BEILSTEIN ARCHIVES

This open access document is posted as a preprint in the Beilstein Archives at https://doi.org/10.3762/bxiv.2021.49.v1 and is considered to be an early communication for feedback before peer review. Before citing this document, please check if a final, peer-reviewed version has been published.

This document is not formatted, has not undergone copyediting or typesetting, and may contain errors, unsubstantiated scientific claims or preliminary data.

Preprint Title	Synthesis of 5-arylacetylene 1,2,4-oxadiazoles and their transformations under superelectrophilic activation conditions
Authors	Andrey I. Puzanov, Dmitry S. Ryabukhin, Anna S. Zalivatskaya, Dmitriy N. Zakusilo, Darya S. Mikson, Irina A. Boyarskaya and Aleksander Vasilyev
Publication Date	30 Juni 2021
Article Type	Full Research Paper
Supporting Information File 1	SI.doc; 8.3 MB
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/0000-0002-3972-9515; Aleksander Vasilyev - https://orcid.org/0000-0003-3628-1492

License and Terms: This document is copyright 2021 the Author(s); licensee Beilstein-Institut.

This is an open access work under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0). Please note that the reuse, redistribution and reproduction in particular requires that the author(s) and source are credited and that individual graphics may be subject to special legal provisions. The license is subject to the Beilstein Archives terms and conditions: https://www.beilstein-archives.org/xiv/terms. The definitive version of this work can be found at https://doi.org/10.3762/bxiv.2021.49.v1

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

Andrey I. Puzanov,[a] Dmitry S. Ryabukhin,[a,b] Anna S. Zalivatskaya,[a,c] Dmitriy N. Zakusilo,[a,c] Darya S. Mikson,[a] Irina A. Boyarskaya,[c] and Aleksander V. Vasilyev[a,c*]

[a] *Department of Chemistry, Saint Petersburg State Forest Technical University, Institutsky per., 5, Saint Petersburg, 194021, Russia.*

[b] *All-Russia Research Institute for Food Additives – Branch of V.M. Gorbatov Federal Research Center for Food Systems of RAS, Liteyniy pr., 55, Saint Petersburg, 191014, Russia*

[c] *Institute of Chemistry, Saint Petersburg State University, Universitetskaya nab., 7/9, Saint Petersburg, 199034, Russia.*

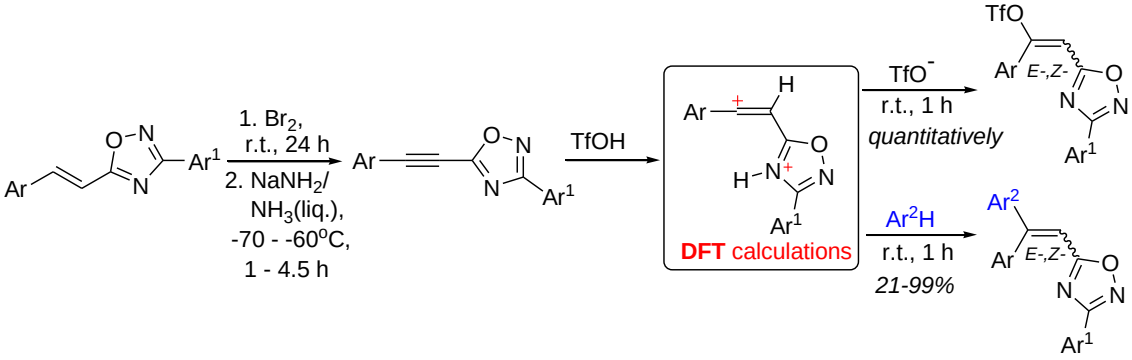
[*]Corresponding author:

A.V. Vasilyev, tel.: 07 812 670 93 52; fax: 07 812 670 93 90, e-mail: aleksvasil@mail.ru, a.vasilyev@spbu.ru

Keywords

acetylene oxadiazoles, hydroarylation, Friedel-Crafts reaction, superelectrophilic activation, triflic acid

Graphical abstract



Abstract

Acetylene derivatives of 1,2,4-oxadiazoles, 5-(2-arylethynyl)-3-aryl-1,2,4-oxadiazoles, have been obtained, for the first time, from 5-(2-arylethenyl)-3-aryl-1,2,4-oxadiazoles by their bromination at the carbon-carbon double bond followed by di-dehydrobromination with $NaNH_2$ in liquid NH_3. Reaction of the acetylene 1,2,4-oxadiazoles with arenes in neat triflic acid TfOH (CF_3SO_3H) at room temperature for 1 h result 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. Addition of TfOH to acetylene bond of these oxadiazoles gives rise quantitatively to *E-/Z*-vinyl triflates. Reaction cationic intermediates have been studied by DFT calculations. The reaction mechanisms have been discussed.

Introduction

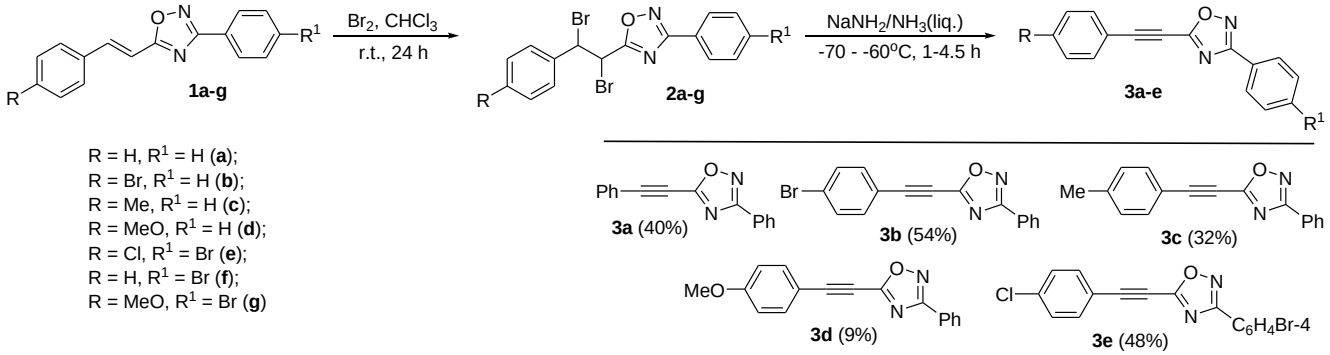
1,2,4-Oxadiazoles have a great importance in chemistry, biology and medicine. Many drugs contain 1,2,4-oxadiazole ring, such as Butalamine [1], Libexin [2], Ataluren [3], Oxolamine [4], Pleconaril [5]. Various oxadiazole derivatives show different kinds of activity against cancer [6-8], tuberculosis [9], gram-positive bacteria [10], and they are used in treatment of epilepsy [11] and Alzheimer disease [12-14]. Synthesis of compounds of the series of 1,2,4-oxadiazole is an actual task in organic and medicinal chemistries (see selected review on this topic [15-24]). However, among all the variety 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 acetylene bond, which is 3-phenylethynyl 1,2,4-oxadiazole [25]. Up to the moment, there are no data on preparation of 1,2,4-oxadiazoles containing conjugated acetylenic substituent in the position 5 of the heterocyclic ring.

Based on our previous works on chemistry of 1,2,4-oxadiazoles in superacids [26, 27], we undertook this study on further investigation of transformations of these heterocyclic compounds in electrophilic media. The main goals of this work were synthesis of 5-arylacetylene 1,2,4-oxadiazoles and study of their reactions with/without arenes under the conditions of superelectrophilic activation by Brønsted superacid CF_3SO_3H (TfOH), strong Lewis acids AlX_3 (X = Cl, Br), or acidic zeolite CBV-720.

Results and Discussion

Synthesis of 5-arylethynyl-1,2,4-oxadiazoles **3** was based on transformations of the corresponding 5-styryl oxadiazoles, 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 LiN(*i*-Pr)$_2$-THF (-40°C, 2 h), afforded complex mixtures of reaction products without desired acetylene oxadiazoles **3**. We succeeded to get compounds **3a-e** by the reaction of **2a-e** with sodium amide in the liquid ammonia [$NaNH_2$-NH_3(liq.)] only at low temperature -70 – -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 – -40°C led to a decrease of the yields of compounds **3**. Apart from that, compounds **2f,g** containing 3-*para*-bromophenyl ring in the heterocyclic core gave no corresponding acetylene oxadiazoles **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 styryl oxadiazole **1e**. The latter may be formed from **3e** under the basic reaction conditions by reduction

under the action of $NaNH_2$. All these data point out instability of acetylene oxadiazoles **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 the nucleophilic reaction conditions, even at very low temperature -70 – -60°C, that resulted in low-moderate yields of the target acetylene derivatives.

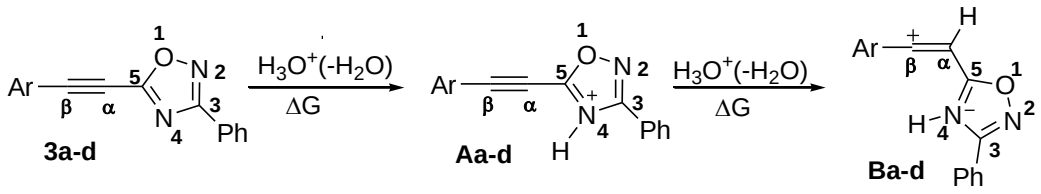


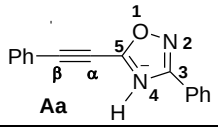
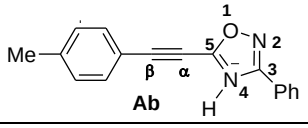
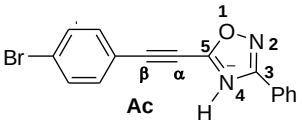
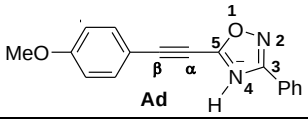
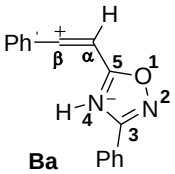
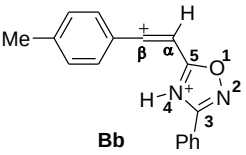
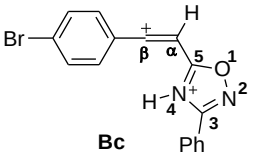
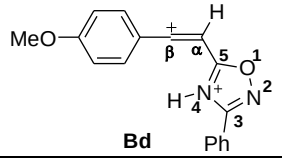
Scheme 1. Synthesis of 5-arylethynyl-3-aryl-1,2,4-oxadiazoles **3a-e**.

Then, electrophilic reactions of acetylene oxadiazoles **3a-d** in different acids were studied. In our recent study on electrophilic activation of 5-styryl 1,2,4-oxadiazoles **1** [26], it was shown by means of NMR and DFT calculation that protonation of these oxadiazoles in Brønsted superacids TfOH and FSO_3H gave reactive N,C-diprotonated species. The protonation of oxadiazoles **1** takes place at nitrogen N^4 and α-carbon of the side chain C=C bond. One would expect the formation of similar dications at the protonation of acetylene oxadiazoles **3** in Brønsted superacids (see Scheme in the head of 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 [28, 29], and Gibbs free energies of protonation reactions with hydroxonium ion (H_3O^+) ΔG_{298} were calculated.

Big negative values of ΔG_{298} (-86.6 – -79.2 kJ/mol) of the first protonation step show that reaction of the formation of N-protonated species **Aa-d** is extremely energetically favorable. For the second protonation (reaction **A→B**) leading to dications **Ba-d**, ΔG_{298} values vary from -28.6 to 18.3 kJ/mol. Taking into account ΔG_{298} values for both protonation steps (**3→A→B**), the formation of N,C-diprotonated species **Ba-d** is energetically favorable. Calculated electronic characteristic of these dications reveal their high electrophilicity, indexes ω are 6.1-8.4 eV. Carbon C^β 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.

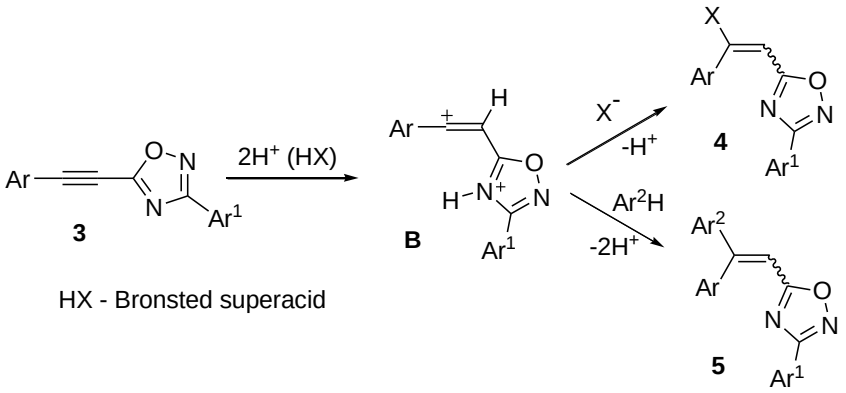
Table 1. Selected electronic characteristics for cations **Aa-d** and **Ba-d** calculated by DFT from protonation of oxadiazoles **3a-d**.



Species	E_{HOMO}, eV	E_{LUMO}, eV	ω,[a] eV	q(C^{β}),[b] e	k(C^{β})$_{LUMO}$,[c] %	q(N^2),[b] e	q(N^4),[b] e	ΔG_{298} of proto-nation, 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
 **Bc**	-7.82	-5.25	8.3	0.45	24.3	0.1	0.4	+18.3
 **Bd**	-7.80	-4.63	6.1	0.40	16.7	-0.11	-0.48	-28.8

[a]Global electrophilicity index $\omega = (E_{HOMO} + E_{LUMO})^2/8(E_{LUMO} - E_{HOMO})$.
[b]Natural charges.
[c]Contribution of atomic orbital into molecular orbital.

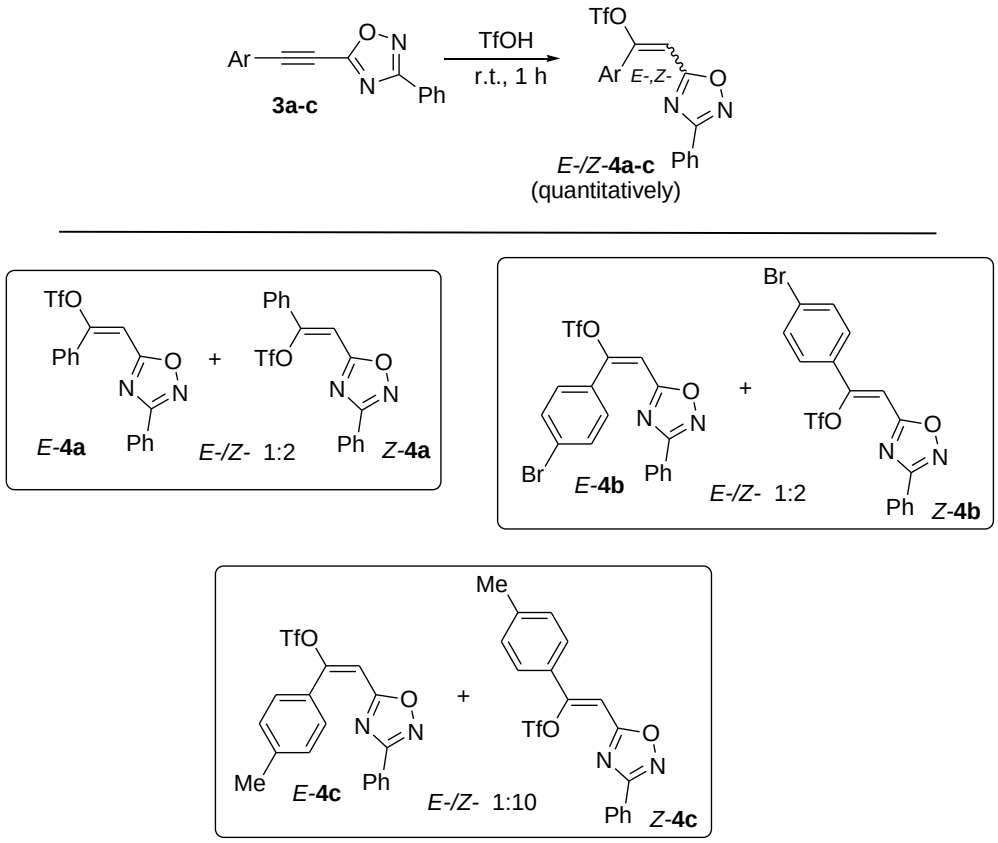
Thus, according our previous data on reactions of 5-styryl 1,2,4-oxadiazoles **1** [26] and results of DFT calculations for protonation of acetylene 1,2,4-oxadiazoles **3** (Table 1), one would propose the following reaction pathways for compounds **3** in Brønsted superacids (Scheme 2). Protonation 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 acetylene bond of starting compounds **3**.



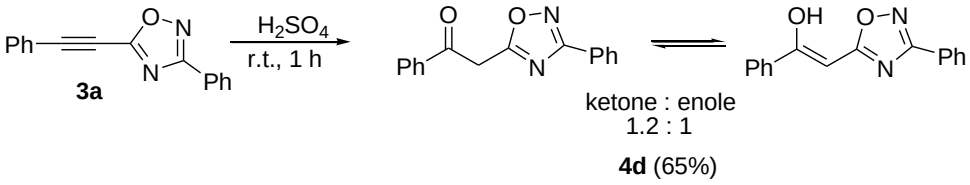
Scheme 2. Plausible reaction mechanism for transformations of acetylene 1,2,4-oxadiazoles **3** in Brønsted superacids.

Indeed, reaction of acetylene 1,2,4-oxadiazoles **3a-c** with excess of TfOH at room temperature for 1 h resulted in the quantitative preparation of *E-/Z*-isomers of vinyl triflates **4a-c** with a predominant formation of *Z*-isomers as product of *anti*-addition of TfOH to acetylene bond (Scheme 3). *E-/Z*-Stereochemistry of compounds **4a-c** was determined by H-F NOESY correlation between vinyl proton (>C=CH–) and CF_3 group from TfO substituent (see Supporting Information). It should be noted that attempts of chromatographic separation of triflates **4a-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 H_2SO_4, oxadiazole **3a** gave product of hydration of acetylene bond **4d** (yield of 65%) existing in solution as equilibrium between ketone and enole forms in a ratio of 1.2 : 1 according to NMR data (see Supporting Information).

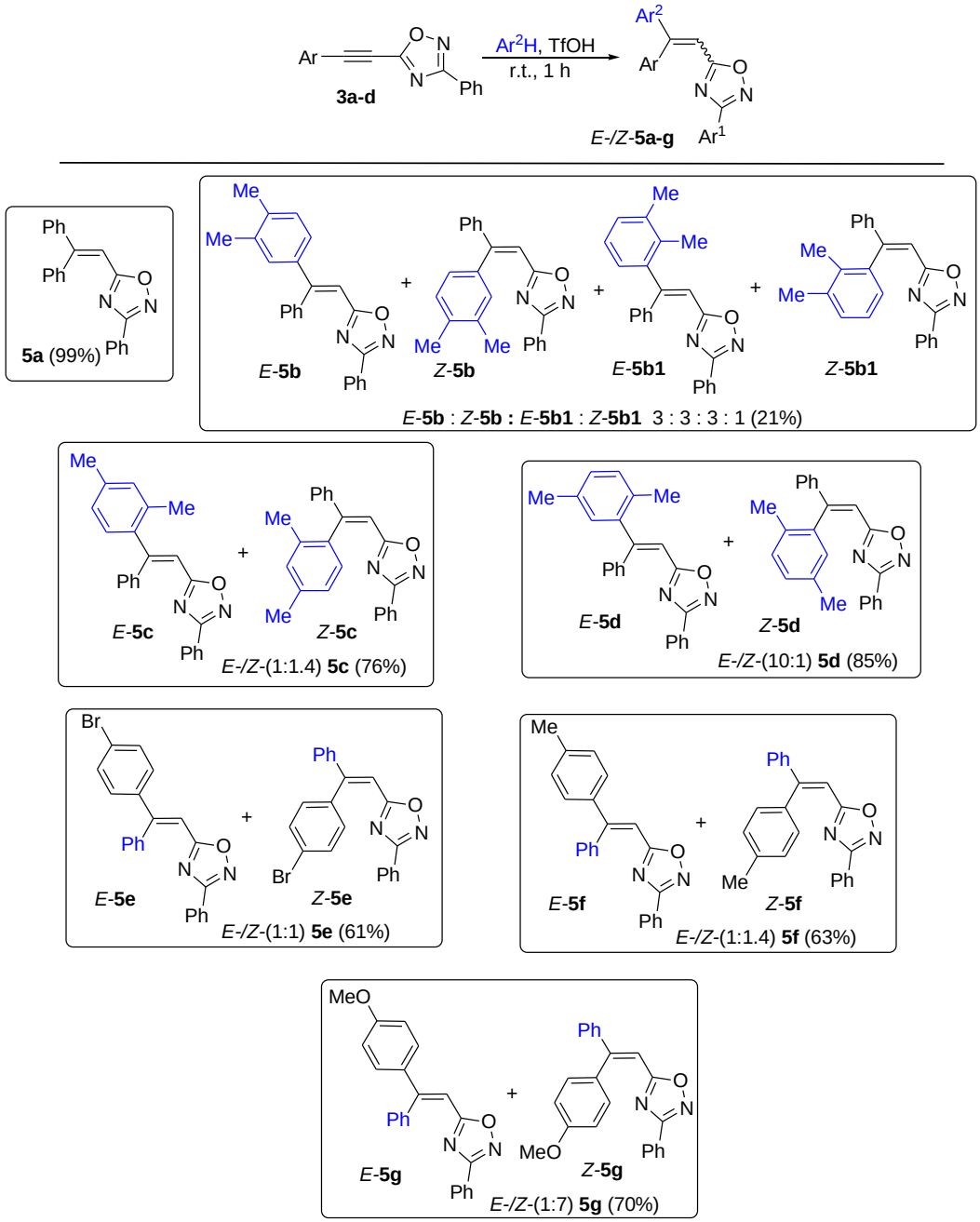


Scheme 3. Quantitative formation of *E-/Z*-vinyl triflates **4a-c** from acetylene 1,2,4-oxadiazoles **3a-c** in TfOH.



Scheme 4. Formation of compound **4d** from acetylene 1,2,4-oxadiazole **3a** in H_2SO_4.

Then, reactions of acetylene 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 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 correlation between vinyl proton and aromatic protons (see Supporting Information). In the case of reaction with *o*-xylene, pairs of *E-/Z*-isomers of two regioisomers, *E-/Z*-**5b** and *E-/Z*-**5b1**, were obtained.

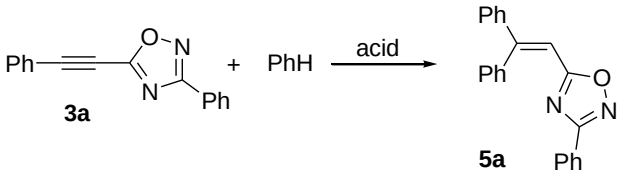


Scheme 5. Hydroarylation of acetylene 1,2,4-oxadiazole **3a-d** by arenes in TfOH leading to compounds *E*-/*Z*-**5a-g**.

We also checked reaction of oxadiazole **3a** with benzene under the action of Lewis acids $AlCl_3$, $AlBr_3$ and acidic zeolite CBV-720 (Scheme 6). However, these Lewis acids showed unsatisfactory results leading to olygomeric materials. A yield of target compound **5a** in reaction with zeolite was lower than in the same reaction in TfOH (compare with data in Scheme 5). Thus, among the tested acidic reagents, TfOH showed better results for hydroarylation of compounds **3**.

Additionally reaction of oxadiazole **3a** with benzene in TfOH (r.t., 1 h) in the presence of cyclohexane, as a hydride ion source, was conducted to achieve ionic hydrogenation of intermediate cationic species. However, no products of ionic hydrogenation were obtained, only product of

hydrophenylation of acetylene bond **5a** was quantitatively isolated (compare with data on Scheme 5).



Acid	Reaction conditions		Yield of **5a**, %
	Temperature, °C	Time, h	
$AlCl_3$	r.t.	1	oligomeric compounds
$AlBr_3$	r.t.	1	oligomeric compounds
Zeolite CBV-720	130	1	56

Scheme 6. Reactions of acetylene oxadiazole **3a** with benzene under the action of various acids.

Conclusion

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

Acknowledgments

This work was supported by Russian Foundation for Basic Research (grant no. 20-03-00074 A).

Supporting information contains experimental procedures, characterization of compounds, ^{1}H and ^{13}C NMR spectra of compounds, data of DFT calculations.

References

1. Palazzo, G.; Corsi, G. *Arzneim.-Forsch.* **1962**, *12*, 545-549.

2. Coupar, I. M.; Hedges, A.; Metcalfe, H. L.; Turner, P. *Pharm. Pharmacol*. **1969**, *21*, 474-475.

3. Jones, A. M.; Helm, J. M. *Drugs* **2009**, *69*, 1903-1910. doi:10.1111/j.2042-7158.1969.tb08294.x

4. Silvestrini, B. *Minerva Medica* **1960**, *51*, 4091–4094.

5. Rotbart, H.A.; Webster, A.D. *Clin. Infect. Dis.* **2001**, *32*, 228–235. doi: 10.1086/318452

6. Zhang, H.Z.; Kasibhatla, S.; Kuemmerle, J.; Kemnitzer, W.; Ollis-Mason, K.; Qiu, L.; Crogan-Grundy, C.; Tseng, B.; Drewe, J.; Cai, S.X. *J. Med. Chem.* **2005**, *48*, 5215 – 5223. doi.org/10.1021/jm050292k

7. Shamsi, F., Hasan, P., Queen, A., Hussain, A., Khan, P., Zeya, B., King, H.M., Rana, S., Garrison, J., Alajmi, M.F., Rizvi, M.M.A., Zahid, M., Imtaiyaz Hassan, M., Abid, M. *Bioorg. Chem.* **2020**, 98, 103754, doi:10.1016/j.bioorg.2020.103754

8. Zhang, H. Z.; Kasibhatla, S.; Kuemmerle, J.; Kemnitzer, W.; Ollis-Mason, K.; Qiu, L.; Crogan-Grundy, C.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2005**, *48*, 5215-5223. doi:10.1021/jm050292k

9. Abhay Atmaram., Upareae Pradip K. Gadekar., H. Sivaramakrishnan., Nishigandha Naik., Vijay M. Khedkar., Dhiman Sarkar., Amit Choudhari., S. Mohana Roopan. *Bioorg. Chem.* **2019**, *86*, 507-512. doi:10.1016/j.bioorg.2019.01.054

10. Janardhanan, J.; Chang, M.; Mobashery, S. The oxadiazole antibacterials. *Curr. Opin. Microbiol.* **2016**, *33*, 13–17. doi:10.1016/j.mib.2016.05.009

11. Mohammadi-Khanaposhtani, M.; Shabani, M.; Faizi, M.; Aghaei, I.; Jahani, R.; Sharafi, Z.; Shamsaei Zafarghandi, N.; Mahdavi, M.; Akbarzadeh, T.; Emami, S. *Eur. J. Med. Chem.* **2016**, *112*, 91–98. doi:10.1016/j.ejmech.2016.01.054

12. Querfurth, H.W.; LaFerla, F.M. *New Engl. J. Med*., **2010**, 362, 329–344. doi: 10.1056/NEJMra0909142

13. Jiang, C.S.; Fu, Y.; Zhang, L.; Gong, J.X.; Wang, Z.Z.; Xiao, W.; Zhang, H.Y.; Guo, Y.W. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 216–220. doi:10.1016/j.bmcl.2014.11.068

14. Mei, W.; Ji, S.; Xiao, W.; Wang, X.D.; Jiang, C.S.; Ma, W.Q.; Zhang, H.Y.; Gong, J.; Guo, Y. *Monatsh. Chem. Chem. Mon.,* **2017**, *148*, 1807–1815. doi:10.1007/s00706-017-1993-x

16. Hemming, K. *J. Chem. Res.* **2001**, *6*, 209-216. doi:10.3184%2F030823401103169603

17. Kayukova, L. A. *Pharm. Chem. J.* **2005**, *39*, 539-547. doi:10.1007/s11094-006-0017-7

18. Hemming, K. 1.2.4-Oxadiazoles. *Comprehensive Heterocyclic Chemistry III.* **2008**, *5*, 243-314.

19. Pace, A.; Pierro, P. *Org. Biomol. Chem.* **2009**, *7*, 4337-4348. doi:10.1039/B908937C

20. Bora, R. O.; Dar, B.; Pradhan, V.; Farooqui, M. *Mini-Rev. Med. Chem.* **2014**, *14*, 355-369. doi:10.2174/1389557514666140329200745

21. Pace, A.; Buscemi, S.; Piccionello, A. P.; Pibiri, I. *Advances in Heterocyclic Chem.* **2015**, *116*, 85-136. doi:10.1016/bs.aihch.2015.05.001

22. Piccionello, A. P.; Pace, A.; Buscemi, S. *Chem. Heterocyclic Comp.* **2017**, *53*, 936-947. doi:10.1007/s10593-017-2154-1

23. Aggarwal, S., Goyal, A., Kaur, R. *Res. J. Pharm. Tech.* **2020**, *13*, 5026-5033. doi:10.5958/0974-360X.2020.00880.X

24. Lelyukh, M.; Demchuk, I.; Harkov, S; Chaban, T; Drapak, I; Chaban, I; Shelepeten, L; Matiychuk, V. *Biointerface Res. Appl. Chem.* **2020**, *10*, 5960-597. doi:10.33263/BRIAC104.960971

25. Claisse, J. A.; Foxton, M. W.; Gregory, G. I.; Sheppard, A. H.; Tiley, E. P.; Warburton, W. K.; Wilson, M. J. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2241-2247. doi:10.1039/P19730002241

26. Zalivatskaya, A. S.; Ryabukhin, D. S.; Tarasenko, M. V.; Ivanov, A. Y.; Boyarskaya, I. A.; Grinenko, E. V.; Vasilyev, A. V. *Beilst. J. Org. Chem.* **2017**, *13*, 883–894. doi:10.3762%2Fbjoc.13.89

27. Golushko, A.A.; Khoroshilova, O.V.; Vasilyev, A.V. *J. Org. Chem.* **2019**, *84*, 7495-7480. doi:10.1021/acs.joc.9b00812

28. Parr, R. G.; v. Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922-1924. doi: 10.1021/ja983494x

29. Chattaraj, P. K.; Giri, S.; Duley, S. *Chem. Rev.* **2011**, *111*, PR43-PR75. doi: 10.1021/cr100149p