ISSN 0012-5008, Doklady Chemistry, 2013, Vol. 448, Part 2, pp. 44–48. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © V.K. Cherkasov, N.O. Druzhkov, T.N. Kocherova, E.N. Egorova, A.S. Shavyrin, 2013, published in Doklady Akademii Nauk, 2013, Vol. 448, No. 4, pp. 422–426.

CHEMISTRY

New Functionalized Sterically Hindered *o*-Aminophenols: Reversible Intramolecular Cyclization

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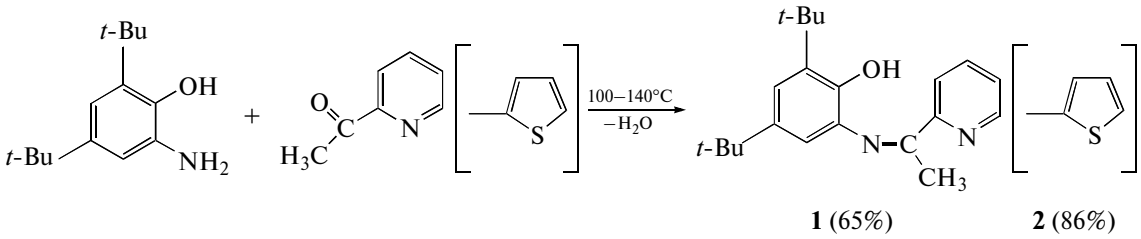
Received July 16, 2012

DOI: 10.1134/S001250081302002X

N-Substituted *o*-aminophenols exhibit redox isomerism when bound in a complex with a metal. The introduction of additional coordinating groups increases not only the ligand denticity but also the number of redox states, which considerably enhances the possibility of using the ligand in coordination chemistry [1–4]. One of the methods to obtain such derivatives consists in the condensation of sterically hindered *o*-aminophenols with different (aliphatic, aromatic) aldehydes and ketones [5, 6] and the 1,2-addition of amines to substituted *o*-benzoquinones [7]. Some N-substituted *o*-aminophenols do not exist in the aminophenol form but are isolated as isomeric benzoxazoles [8, 9].

This study is aimed at synthesizing new sterically hindered *o*-aminophenols derived from acetyl-substituted heterocyclic compounds and 3-(2,6-diisopropylphenylimino)butan-2-one (ImKet) [10].

N-Substituted *o*-aminophenols (**1** and **2**) were obtained by the reaction of 2-amino-4,6-di-*tert*-butylphenol with α-acetyl derivatives of pyridine and thiophene (Scheme 1).



Scheme 1.

Isolated compounds **1** and **2** are yellow solids soluble in organic solvents and slowly oxidized in air. Their composition was confirmed by elemental analysis while the structure was established by NMR spectroscopy.

^{1}H NMR spectra of compounds **1** and **2** show narrow intense singlets of the *tert*-butyl (δ 1.26–1.44 ppm), methyl (δ 1.87–2.51 ppm), and hydroxy group protons (δ 5.51–6.47 ppm), and a set of signals of the aromatic protons of the aminophenol moiety and pyridine (thiophene) substituent (δ 6.70–8.55 ppm).

The reaction of 2-amino-4,6-di-*tert*-butylphenol with ImKet led to a colorless crystalline solid identified by spectral methods (^{1}H, ^{13}C NMR) and nitrogen–proton correlation procedure (NHCORR) as dihydrobenzoxazole **3** rather than N-substituted *o*-aminophenol (Scheme 2).

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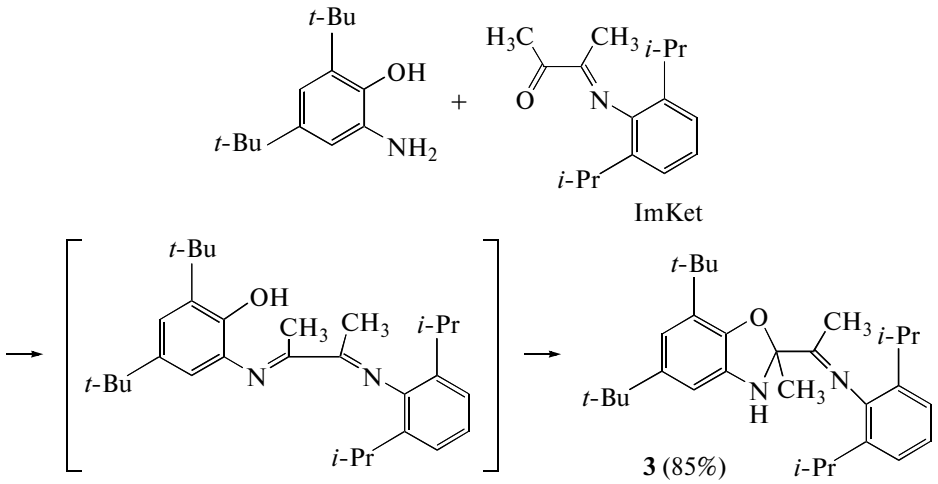


Scheme 2.

The IR spectrum of compound **3** exhibits characteristic absorption bands of stretching vibrations of imine ($\nu_{C=N}$ 1666 cm^{-1}) and amine (ν_{N-H} 3291 cm^{-1}) groups.

The ^1H NMR spectrum of compound **3** shows the signals of the *tert*-butyl protons (δ 1.26 and 1.36 ppm) and a multiplet of aromatic protons of the aminophenol and *N*-aryl rings (δ 6.74–7.14 ppm). The spectrum also displays the doublets of methyl groups of the isopropyl substituents (δ 0.79–0.83 ppm, $J = 6.88$ Hz), septets of methyne protons (δ 2.23 and 2.64 ppm, $J =$ 6.88 Hz), and narrow singlets of nonequivalent methyl groups (δ 1.80 and 1.86 ppm).

The structure of compound **3** was confirmed by the data of X-ray diffraction study (Fig. 1).

Crystals for X-ray diffraction analysis were obtained from CH_3CN. The X-ray diffraction study was performed on a Smart APEX automated diffractometer (graphite monochromator, MoK_α radiation, ω–φ scanning, exposure of 10 s/frame). The structure was solved by direct methods and refined by least squares on F^2_{hkl} in anisotropic approximation for all nonhydrogen atoms. Hydrogen atoms were located from difference electron density maps and refined isotropically. All computations were carried out with the use of the SHELXTL v. 6.10.1x software package.

The crystallographic data for compound **3**: $C_{30}H_{44}N_2O$, triclinic crystal system, space group $P1$, unit cell parameters $a = 11.2464(9)$ Å, $b = 15.8609(1)$ Å, $c = 18.5268(1)$ Å; $\alpha = 102.754(2)°$, $\beta = 107.317(2)°$, $\gamma = 109.440(2)°$; $V = 2781.0(4)$ Å^3, $Z = 4$, $d =$ 1.072 g cm^{-3}, $\mu = 0.064$ mm^{-1}, $F(000) = 984$, $R_1 =$ 0.0667, $wR_2 = 0.1528$. The crystallographic data were deposited with the Cambridge Structural Database (CCDC 890194), deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk.

It is known from the literature [8, 9] that two isomeric forms of certain *N*-substituted *o*-aminophenols exist in equilibrium: open (*o*-aminophenol) and cyclic (benzoxazole). To reveal whether such an equilibrium occurs for the obtained compounds, we conducted an experiment with the use of different solvents (C_6D_6, DMSO, CD_3CN, CD_3OD).

The ^1H NMR spectra of compounds **1**–**3** immediately after dissolution in CD_3OD were found to correspond completely to the expected spectra. However, the integrated intensity of the signal of the methyl group at the imine carbon atom in compounds **1** and **2** and the quaternary carbon atom in compound **3** considerably decreases within 3–5 min, while new broadened signals shifted upfield appear at the same time (Fig. 2).

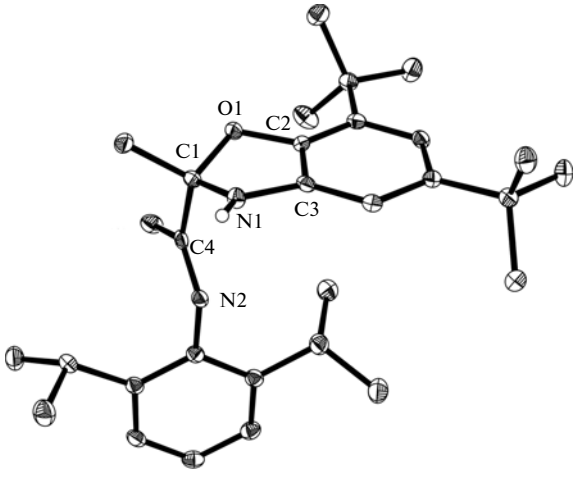


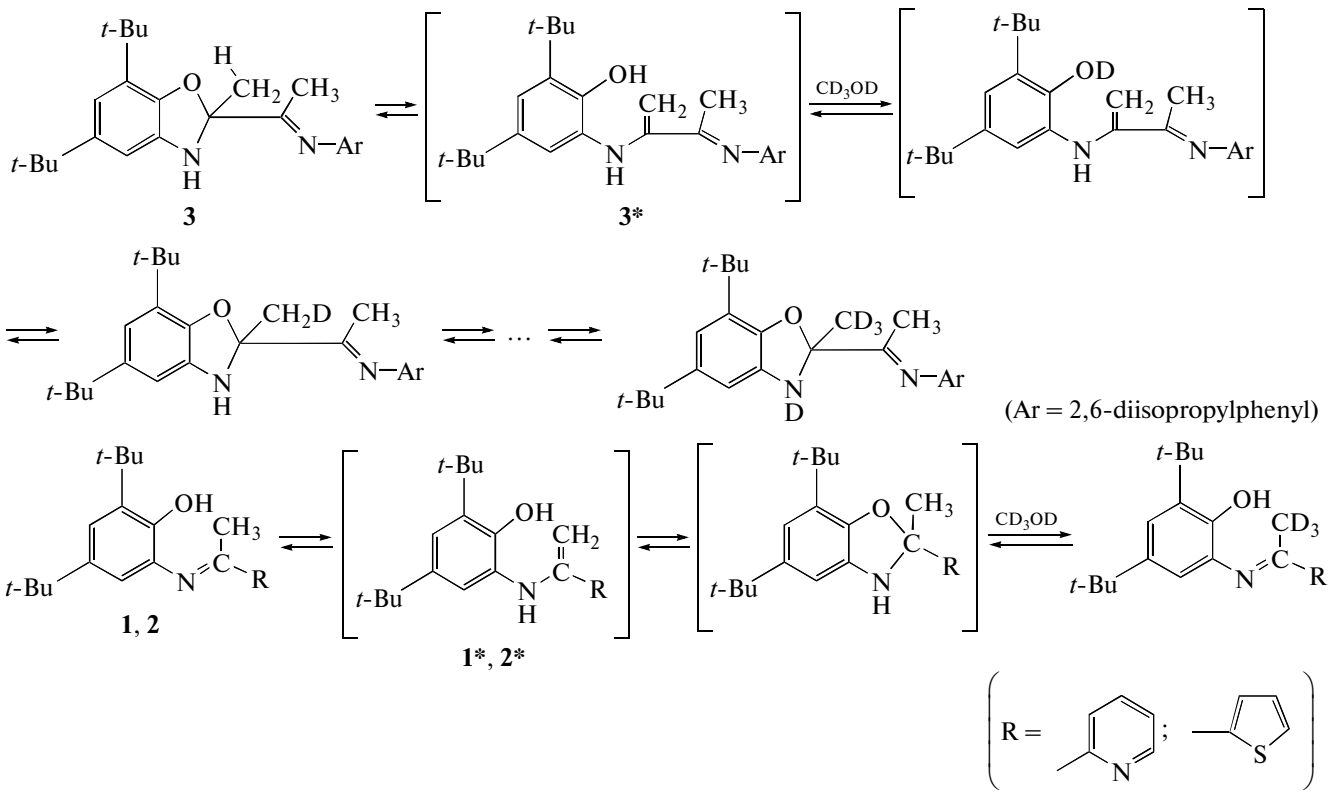
Fig. 1. Molecular structure of compound **3**. Hydrogen atoms are omitted except for the proton of the amino group. The main bond distances (Å): O1–C2, 1.393(3); O1–C1, 1.464(3); N1–C1, 1.464(3); N2–C4, 1.277(3).

These changes indicate the exchange of hydrogen atoms of the methyl group for deuterium. In spite of the fact that the exchange of hydrogen atoms in OH or NH groups for deuterium in CD_3OD is widely known, the selective deuteration of methyl group under these conditions is unusual.

Nonetheless such an exchange can be explained by the existence of cyclization–decyclization equilibrium in solution that proceeds through the enamine form containing OH group (**1***–**3***), which is readily deuterated with CD_3OD (Scheme 3). Subsequently, deuterium from the resulting OD group comes to the methyl group. In the presence of a CD_3OD excess, the methyl hydrogen atoms are gradually replaced by deuterium to give completely deuterated CD_3 groups and partially deuterated CHD_2 and CH_2D groups.

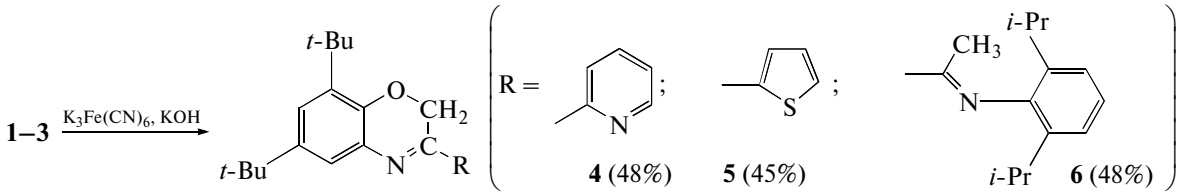
After recrystallization of compound **3** from CD_3OD, a ^2H NMR spectrum in $CDCl_3$ was obtained. The spectrum shows a signal with chemical shift of 1.8 ppm corresponding to the chemical shift of the methyl protons in compound **3** (1.83 ppm). This is direct evidence for the reaction proposed by us. The intensity of ^2H signals due to the CHD_2 and H_2D groups located in proximity to the main peak is substantially lower; taking into account the reaction conditions, we may affirm that the deuteration results mainly in a product containing the completely deuterated CD_3 group.

The ^{13}C NMR spectrum of compound **2** shows a multiplet at 16 ppm resulting from a superposition of the septet of CD_3 group and the signals of CHD_2 and CH_2D groups (J(C–D) = 0.19 Hz), Fig. 3.



Scheme 3.

The oxidation of compounds **1–3** with alkaline solution of potassium ferricyanide leads to substituted benzoxazines (Scheme 4).



Scheme 4.

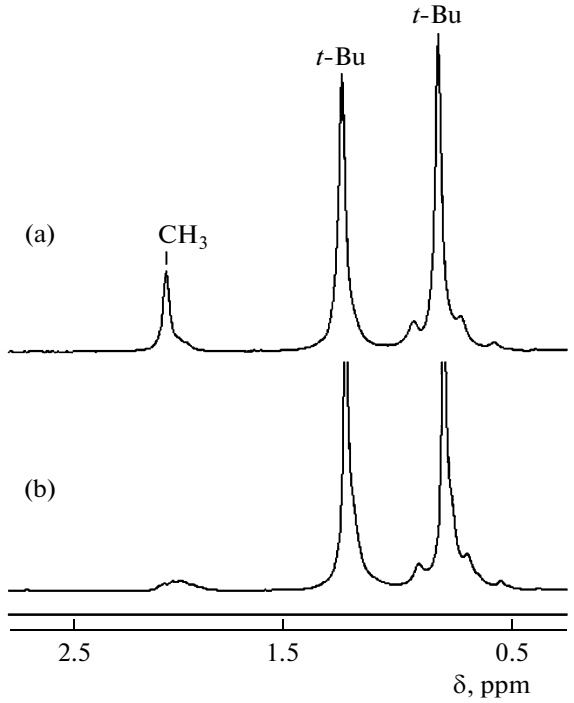


Fig. 2. Fragments of ^{1}H NMR spectra of compound **2** in CD_3OD: (a) immediately after dissolution of **2** in CD_3OD, (b) 10 min later.

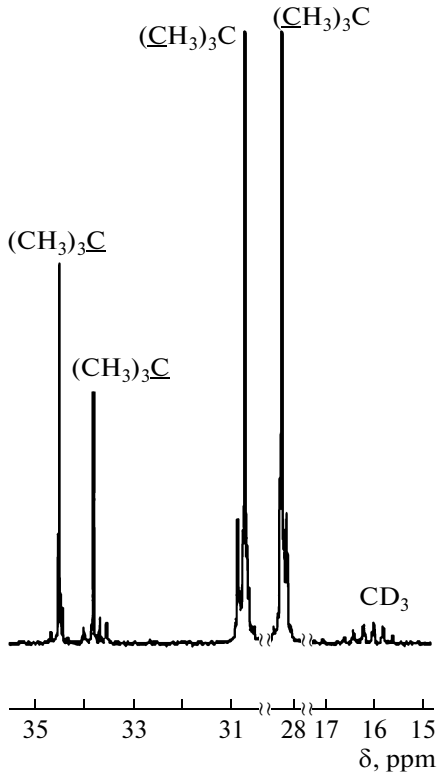


Fig. 3. A fragment of ^{13}C NMR spectrum of compound **2** in CD_3OD.

The ^{1}H NMR spectra of compounds **4** and **5** show the narrow intense singlets of the *tert*-butyl protons (1.33–1.41 ppm) and the signals of the protons of resultant CH_2 groups (4.91–5.24 ppm). The spectral region of aromatic protons displays the multiplets of protons of aminophenol and pyridine (thiophene) substituents (7.13–8.65 ppm).

The ^{1}H NMR spectrum of compound **6** exhibits intense singlets of protons of the *tert*-butyl (1.33–1.41 ppm) and methyl (2.07 ppm) groups, a septet of methyne protons (2.64 ppm, $J = 6.88$ Hz), two doublets of methyl protons of isopropyl substituents (1.14 and 1.15 ppm, $J = 6.88$ Hz), and a multiplet of aromatic protons (7.08–7.34 ppm). Moreover, a proton peak of the CH_2 group of compound **6** is present. The structure of compound **6** was also confirmed by ^{13}C NMR and DEPT (61.2 ppm) data.

The formation of products of methyl groups dehydration **4**–**6** upon oxidation of compounds **1**–**3** can be also explained by the existence in solution of enamine species **1***–**3*** containing the methylene moiety.

Thus, we synthesized new compounds derived from acetyl-substituted heterocyclic molecules and 3-(2,6-di-*iso*-propylphenylimino)butan-2-one and established that compounds **1**–**3** in solution are characterized by the presence of equilibrium between aminophenol and cyclic (benzoxazole) forms that occurs through formation of isomeric enamine species. The existence of this equilibrium is responsible for the complete exchange of the methyl in close proximity to the benzoxazole ring for deuterium in a CD_3OD medium. The oxidation of compounds **1**–**3** gives rise to benzoxazine structures.

ACKNOWLEDGMENTS

This work was supported by the Council for Grants of the President of the Russian Federation for Support of Leading Scientific Schools (grant no. NSh 1113.2012.3), the Russian Foundation for Basic Research (project nos. 11–03–97041-r_povolzh'e_a and 12–03–31348\12_mol), and the Ministry of Education and Science of the Russian Federation (the Federal Target Program "Scientific and Scientific-Pedagogical Personnel of the Innovative Russia in 2009–2013," State Contract no. 8465).

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