AlBr₃-Promoted stereoselective anti-hydroarylation of the acetylene bond in 3-arylpropynenitriles by electron-rich arenes: synthesis of 3,3-diarylpropenenitriles

Yelizaveta Gorbunova¹, Dmitry S. Ryabukhin²,³ and Aleksander V. Vasilyev*¹,³,§

Abstract
Reactions of 3-arylpropynenitriles (ArC≡CCN) with electron-rich arenes (Ar′H, benzene and its polymethylated derivatives) under the action of aluminum bromide (AlBr₃, 6 equiv) at room temperature for 0.5–2 h result in the stereoselective formation of 3,3-diarylpropenenitriles (Ar(Ar′)C=CHCN) in yields of 20–64%, as products of mainly anti-hydroarylation of the acetylene bond. The obtained 3,3-diarylpropenenitriles in triflic acid CF₃SO₃H (TfOH) at room temperature for 1 h are cyclized into 3-arylindenones in yields of 55–70%.

Introduction
Conjugated acetylene nitriles (propynenitriles, R–C≡C–C≡N) are versatile building blocks in organic synthesis for the preparation of a plethora of functionalized compounds and heterocycles. The presence of conjugated acetylene and nitrile bonds in these compounds leads to an enhancement of reactivity of both functional groups. Thus, propynenitriles take part in electrophilic [1,2] and nucleophilic [3-6] addition reactions onto the acetylene bond leading to various substituted nitriles. Reactions onto both acetylene and nitrile groups are widely used for the construction of various heterocyclic systems [7-15].

Recently, we have shown that reactions of 3-arylpropynenitriles (cinnamonitriles, ArCH=CHCN) with arenes (Ar′H) under the superelectrophilic activation by the Brønsted super-
acid CF₃SO₃H (TfOH, triflic acid) or the strong Lewis acid AlBr₃ result in the formation of 3,3-diarylpropanenitriles (Ar(Ar')CHCH₂CN) through the regioselective hydroarylation of the carbon–carbon double bond. In TfOH, the reactions proceed further to 3-arylindanones, as products of the intramolecular aromatic acylation of the 3,3-diarylpropanenitriles by the electrophilically activated nitrile group [16,17]. Based on this study and our work on electrophilic transformations of alkynes [18-20], we investigated reactions of 3-arylp propane nitriles under electrophilic activation conditions (see [21] for the chemistry of superelectrophilic species). The goal of this work was to study the reactions of 3-arylp propane nitriles with arenes under the action of the strong Lewis acids, aluminum halogenides AlX₃ (X = Cl, Br) and the Brønsted superacid TfOH (CF₃SO₃H).

Results and Discussion
It was found that acetylene nitriles 1a–c reacted with arenes in the presence of excess AlBr₃ (6 equiv) at room temperature for 0.5–2 h to afford E,Z-3,3-diarylpropanenitriles 2a–o as products of the regioselective hydroarylation of the acetylene bond (Scheme 1). These reactions proceeded only with an excess of AlBr₃ (6 equiv). Thus, running the reaction of nitrile 1a with benzene under the action of less amount AlBr₃ (1–4 equiv) resulted in an incomplete conversion of the starting compound 1a and a low yield of the target product 2a (<10%).

The yields of the compounds 2 were moderate (20–64%) that may be caused by possible transformations of the nitrile group in the electrophilic medium leading to oligomeric material [22]. The reaction proceeded rather regioselectively giving mainly

![Scheme 1: AlBr₃-promoted hydroarylation of the acetylene bond of 3-arylp propane nitriles 1a-c by arenes with the formation of 3,3-diarylpropanenitriles E,Z-2a-o.](image)
Z-isomers of nitriles 2, as products of anti-addition of hydrogen and the aryl group to the carbon–carbon triple bond. Only in three cases, mixtures of E,Z-isomers (2b,1n) in a ratio of ≈1:1 were obtained. The E,Z-configuration of compounds 2a–o was determined by NOESY correlations between the vinyl proton and the aromatic protons or methyl groups in neighboring aryl substituents (see Supporting Information File 1). However, the configuration of nitrile 2o was unclear. Benzene, o-, m-, p-xylene, and 1,2,4-trimethylbenzene (mesitylene) were included in the hydroarylation of nitriles 1. Reactions of nitriles 1a–e with o-xylene led to the formation of regioisomers derived from the electrophilic substitution at different positions of this arene. Thus, nitrile 1a gave two types of regioisomers 2n and 2o. After reactions of nitriles 1b,c with o-xylene, compounds 2l and 2m correspondingly were obtained; other regioisomers were not isolated in amounts that were high enough for their identification.

This transformation was also tested with another strong Lewis acid, aluminum chloride (AlCl₃), for the reaction of nitrile 1a with benzene. However, in this case, mainly oligomeric material was obtained and the yield of the target reaction product 2a was lower (20%) than in the same reaction with AlBr₃. This result revealed the less effectiveness of AlCl₃ for the hydroarylation of nitriles 1.

One may propose the following reaction mechanism (Scheme 2). The coordination of AlBr₃ to both the nitrile and acetylene bonds of the starting compound 1 furnishes the highly electrophilic species A bearing a positive charge on the acetylenic carbon atom C3. The subsequent reaction of species A with the arene molecule via electrophilic aromatic substitution results in the formation of species B. The most probably, this stage proceeds stereoselectively due to spatial factors, with the incoming arene ArH attacking the acetylene bond in an anti-position to the bulky AlBr₃, that determines the final predominant formation of the mainly anti-hydroarylation products of the starting nitriles 1. At the last step of the reaction, a proton substitutes AlBr₃, and final hydrolysis of the reaction mixture gives rise to nitriles 2.

It should be noted that this AlBr₃-promoted hydroarylation of acetylene nitriles 1 (Scheme 1) is a novel transition-metal (Pd, Pt, Rh, etc.-) free stereoselective way for the synthesis of compounds 2. These compounds can be alternatively obtained by a Pd-catalyzed Heck reaction of 3-arylpropenenitriles with iodoarenes [23] or by a Cu-catalyzed hydroarylation of 3-arylpropenenitriles with arylboronic acid [24,25]. There is one example of use of dicyanoacetylene in a similar AlCl₃-catalyzed hydroarylation of an acetylene bond in the synthesis of cyclophanes [26].

Additionally, the cyclization of two selected nitriles 2c,g into 3-arylindanones 3a,b correspondingly was carried out in triflic acid TiOH (CF₃SO₂H) at room temperature for 1 h (Scheme 3). The intramolecular aromatic substitution by the electrophilically activated nitrile group took place in the more electron-rich methylated aryl ring. A similar cyclization of 3,3-diarylpropenenitriles into 3-arylindanones in TiOH was described by us previously [17]. It should be specially emphasized that the synthesis of indenones is an important goal in organic chemistry since this structural motif is associated with interesting chemical and biological properties [27-32].

We also conducted reactions of nitriles 1a–e with arenes in TiOH at room temperature, which, however, led to complex mixtures of reaction products. Only in the cases of the reaction of nitriles 1a,b with benzene in TiOH, the hydrophenylation...
products, i.e., nitriles 2a,b, were obtained (Scheme 4; compare with synthesis of 2a,b in Scheme 1).

In general, the comparison of reactions of 3-arylpropenitriles (cinnamonnitriles; ArCH=CHCN) (see our work [17]) and 3-arylpropynitriles 1 (this work) under electrophilic activation reveals unambiguously that the electrophilic intermediates generated from acetylene nitriles 1 possess higher reactivity. Thus, the hydroarylation of 3-arylpropynitriles 1 promoted by AlBr₃ proceeds at room temperature (Scheme 1), whereas the same reaction of 3-arylpropenitriles needs elevated temperature up to 80 °C [17]. Reactions of acetylene nitriles 1 with arenes in TfOH have complex character, contrary to 3-arylpropenitriles, which react smoothly with arenes in TfOH at room temperature [17].

Conclusion
We have developed a novel transition-metal (Pd, Pt, Rh, etc.)-free procedure for the regio- and stereoselective hydroarylation of the carbon–carbon triple bond in 3-arylpropynitriles by arenes under electrophilic activation by aluminum bromide AlBr₃. The obtained 3,3-diarylpropenenitriles were cyclized into 3-arylindenones in triflic acid CF₃SO₃H (TfOH).

Supporting Information
Supporting Information File 1
Experimental procedures, compound characterization, and ¹H and ¹³C NMR spectra of compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-180-S1.pdf]

Acknowledgements
Spectral studies were performed at the Center for Magnetic Resonance and the Center for Chemical Analysis and Materials Research of Saint Petersburg State University, Saint Petersburg, Russia.

Funding
This work was supported by Russian Scientific Foundation (grant no. 21-13-00006).

ORCID® iDs
Aleksander V. Vasilyev - https://orcid.org/0000-0003-3628-1492

References
1. Guan, Z.; Liu, Z.; Shi, W.; Chen, H. Tetrahedron Lett. 2017, 58, 3602–3606. doi:10.1016/j.tetlet.2017.07.104
2. Perlmutter, P.; Chin Teo, C. Tetrahedron Lett. 1984, 25, 5951–5952. doi:10.1016/s0040-4039(01)81730-5
3. Kishida, Y.; Terada, A. Chem. Pharm. Bull. 1968, 16, 1351–1359. doi:10.1248/cpb.16.1351
4. Zhou, W.; Zhang, Y.; Li, P.; Wang, L. Org. Biomol. Chem. 2012, 10, 7184–7196. doi:10.1039/c2ob25969a
5. Trofimov, B. A.; Andriyankova, L. V.; Nikitina, L. P.; Belyaeva, K. V.; Mali'kina, A. G.; Monin, A. V.; Usakov, I. A. Tetrahedron Lett. 2013, 54, 4693–4696. doi:10.1016/j.tetlet.2013.06.095
6. Yadia, R.; Rehman, H.; Rao, J. M.; Mahesh, V. K. Tetrahedron 1989, 45, 7093–7098. doi:10.1016/s0040-4020(01)819177-8
7. Zhang, J.; Zhang, Q.; Ji, X.; Meng, L.-G. Synlett 2019, 30, 1095–1099. doi:10.1055/s-0037-1610708
8. Liu, P.; Clark, R. J.; Zhu, L. J. Org. Chem. 2018, 83, 5092–5103. doi:10.1021/acs.joc.8b00424
9. Rama Rao, V. V. V. N. S.; Lingaiah, B. P. V.; Yadla, R.; Shanthanan Rao, P.; Ravikumar, K.; Swamy, G. Y. S. K.; Narsimulu, K. J. Heterocycl. Chem. 2006, 43, 673–679. doi:10.1002/jhet.5570430321
10. Trofimov, B. A.; Mali'kina, A. G.; Nosyreva, V. V.; Shemyakina, O. A.; Albanov, A. I.; Aitonin, A. V.; Kazheva, O. N.; Alexandrov, G. G.; Dyachenko, O. A. Tetrahedron Lett. 2012, 53, 927–930. doi:10.1016/j.tetlet.2011.12.035
11. Barton, P. Tetrahedron Lett. 2018, 59, 815–817. doi:10.1016/j.tetlet.2018.01.042
12. Chen, Y.-R.; Duan, W.-L. J. Am. Chem. Soc. 2013, 135, 16754–16757. doi:10.1021/ja407373g
13. Dückert, H.; Khedkar, V.; Waldmann, H.; Kumar, K. Chem. – Eur. J. 2011, 17, 5130–5137. doi:10.1002/chem.201003572
14. Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. Angew. Chem., Int. Ed. 2009, 48, 4572–4576. doi:10.1002/anie.200901484
15. McCauley, J. A.; Theberge, C. R.; Liverton, N. J. Org. Lett. 2000, 2, 3389–3391. doi:10.1021/ol000649j
16. Gorbunova, Y.; Zakusilo, D. N.; Vasilyev, A. V. Tetrahedron Lett. 2019, 60, 961–964. doi:10.1016/j.tetlet.2019.02.047
17. Gorbunova, Y.; Zakusilo, D. N.; Boyarskaya, I. A.; Vasilyev, A. V. Tetrahedron 2020, 76, 131264. doi:10.1016/j.tet.2020.131264
18. Vasilyev, A. V. Russ. Chem. Rev. 2013, 82, 187–204. doi:10.1070/rc2013v082n03abeh004345
19. Kazakova, A. N.; Vasilyev, A. V. Russ. J. Org. Chem. 2017, 53, 485–509. doi:10.1134/s1070428017040017
20. Vasilyev, A. V. Adv. Org. Synth. 2018, 8, 81–120. doi:10.2174/9781681085647118080005
21. Olah, G. A.; Klumpp, D. A. Superlectrophiles and their chemistry; John Wiley & Sons: Hoboken, NJ, USA, 2008.
22. Salnikov, G. E.; Genae, A. M.; Vasilyev, V. G.; Shubin, V. G. Org. Biomol. Chem. 2012, 10, 2282–2288. doi:10.1039/c2ob06841a
23. Masliorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Pleixats, R.; Roglans, A. Synthesis 2002, 1903–1911. doi:10.1055/s-2002-33918
24. Yamamoto, Y.; Asatani, T.; Kirai, N. Adv. Synth. Catal. 2009, 351, 1243–1249. doi:10.1002/adsc.200900067
25. Yoo, K.; Kim, H.; Yun, J. Chem. – Eur. J. 2009, 15, 11134–11138. doi:10.1002/chem.200901262
26. Matsuda-Sentou, W.; Shinmyozu, T. Eur. J. Org. Chem. 2000, 3195–3203. doi:10.1002/1099-0690(200009)2000:18<3195::aid-ejoc3195>3.0.co;2-1
27. Nigam, R.; Babu, K. R.; Ghosh, T.; Kumari, B.; Khan, F. A.; Das, P.; Anindya, R. Chem. Biol. Drug Des. 2021, 97, 1170–1184. doi:10.1111/cbdd.13839
28. Hu, B.; Cheng, X.; Hu, Y.; Liu, X.; Karaghiosoff, K.; Li, J. Angew. Chem., Int. Ed. 2021, 60, 15497–15502. doi:10.1002/anie.202103465
29. Song, J.; Sun, H.; Sun, W.; Fan, Y.; Li, C.; Wang, H.; Xiao, K.; Qian, Y. Adv. Synth. Catal. 2019, 361, 5521–5527. doi:10.1002/adsc.201901309
30. Zhang, Y.; Sun, K.; Lv, Q.; Chen, X.; Qu, L.; Yu, B. Chin. Chem. Lett. 2019, 30, 1361–1368. doi:10.1016/j.cclet.2019.03.034
31. Ramesh, K.; Satyanarayana, G. Eur. J. Org. Chem. 2018, 4135–4146. doi:10.1002/ejoc.201800591
32. Ryabukhin, D. S.; Fukin, G. K.; Vasilyev, A. V. Tetrahedron 2014, 70, 7865–7873. doi:10.1016/j.tet.2014.09.006

License and Terms
This is an Open Access article 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 Journal of Organic Chemistry terms and conditions: (https://www.beilstein-journals.org/bjoc/terms)

The definitive version of this article is the electronic one which can be found at: https://doi.org/10.3762/bjoc.17.180