Synthesis of 5-arylacetylenyl-1,2,4-oxadiazoles and their transformations under superelectrophilic activation conditions

Andrey I. Puzanov¹, Dmitry S. Ryabukhin¹,², Anna S. Zalivatskaya¹,³, Dmitriy N. Zakusilo¹,³, Darya S. Mikson¹, Irina A. Boyarskaya³ and Aleksander V. Vasilyev*¹,³,§

Abstract

Acetylene derivatives of 1,2,4-oxadiazoles, i.e., 5-(2-arylethynyl)-3-aryl-1,2,4-oxadiazoles, have been obtained, for the first time reported, from 5-(2-arylethenyl)-3-aryl-1,2,4-oxadiazoles by their bromination at the carbon–carbon double bond followed by di-dehydrobromination with NaN₃ in liquid NH₃. The reaction of the acetylenyl-1,2,4-oxadiazoles with arenes in neat triflic acid (CF₃SO₂H) at room temperature for 1 h resulted in the formation of E/Z-5-(2,2-diarylethenyl)-3-aryl-1,2,4-oxadiazoles as products of regioselective hydroarylation of the acetylene bond. The addition of TfOH to the acetylene bond of these oxadiazoles quantitatively resulted in E/Z-vinyl triflates. The reactions of the cationic intermediates have been studied by DFT calculations and the reaction mechanisms are discussed.

Introduction

1,2,4-Oxadiazoles have a great importance in chemistry, biology and medicine. Many drugs contain an 1,2,4-oxadiazole ring, such as butalamine [1], libexin [2], ataluren [3], oxolamine [4], and pleconaril [5]. Various oxadiazole derivatives show different kinds of activity against cancer [6,7], tuberculosis [8], Gram-positive bacteria [9], and they are used in treatment of
eignes [10] and Alzheimer disease [11-13]. The synthesis of compounds of the 1,2,4-oxadiazole series is an actual task in organic and medicinal chemistry (see selected reviews on this topic [14-22]). However, among all the varieties of 1,2,4-oxadiazoles, their acetylenic derivatives are quite rare. To the best of our knowledge, there is only one example of 1,2,4-oxadiazole conjugated with an acetylene bond, which is 3-phenylethynyl-1,2,4-oxadiazole [23]. Up to the moment, there are no data on the preparation of 1,2,4-oxadiazoles containing a conjugated acetylenic substituent in the position 5 of the heterocyclic ring.

Based on our previous works on the chemistry of 1,2,4-oxadiazoles in superacids [24,25], we undertook this study on further investigation of the transformations of these heterocyclic compounds in electrophilic media. The main goals of this work were the synthesis of 5-arylacetylenyl-1,2,4-oxadiazoles and the study of their reactions with/without arenes under the conditions of superelectrophilic activation by the Brønsted superacid CF$_3$SO$_2$H (TfOH), the strong Lewis acids AlX$_3$ (X = Cl, Br), or the acidic zeolite CBV-720.

**Results and Discussion**

The synthesis of 5-arylethynyl-1,2,4-oxadiazoles 3 was based on transformations of the corresponding 5-styryloxadia- zoles, i.e., 5-(2-arylethenyl)-3-aryl-1,2,4-oxadiazoles 1a–g (Scheme 1). Bromination of the side chain carbon–carbon double bond in oxadiazoles 1a–g led to pairs of diastereomers of dibromo derivatives 2a–g. Then, several bases were tested for the di-dehydrobromination of compounds 2a–g. However, treatment of 2a–g in the following systems, KOH–EtOH (reflux, 2 h), BuLi–THF (−40 °C, 2 h), t-BuOK–THF (reflux, 2 h), or Li(NiPr)$_2$–THF (−40 °C, 2 h), afforded complex mixtures of reaction products without desired acetylenyloxadiazoles 3. We succeeded to get compounds 3a–e by the reaction of 2a–e with sodium amide in liquid ammonia [NaNH$_2$–NH$_3$ (liq.)] only at low temperature −70 to −60 °C (Scheme 1). However, the yields of target compounds were moderate 32–54% (for 3a–c,e) or even low 9% (for 3d). Running this reaction at higher temperature −50 to −40 °C led to a decrease of the yields of compounds 3. Apart from that, compounds 2f,g containing a 3-para-bromophenyl moiety in the heterocyclic core gave no corresponding 5-acetylenyloxadiazoles 3 in the system NaNH$_2$–NH$_3$ (liq.), only mixtures of oligomeric materials were formed. Moreover, compound 3e was obtained as an inseparable mixture with styryloxadiazole 1e. The latter may be formed from 3e under the reduction by the solution that contained NaNH$_2$. All these data point out the instability of 5-acetylenyloxadiazoles 3 in strong basic and nucleophilic media. Oxadiazoles 3, which were initially formed from compounds 2 in the system NaNH$_2$–NH$_3$ (liq.), underwent further secondary transformations under nucleophilic reaction conditions, even at very low temperature −70 to −60 °C, that resulted in low to moderate yields of the target acetylene derivatives.

Then, electrophilic reactions of 5-acetylenyloxadiazoles 3a–d in different acids were studied. In our recent study on the electrophilic activation of 5-styryl-1,2,4-oxadiazoles 1 [24], it was shown by means of NMR spectroscopy and DFT calculation that the protonation of these oxadiazoles in Brønsted superacids
TfOH and FSO₃H gave reactive N,C-diprotonated species. The protonation of oxadiazoles 1 takes place at the nitrogen N4 and the α-carbon of the side chain C=C bond. One would expect the formation of similar dications at the protonation of acetylenyl-oxadiazoles 3 in Brønsted superacids (see Table 1). Table 1 contains data on DFT calculations of cations Aa–d (N-protonated forms) and Ba–d (N,C-diprotonated forms) derived at the protonation of oxadiazoles 3a–d. Charge delocalization, contribution of atomic orbital into LUMO, global electrophilicity indices ω [26,27], and Gibbs free energies of protonation reactions with hydroxonium ion (H₃O⁺) ΔG₂₉₈ were calculated. Big negative values of ΔG₂₉₈ (−86.6 to −79.2 kJ/mol) of the first protonation step show that the formation of N-protonated

| Species | EₑHOMO, eV | EₑLUMO, eV | ω,a eV | q(Cβ),b e | k(Cβ)LUMO,c % | q(N2),b e | q(N4),b e | ΔG₂₉₈ of protonation, kJ/mol |
|---------|-----------|-----------|------|---------|-------------|---------|---------|------------------------|
| Cations A (N-protonated species) |
| Aa      | −7.44     | −3.56     | 3.9  | 0.23    | 7.2         | −0.13   | −0.49   | −80.8                  |
| Ab      | −7.23     | −3.49     | 3.8  | 0.23    | 7.4         | −0.13   | −0.50   | −83.4                  |
| Ac      | −7.28     | −3.62     | 4.0  | 0.23    | 7.4         | −0.13   | −0.49   | −79.2                  |
| Ad      | −6.84     | −3.38     | 3.8  | −0.30   | 6.1         | −0.14   | −0.53   | −86.6                  |
| Dications B (N,C-diprotonated species) |
| Ba      | −7.83     | −5.28     | 8.4  | 0.47    | 30.0        | −0.11   | −0.47   | +18.0                  |
| Bb      | −7.82     | −5.04     | 7.4  | 0.44    | 29.0        | −0.11   | −0.48   | −1.2                   |

Table 1: Selected electronic characteristics for cations Aa–d and Ba–d calculated by DFT from protonation of oxadiazoles 3a–d.
Table 1: Selected electronic characteristics for cations Aα–d and Bα–d calculated by DFT from protonation of oxadiazoles 3α–d. (continued)

| Species | ω (eV) | Q(H) | Q(Cβ) | ΔG298 (kJ/mol) |
|---------|--------|------|-------|----------------|
| Aα      | -7.82  | -5.25| 8.3   | 24.3           |
| Bα      | +18.3  | 0.1  | 0.4   |                |

| Species | ω (eV) | Q(H) | Q(Cβ) | ΔG298 (kJ/mol) |
|---------|--------|------|-------|----------------|
| Aβ      | -7.80  | -4.63| 6.1   | 16.7           |
| Bβ      | -28.8  | -0.11| -0.48 |                |

aGlobal electrophilicity index ω = (E_HOMO + E_LUMO)^2/(E_LUMO - E_HOMO). bNatural charges. cContribution of atomic orbital into molecular orbital.

species Aα–d is extremely energetically favorable. For the second protonation (reaction A → B) leading to dications Bα–d, the ΔG298 values vary from -28.6 to 18.3 kJ/mol. Although the second protonations are sometimes mildly endergonic (and hence there would be an unfavourable equilibrium between species A and B), the capture of the dication B by a nucleophile is likely to be very exergonic and this can drive the reaction through to the products. Calculated electronic characteristic of these dications reveal their high electrophilicity, the indexes ω are 6.1–8.4 eV. Carbon Cβ bears a large positive charge (0.40–0.47 e) and gives a big contribution into LUMO (16.7–30%), pointing out that this carbon is a reactive electrophilic center by charge and orbital factors.

Thus, according our previous data on reactions of 5-styryl-1,2,4-oxadiazoles 1 [24] and results of the DFT calculations for protonation of 5-acetylenyl-1,2,4-oxadiazoles 3 (Table 1), one would propose the following reaction pathways for compounds 3 in Brønsted superacids (Scheme 2). Protonation of oxadiazole 3 affords dication B, which may react with counter anion of acid X^- giving rise to vinyl derivatives 4. In the presence of nucleophilic arene molecules, species B should afford substances 5 as products of hydroarylation of the acetylene bond of the starting compounds 3.

Indeed, reaction of 5-acetylenyl-1,2,4-oxadiazoles 3α–c with excess of TIOH at room temperature for 1 h resulted in the quantitative preparation of E/Z-isomers of vinyl triflates 4α–c with a predominant formation of Z-isomers as product of an anti-addition of TIOH to the acetylene bond (Scheme 3). E/Z-Stereochemistry of compounds 4α–c was determined by H,F-NOESY correlation between vinyl proton (>C=CH–) and the CF3 group from the TfO substituent (see Supporting Information File 1). It should be noted that attempts of chromatographic separation of triflates 4α–c into individual E- and Z-isomers on silica gel led to a decrease of their yields and a change in E/Z-ratio. That reveals instability of these compounds on silica gel.

In the same reaction in H2SO4 (Scheme 4), oxadiazole 3a gave the product of hydration of the acetylene bond (4d, yield of 65%) existing in solution as equilibrium between ketone and enol forms in a ratio of 1.2:1 according to NMR data (see Supporting Information File 1).
Scheme 3: Quantitative formation of E/Z-vinyl triflates 4a–c from 5-acetylenyl-1,2,4-oxadiazoles 3a–c in TfOH.

Then, reactions of 5-acetylenyl-1,2,4-oxadiazole 3a–d with arenes (benzene and o-, m-, p-xylenes) in TfOH at room temperature for 1 h leading to products of hydroarylation of the acetylene bond, compounds (E/Z)-5a–g, were carried out (Scheme 5). This reaction gave E/Z-isomers 5b–g, their stereochemical configuration was determined by H,H NOESY correlations between the vinyl proton and aromatic protons (see Supporting Information File 1). In the case of the reaction with o-xylene, pairs of E/Z-isomers of two regioisomers, (E/Z)-5b and (E/Z)-5b1, were obtained.

We also checked the reaction of oxadiazole 3a with benzene under the action of Lewis acids AlCl₃, AlBr₃ and acidic zeolite CBV-720 (Table 2). However, these Lewis acids showed unsatisfactory results leading to oligomeric materials (Table 2, entries 1 and 2). Probably, due to some secondary reactions of the formed compound 5a with AlCl₃, AlBr₃. The yield of target compound 5a in the reaction with zeolite was lower than in the same reaction in TfOH (compare entry 3 in Table 2 with data shown in Scheme 5). Thus, among the tested acidic reagents, TfOH showed better results for the hydroarylation of compounds 3.

Additionally, the reaction of oxadiazole 3a with benzene in TfOH (rt, 1 h) in the presence of cyclohexane, as a hydride ion source, was conducted to achieve the ionic hydrogenation of intermediate cationic species. However, no products of ionic hydrogenation were obtained, only the product of the hydrophenylation of the acetylene bond 5a was quantitatively isolated (compare with data shown in Scheme 5).
Conclusion

For the first time reported, we have synthesized 5-arylacetylene derivatives of 1,2,4-oxadiazoles, i.e., 5-(2-arylethynyl)-3-aryl-1,2,4-oxadiazoles. In the Brønsted superacid TfOH, these oxadiazoles react in a way of electrophilic addition to the acetylene bond. They give products of hydroarylation of the acetylene bond in the reaction with arenes or vinyl triflates in reaction with TfOH without arenes.
Table 2: Reactions of 5-acetylenyloxadiazole 3a with benzene under the action of various acids.

| Entry | Acid       | Reaction conditions | Yield of 5a, % |
|-------|------------|---------------------|---------------|
|       |            | Temperature, °C     | Time, h       |
| 1     | AlCl₃      | rt                  | 1             | oligomeric compounds |
| 2     | AlBr₃      | rt                  | 1             | oligomeric compounds |
| 3     | Zeolite CBV-720 | 130              | 1             | 56             |

Supporting Information

Supporting Information File 1
Experimental procedures, characterization data and ¹H and ¹³C NMR spectra of compounds, as well as data of DFT calculations.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-158-S1.pdf]

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ORCID® iDs
Andrey I. Puzanov - https://orcid.org/0000-0001-8879-5941
Dmitry S. Ryabukhin - https://orcid.org/0000-0001-5345-0038
Dmitriy N. Zakusilo - https://orcid.org/0000-0002-3628-1492
Aleksander V. Vasilyev - https://orcid.org/0000-0003-3628-1492

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