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SHORT COMMUNICATIONS

Reduction of Substituted 5-(Nitromethyl)- 3-phenyl-1,2,4-oxadiazoles

A. G. Tyrkov and A. N. Usova

Astrakhan' State University, Astrakhan', 414056 Russia
e-mail: tyrkov@rambler.ru

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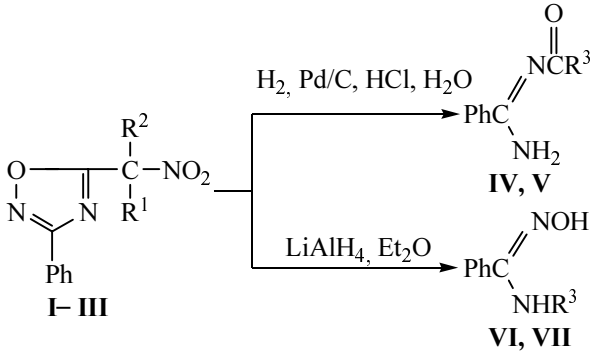
Reduction of 3,5-substituted 1,2,4-oxadiazoles are poorly studied in the literature The catalytic hydrogenation of 5-amino-3-phenyl-1,2,4-oxadiazole on Pd/C is known to involve the heterocycle rupture at the N–O bond to give N-carbamoylbenzamidine [1], and the reduction of 3,5-diphenyl-1,2,4-oxadiazole with $LiAlH_4$ proceeds with the cleavage of the azole ring at the C–O bond affording N-benzylbenzimidoxime [2]. The hydrogenation of more complex 1,2,4-oxadiazole derivatives is not mentioned in the literature.

Ethyl (nitro)(3-phenyl-1,2,4-oxadiazol-5-yl)-(chloro)acetate **I** and its analogs, ethyl (dinitro)(3-phenyl-1,2,4-oxadiazol-5-yl)acetate **II** and 5-trinitromethyl-3-phenyl-1,2,4-oxadiazole **III** contain polyfunctional substituents in position *5* of the heterocycle and are interesting objects for the study of these transformations. With the goal to investigate further how the nature of substituted 5-(nitromethyl)-1,2,4-oxadiazoles affects the direction of their reduction process we studied the hydrogenation of nitroalkanes **I–III** effected by various reducing agents, namely, Pd/C and $LiAlH_4$. We have selected for the study compounds **I–III** for the problem is urgent of developing new synthetic routes involving nitro group reduction and ester function hydrolysis and leading to arylamidine derivatives containing an N-aminomalonic moiety. The possibility to carry out a process of this sort was demonstrated formerly [3]. The aminomalonic moiety appears in the structure of a number of pharmaceuticals that are chemical precursors of noradrenaline and other mediators [4].

We established that hydrogenation of nitroalkanes **I** and **II** on palladium catalyst involved an opening of the oxadiazole ring at the N–O bond and partial reduction of the substituents in position *5* of the heterocycle resulting in N-glycylbenzamidine **IV** hydrochloride. Similarly occurred the catalytic hydrogenation of nitroalkane **III**, but the trinitromethyl fragment suffered elimination, and the final product was N-formylbenzamidine **V**. The reduction of 1,2,4-oxadiazoles **I–III** on Pd catalyst was carried out at atmospheric pressure and 25–30°C in 2–2.5% solution of hydrochloric acid. The weight of the catalyst was 5% with respect to the substrate for hydrogenation.



$R^1 = CO_2Et$, $R^2 = Cl$ (**I**), NO_2 (**II**), $R^1 = R^2 = NO_2$ (**III**), $R^3 = CH_2NH_3Cl$ (**IV**), H (**V**), $(CH_2)_2NH_2$ (**VI**), Me (**VII**).

In contrast to catalytic hydrogenation the nitroalkanes **I–III** reduction in the presence of $LiAlH_4$ occurred with heterocycle cleavage at the C–O bond and gave *N*-(2-aminoethyl)benzimidoxime **VI** at the use of compounds **I** and **II** or N-methylbenzimidoxime **VII** from compound **III**. The reduction of the nitromethyl substituents occurred in the same way as at the catalytic hydrogenation of 1,2,4-oxadiazoles **I–III** on Pd catalyst.

Catalytic hydrogenation of 1,2,4-oxadiazoles I–III on Pd catalyst. Into a flask for hydrogenation was

charged 3.2 g of activated carbon of OUB grade, 0.16 g of $PdCl_2$, 2.7 ml of concn. HCl, and 40 ml of water. The catalyst was hydrogenated till complete saturation with hydrogen. Then 5 mmol of compound **I**–**III** [5–7] was charged, and the reduction was carried out at 25–30°C till consumed amount of hydrogen reached the value calculated according to the number of nitro groups. The catalyst was filtered off and washed with several portions of warm water by decanting. The total volume of filtrate (100 ml) was evaporated at reduced pressure, and the residues after reaction with compounds **I** and **II** were recrystallized from ethanol. The residue after reaction with compound **III** was subjected to chromatography on a column 250×10 mm packed with activated silica gel of the grade Silicagel 100/400 μ, eluent for compound **V** ethanol.

2-Amino-*N*-[amino(phenyl)methylene]acetamide hydrochloride (IV). Yield 74%, mp 175–178°C. IR spectrum, ν, cm^{-1}: 3360–3250 (NH_2), 3200–2600 (NH_3^+), 1720–1710 (C=O). Found, %: C 50.37; H 5.43; N 19.42. $C_9H_{11}N_3O_3 \cdot HCl$. Calculated, %: C 50.59; H 5.62; N 19.67.

***N*-Formylbenzamidine (V)** . Yield 67%, mp 112–113°C. IR spectrum, ν, cm^{-1}: 3360–3250 (NH_2), 1710 (C=O). ^1H NMR spectrum, δ, ppm: 10.15 s (1H, CH), 7.74 m (5H, H arom), 6.82 br.s (2H, NH_2). Found, %: C 64.61; H 5.24; N 18.73. $C_8H_8N_2O$. Calculated, %: C 64.86; H 5.41; N 18.92.

Reduction of 1,2,4-oxadiazoles I–III with lithium aluminum hydride. To a solution of 1.8 g of $LiAlH_4$ in 50 ml of anhydrous ethyl ether was added at stirring a solution of 5 mmol of nitroalkane **I-III** in 20 ml of ether with a rate sufficient to keep the reaction mixture at weak boiling. The reaction mixture was stirred for 4 h at 25°C, then cooled to 5°C, and a minimal amount of ice water was added till the hydrogen liberation stopped. The precipitate was filtered off and washed with 15 ml of ether. The combined ether solution was dried with NaOH and evaporated at reduced pressure. The residue was subjected to chromatography, as described above. Eluent for compounds **VI** and **VII** chloroform

***N*-(2-Aminoethyl)benzimidoxime (VI)**. Yield 70%, mp 76–78°C. IR spectrum, ν, cm^{-1}: 3540 (OH), 3450–3300 (NH_2). ^1H NMR spectrum, δ, ppm: 7.76 m (5H, H arom), 6.55 br.s (1H, NH), 3.56–3.52 m (4H, CH_2), 1.62 br.s (2H, NH_2). Found, %: C 60.05; H 6.97; N 23.13. $C_9H_{13}N_3O$. Calculated, %: C 60.34; H 7.26; N 23.46.

***N*-Methylbenzimidoxime (VII)**. Yield 72%, mp 46–48°C. IR spectrum, ν, cm^{-1}: 3550 (OH), 3340 (NH). ^1H NMR spectrum, δ, ppm: 7.75 m (5H, H arom), 6.50 br.s (1H, NH), 3.12 d (3H, CH_3). Found, %: C 63.82; H 6.45; N 18.48. $C_8H_{10}N_2O$. Calculated, %: C 64.00; H 6.67; N 18.67.

IR spectra were recorded on spectrophotometer IKS-29 from pellets with KBr (compounds **IV** and **V**) and from solutions in chloroform (compounds **VI** and **VII**). ^1H NMR spectra were registered on spectrometer Tesla BS-487C (80 MHz) in acetone-d_6 , internal reference HMDS.