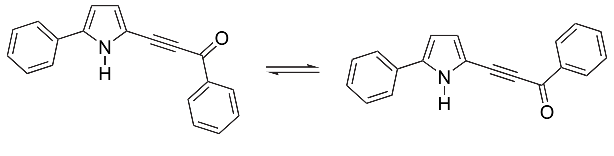
Thus, these metal oxides and salts are specific active surfaces for effecting chemo-, regio-, and stereoselective addition of pyrrole **1** (by its C-2-position) to the triple bond of acetylene **2**.

In all cases, dipyrrolylethene **5** is formed in much smaller amounts (0–19%). This is obviously the product of substitution of the bromine atom in the intermediate **4** by the pyrrolyl moiety (Scheme 4).

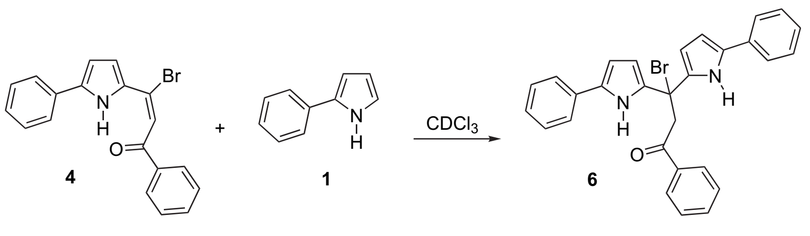


Scheme 4.

Apparently, the cross-coupling, resulting in the formation of the ethynylpyrrole **3**, proceeds via the intermediate **4**, which further eliminates HBr. This is supported by the observation that when the intermediate **4** (prepared on ZrO_2) is passed through an Al_2O_3 column the ethynylpyrrole **3** is isolated. It is noteworthy that in this case the pyrrole **3** crystallized mostly as its cis-rotamer (prisms) (Fig. 1).



Previously, this type of isomerism of the $C_{sp}-C_{sp^3}$ bond in the crystalline state for the same compound was noted briefly,[1b] where both cis-rotamer and trans-rotamer (needles) were isolated.



Scheme 2.

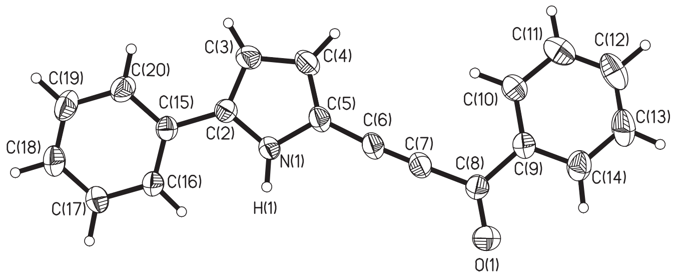
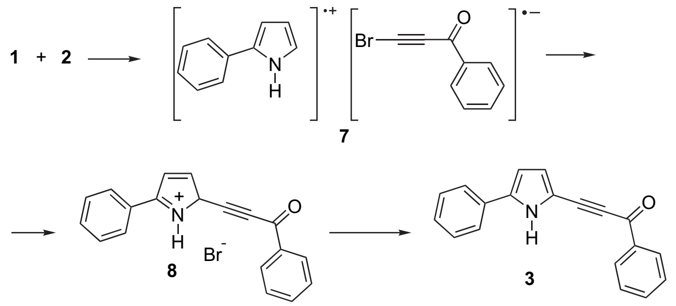


Figure 1. General view of 2-(2-benzoylethynyl)-5-phenylpyrrole **3**.

X-ray analysis data for a new polymorphous modification of ethynylpyrrole **3**, given in Section 3, correlate well with the data obtained earlier for cis-rotamer.[1b]

Obviously, the route to ethynylpyrrole **3** via the charge-transfer complex **7** and further the salt **8** avoiding the adduct **4** has not been excluded (Scheme 5). Such a reaction may be realized as a parallel or complementary channel of the above HBr elimination from the adduct **4**.



Scheme 5.

It is known that reactions on the metal oxide surfaces often proceed by one-electron transfer and hence for an investigation of their mechanisms, the ESR technique is appropriate.[4]

We have monitored the reaction between the pyrrole **1** and acetylene **2** on active surfaces of the oxides: ZnO, Al_2O_3 (pH 9.5), SiO_2, TiO_2, ZrO_2 and the salts: $CaCO_3$, $ZrSiO_4$ by the ESR technique and found singlets with *g*-factors in the region of free radicals (Table 2).

The value of *g*-factors changes depending on the surface nature and varies within 0.0006. The asymmetric signals detected for $ZrSiO_4$, TiO_2, and ZrO_2 under microwave power saturation split in two lines (Fig. 2).

The line with *g*-factor 2.0023 is assigned to the 2-phenylpyrrole cation–radical. The second line with *g*-factors 2.0032–2.0044 (depending on active surface nature) is likely to be attributed to the complex of bromobenzoylacetylene anion–radical with active surface. At the same time, microwave power saturation applied to the reaction mixtures on oxides Al_2O_3 and ZnO does not cause the ESR signal splitting. Probably, the components of the reaction mixture activated by the crystal lattice first undergo charge transfer to deliver the ion–radical pair. Depending on acid–base properties of the active surface the ion-pair components behave diversely: on the acidic surfaces the radical cation should be stabilized, while on the basic ones it is deprotonated to a neutral radical, thus leading to different reaction products **3** and **4**, respectively.

Table 2
ESR signal characteristics for the reaction of 2-phenylpyrrole with bromobenzoylacetylene on active surfaces

Active surface	$N\times10^{16}$, spin/g	*g*-Factor	Δ*H*, mT
ZnO	35	2.0030	0.660
Al_2O_3 (pH 9.5)	10	2.0026	0.600
SiO_2 (Merck)	7.0	2.0028	0.600
$CaCO_3$	6.9	2.0030	0.533
TiO_2	11	2.0027	0.710
ZrO_2	4.0	2.0024	0.622
$ZrSiO_4$	8.7	2.0024	0.580

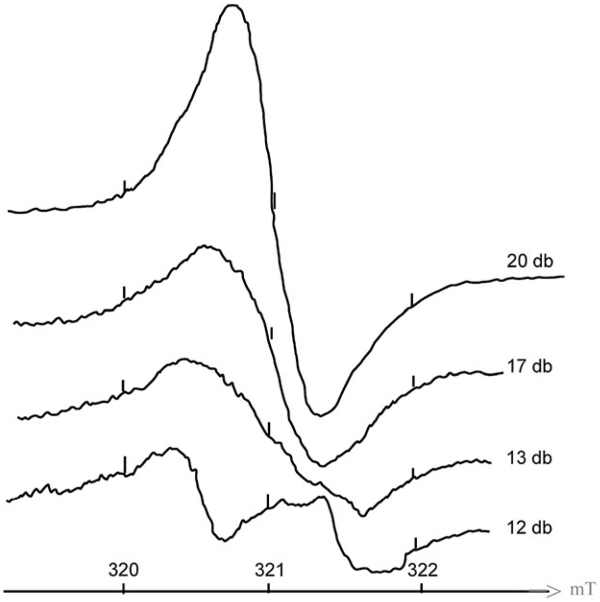


Figure 2. ESR spectra of dry reaction mixture of 2-phenylpyrrole/bromobenzoylacetylene/TiO_2, recorded under different microwave power.

Thus, the experimental data point to the fact that ethynylation of pyrroles with bromobenzoylacetylene may involve a one-electron transfer stage delivering ion–radicals stabilized by the crystalline lattice of the active surface.

The active surface participation in the ion–radical generation is also confirmed by the appearance of the corresponding but very weak signals in ESR spectra of the separated pairs: Al_2O_3–2-phenylpyrrole and Al_2O_3–bromobenzoylacetylene. Thus, approximately 0.5 h after preparation, 2-phenylpyrrole on Al_2O_3 turns beige. In the ESR spectrum appears a weak (3×10^{14} spin/g) broad (1.1 mT) singlet with *g*-factor 2.0024, narrowing and increasing with time. Bromobenzoylacetylene on Al_2O_3 just after the preparation becomes pink and its ESR spectrum shows very weak (10^{14} spin/g) and narrow (0.33 mT) singlet with *g*-factor 2.0032, which does not practically change with time.

In conclusion, a novel approach for the direct room temperature chemo-, regio-, and stereoselective C-2-ethynylation and -ethenylation of pyrroles with haloacetylenes on metal oxides' and salts' active surfaces under transition-metal and solvent-free conditions has been generalized for the first time. New active surfaces such as metal oxides and salts have been found to be effective for the above reactions. The reaction follows one-electron transfer mechanism to form ion–radical intermediates stabilized by the metal oxide active surfaces. The new concept contributes to both synthetic pyrrole and acetylene chemistry.

3. Experimental

3.1. General

^1H (400.13 MHz) and ^{13}C (101.6 MHz) NMR spectra were recorded on a 'Bruker DPX250' instrument with $CDCl_3$ as solvent and HMDS as the internal standard. The assignment of signals in the ^1H NMR spectrum was made using COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on HSQC and HMBC experiments.

X-ray diffraction study of **3** was carried out with an Enraf–Nonius CAD-4 diffractometer at room temperature ($\omega/2\theta$-scanning, Mo Kα radiation, graphite monochromator). Crystalline structure was solved by direct methods followed by Fourier synthesis using SHELXS-97.[5a] All non-hydrogen atoms were refined using anisotropic full-matrix approximation using SHELXL-97.[5b] Coordinates of hydrogen atoms were defined experimentally and refined isotropically. Atom coordinates, bond lengths, and angle values were deposited at Cambridge Crystallographic Data Center (CCDC). These data are available via www.ccdc.cam.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 678754.

Crystal and experimental data: $C_{19}H_{13}NO$, M=271.30, monoclinic, $C2/c$, a=16.748(3) Å, b=7.225(1) Å, c=23.818(5) Å, β=97.78(3)°, V=2855.6(1) Å^3, Z=8, D_{calcd}=1.26 g cm^{-3}, μ=0.078 mm^{-1}, reflections observed/independent 4507/3094, 243 parameters refined, R=0.037 for 1841 reflections with [$F_0>4\sigma(F_0)$].

The crystal structure is formed by one crystallographic independent molecule (Fig. 1), taking general position in the unit cell. The molecule has practically plane conformation and dihedral angles formed by planes of pyrrole and phenyl cycles C(15)C(16)···C(20) and C(9)C(10)···C(14) are 11.9 and 2.9°, respectively. Dihedral angle between planes of phenyl cycles is 11.1°. Angles C(5)–C(6)–C(7) and C(6)–C(7)–C(8) of acetylene moiety is equal to 175.6(1) and 178.4(1)°, correspondingly.

The molecules form piles along axis *b*. The disposition of molecules relative to each other is favorable to the occurrence of strongly shortened intermolecular interactions N(1)–H(1)···O(1). Bond lengths N(1)–H(1) and H(1)···O(1) is equal to 0.92(1) and 1.98(2) Å, respectively, and angle N(1)–H(1)···O(1) is 172(1)°. Sum of van-der-Waals radii of the H···O atoms is 2.45 Å.[6]

ESR spectra were recorded at room temperature using an SE/X-2547 Radiopan (Poland) spectrometer equipped with a magnetometer and a high frequency gauge. Concentrations of paramagnetic centers were calculated by known techniques.[7]

3.2. The reaction of 2-phenylpyrrole 1 with bromobenzoylacetylene 2 on active surface: typical procedure

Equimolar amounts of pyrrole (0.143 g, 1 mmol) and bromobenzoylacetylene (0.209 g, 1 mmol) were regularly grinded in porcelain mortar with active surface (3.5 g, 10-fold amount) at ambient temperature for 1 h. The reaction was monitored using ^{1}H NMR (CDCl$_3$) technique (samples were taken from the reaction mixture in 10 and 60 min). The ratio of the reaction products was determined by the integral intensity of signals of H-atoms: H-3, H-4 for pyrrole **1** (6.29 and 6.51 ppm), pyrrole **3** (6.59 and 6.93 ppm), and pyrrole **4** (6.76 and 7.11 ppm); Hα for pyrrole **5** (6.86 ppm) and H-atoms of CH$_2$ group for pyrrole **6** (5.70 ppm).

Pyrroles **3–5** used as reference were prepared according to the procedures reported earlier.[1]

3.3. The reaction of 2-phenylpyrrole with bromobenzoylacetylene on ZrO$_2$

A Equimolar amounts of pyrrole (0.143 g, 1 mmol) and bromobenzoylacetylene (0.209 g, 1 mmol) were regularly grinded in porcelain mortar with ZrO$_2$ (3.5 g, 10-fold amount) at ambient temperature for 1 h. The mixture self-heated up to 30 °C and became bright yellow. Gradually the color changed to brown. The reaction mixture was placed on the column with ZrO$_2$ and eluted with hexane to afford 0.211 g (60%) of 2-(1-bromo-2-benzoylethenyl)pyrrole **4**.

B Equimolar amounts of pyrrole (0.143 g, 1 mmol) and bromobenzoylacetylene (0.209 g, 1 mmol) were regularly grinded in porcelain mortar with ZrO$_2$ (3.5 g, 10-fold amount) at ambient temperature for 1 h. The mixture self-heated up to 30 °C and became bright yellow. Gradually the color changed to brown. The reaction mixture was placed on the column with Al$_2$O$_3$ and eluted with hexane and then with diethyl ether to afford 0.042 g (12%) of 2-(1-bromo-2-benzoylethenyl)pyrrole **4** (hexane) and 0.176 g (65%) of 2-benzoylethynylpyrrole **3** (diethyl ether).

*3.3.1. 3-Bromo-1-phenyl-3,3-bis(5-phenyl-1H-pyrrol-2-yl)-1-propanone (**6**)*

^{1}H NMR (CDCl$_3$) δ 12.44 (br s, 2H, NH), 8.23 (m, 2H, H$_o$ COPh), 8.11 (m, 4H, H$_o$ 5-Ph), 7.45–7.30 (m, 9H, H$_m$, H$_p$ Ph, COPh), 7.36 (br s, 2H, H-3), 6.90 (br s, 2H, H-4), 5.70 (br s, 2H, CH$_2$); ^{13}C NMR (CDCl$_3$) δ 195.5 (C=O), 153.2 (C^5), 142.3 (C$_i$ COPh), 136.4 (C^2), 135.7 (C$_i$ Ph), 133.7 (C$_p$ COPh), 131.1 (C^3), 129.4 (C$_o$ COPh), 128.9 (C$_m$ Ph), 128.7 (C$_m$ COPh), 128.3 (C$_p$ Ph), 128.1 (C$_o$ Ph), 124.7 (*C*–Br), 117.0 (C^4), 46.2 (CH$_2$).

Acknowledgements

This work was supported by the Russian Foundation for Basic Research (grant no 05-03-32289).

References and notes

1. (a) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513–6516; (b) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Sinegovskaya, L. M.; Potekhin, K. A.; Fedyanin, I. V. *Mendeleev Commun.* **2005**, *6*, 229–232; (c) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Demenev, A. P.; Mikhaleva, A. I.; Ushakov, I. A.; Vakul'skaya, T. I.; Petrova, O. V. *Zh. Org. Khim.* **2006**, *42*, 1348–1355; (d) Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I.; Ushakov, I. A.; Vasil'tsov, A. M.; Ivanov, A. V.; Trofimov, B. A. *Tetrahedron Lett.* **2006**, *47*, 7139–7141; (e) Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Stepanova, Z. V.; Petrova, O. V.; Ushakov, I. A.; Mikhaleva, A. I. *Tetrahedron Lett.* **2007**, *48*, 4661–4664.
2. (a) McKillop, A.; Young, D. W. *Synthesis* **1979**, *401–422*, 481–500; (b) Ranu, B. C.; Bhar, S.; Chakraborty, R.; Das, A. R.; Saha, M.; Sarkar, A.; Chakraborti, R.; Sarkar, D. C. *Indian Inst. Sci.* **1994**, *74*, 15–33; (c) Basyuk, V. A. *Russ. Chem. Rev.* **1995**, *64*, 1003–1020; (d) Banerjee, A. K.; Mimo, M. S. L.; Vegas, W. J. V. *Russ. Chem. Rev.* **2001**, *70*, 971–990.
3. (a) Veselovsky, V. V.; Gybin, A. S.; Lozanova, A. V.; Moiseenkov, A. M.; Smit, W. A.; Caple, R. *Tetrahedron Lett.* **1988**, *29*, 175–178; (b) Sviridova, L. A.; Golubeva, G. A.; Lescheva, M. F.; Mizgunov, A. V. *Khim. Geterosikl. soed.* **1995**, 1489–1493; (c) Yong, Z. J.; Yasuda, N.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* **2003**, *44*, 8765–8768.
4. (a) Rooney, J. J.; Pink, R. C. *Trans. Faraday Soc.* **1962**, *58*, 1632–1641; (b) Corma, A.; Garcia, H. *Top. Catal.* **1998**, *6*, 127–140; (c) Tanaka, M.; Kobayashi, K. *Chem. Commun.* **1998**, 1965–1966; (d) Biancardo, M.; Argazzi, R.; Bignozzi, C. A. *Inorg. Chem.* **2005**, *44*, 9619–9621.
5. (a) Sheldrick, G. M. *SHELXS-97*; University of Göttingen: Germany, 1997; (b) Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Germany, 1997.
6. Zefirov, Yu. V. *Kristallographia* **1999**, *44*, 1091–1093.
7. Poole, C. P. *Electron Spin Resonance. A Comprehensive Treatise on Experimental Techniques*; Wiley-Interscience: New York, NY, 1983.