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1,2,5-Oxadiazolo[3,4-*g*]indoles *via* annelation of 6,7-dihydrobenzo[*c*][1,2,5]oxadiazol-4(5*H*)-one oxime with acetylene

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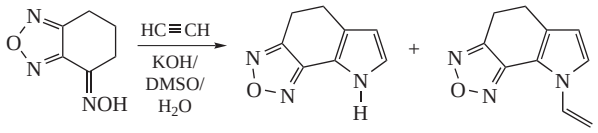
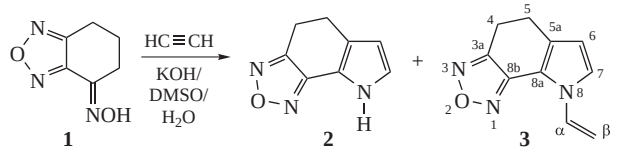
6,7-Dihydrobenzo[*c*][1,2,5]oxadiazol-4(5*H*)-one oxime is annelated with acetylene in the KOH/DMSO/H_2O system under pressure to give *NH*- or *N*-vinyl-5,8-dihydro-4*H*-[1,2,5]-oxadiazolo[3,4-*g*]indoles in 29 and 68% yields, respectively. These derivatives are readily aromatized with DDQ at room temperature to the expected indoles.



1,2,5-Oxadiazoles attract growing attention as components of high energetic compositions[1,2] and pharmaceutically important compounds (*e.g.*, with antibacterial,[3] cytotoxic[4] and anti-parasitic[5] activities, effective medicine against glaucoma, inhibitors of α-carbonic anhydrase,[6] modulators of tyrosine kinase activity,[7] antagonists of NK3 receptors,[8] compounds preventing heart arrhythmia[9]). The fusion of these heterocycles with the indole scaffold, a classic parent of numerous pharmaceuticals and rewarding platform for drug design, may open new opportunities both in material science and medicinal chemistry. To our knowledge, no syntheses of 1,2,5-oxadiazolo[3,4-*g*]indoles still documented. A possible route to these compounds could be the Trofimov reaction[10] with available 6,7-dihydrobenzo[*c*][1,2,5]oxadiazol-4(5*H*)-one oxime,[11] *i.e.*, its annelation with acetylene in the KOH/DMSO system.

Recently it was reported that 3,4-dihydrophenazinone oxime failed to give the expected pyrrolophenazine when reacted with acetylene under the above conditions but was transformed into phenazin-1-amine.[12] Besides, 3-methyl-7,8-dihydrocinnolin-5(6*H*)-one oxime appeared to be incapable of fusing cleanly with pyrrole ring by the same protocol, instead, a complex mixture, containing apart from the expected pyrroles and their aromatized derivatives, 3-methylcinnolin-5-amine and vinylated tricyclic pyrrolopyridines was obtained.[13]

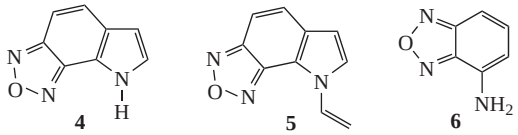
In view of these data, the possibility of building the pyrrole ring over the 6,7-dihydrobenzo[*c*][1,2,5]oxadiazol-4(5*H*)-one oxime moiety seemed to be uncertain. However, after a series of experiments we have managed to find the conditions for annelation of oxime **1** with acetylene and to access the expected dihydrooxadiazoloindoles **2** and **3** (Scheme 1).† The suitable conditions



Scheme 1

for the selective preparation of *NH*-indole **2** (29% yield) were as follows: KOH (equimolar amount relative to oxime **1**), 60% aqueous DMSO, 110 °C, 4 h, acetylene under pressure (~15 atm at ambient temperature which reached ~20 atm upon heating). For the selective synthesis of *N*-vinyldihydrooxadiazoloindole **3** in 68% yield it was necessary to lower the content of water to 20% and prolong the reaction time up to 5 h.

When the reaction was conducted in DMSO without water additive, dihydroindoles **2**, **3**, their aromatized derivatives **4**, **5**, and benzo[*c*][1,2,5]oxadiazol-4-amine **6** were formed. The ratio of the products depended on the reaction conditions (Table 1, entries 1, 2). Under atmospheric pressure (flow reactor) and without water the reaction, even under much harsher conditions



† *5,8-Dihydro-4*H*-[1,2,5]oxadiazolo[3,4-*g*]indole* **2**. A mixture of oxime **1** (4.59 g, 30 mmol), KOH·0.5H_2O (1.95 g, 30 mmol), DMSO (150 ml) and water (60 ml) was placed in a 1000-ml steel autoclave. The mixture was saturated with acetylene (initial pressure 15 atm) and heated (110 °C) under stirring for 4 h. After cooling to room temperature, the reaction mixture was diluted with saturated solution of NaCl (250 ml), solid NH_4Cl was added (2.00 g, 37 mmol), and the precipitate was filtered off. The water layer was extracted with chloroform (8×50 ml), the combined extracts were washed with water (5×50 ml) and dried over $CaCl_2$. After removing the solvent, the residue was dissolved in chloroform (15 ml) and the solution was washed with 20% KOH solution (for elimination of unreacted oxime **1**, 5×10 ml), washed with water (2×20 ml), dried over $CaCl_2$ and concentrated. The crystallization of the residue from *n*-hexane gave indole **2** (1.40 g, 29%).

Analogously, from oxime **1** (4.59 g, 30 mmol), KOH·0.5H_2O (1.95 g, 30 mmol), DMSO (150 ml) and water (30 ml) at 110 °C (5 h), 8-vinyl-5,8-dihydro-4*H*-[1,2,5]oxadiazolo[3,4-*g*]indole **3** (3.82 g, 68%) was obtained.

Aromatization procedures of indoles **2** and **3** and full characterization of products **2**–**6** are given in Online Supplementary Materials.

Table 1 Effect of conditions on the product composition for the reaction of oxime **1** and acetylene in an autoclave.[a]

Entry	*T*/°C	*t*/h	H_2O : DMSO ratio	Conversion of **1** (%)	Product composition (^{1}H NMR) (%)				
					2	**3**	**4**	**5**	**6**
1	90	3	no H_2O	84	24	30	–	5	4
2	100	3	no H_2O	86	15	36	4	10	4
3	100	4	1 : 10	86	29	33	–	–	–
4	100	4	1 : 5	71	25	4	–	–	–
5	110	4	1 : 5	93	9	53	–	–	–
6	110	5	1 : 5	97	8	76	–	–	–
7	110	4	2 : 5	77	39	4	–	–	–

[a] Reaction conditions: **1** (30 mmol), KOH (30 mmol), DMSO (150 ml), acetylene pressure 15 atm (at ambient temperature).

(140 °C, 13 h) with the complete conversion of oxime **1** afforded a mixture of products in total 21% yield, from which 3% of indole **3**, 3% of **4**, 12% of **5** and 3% of amine **6** were isolated. The loss of the major part of the starting material was likely due to the ring-opening of the oxadiazole moiety under the action of KOH to give water soluble cyano oximes.[14]

A general impression about the influence of the process conditions on the product composition is given by Table 1, where the unexpected positive effect of water additives on the reaction outcome cannot be neglected. When H_2O : DMSO ratio was 2 : 5 (entry 7), indole **2** was selectively obtained. For the selective synthesis of *N*-vinyl derivatives **3**, the ratio of 1 : 5 was needed (entries 5, 6). This observation reveals a novel facet of the Trofimov reaction, which usually requires minimum content of water in DMSO in order to sustain the superbasic conditions.[15] The water additives apart from the promoting the annelation of oxime **1** with acetylene, prevents aromatization of the dihydro derivatives **2**, **3** thus improving the reaction selectivity. Pure dihydro derivatives **2**, **3** are easily aromatized into compounds **4**, **5**, respectively, upon oxidation with DDQ at ambient temperature in up to 86% yields. The side transformation of the starting oxime **1** into amine **6** likely follows the same mechanism as was rationalized for reduction of 3-methyl-7,8-dihydrocinnolin-5(6*H*)-one oxime, to the similar 3-methylcinnolin-5-amine under analogous conditions.[13]

In conclusion, the annelation of available dihydrobenzoxadiazolone oxime with acetylene in the KOH/DMSO/H_2O system, *via* the tandem sequence typical of the Trofimov reaction, opens a short route to a novel family of oxadiazoloindoles. Among the latter of a particular synthetic interest is *N*-vinyldihydrooxadiazoloindole derivative, obtained in 68% isolated yield, as a new prospective monomer and rewarding platform for further derivatization targeting to medicinal chemistry and material science.

The main results were obtained using the equipment of Baikal analytical center of collective using SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.016.

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