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An effective method for the synthesis of 1,5-disubstituted 4-halo-1*H*-1,2,3-triazoles from magnesium acetylides

Iuliia V. Karsakova[1], Alexander Yu. Smirnov[2]*, Mikhail S. Baranov[2,3]

[1] *Moscow M. V. Lomonosov State University, 1, Build. 3, Leninskie Gory, Moscow 119991, Russia; e-mail: julia.karsakova@yandex.ru*

[2] *Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, 16/10 Miklukho-Maklaya St., Moscow 117997, Russia; e-mail: alexmsu@yandex.ru*

[3] *Pirogov Russian National Research Medical University, 1 Ostrovityanova St., Moscow 117997, Russia; e-mail: baranovmikes@gmail.com*

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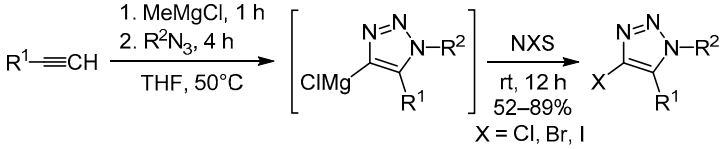


A simple one-pot two-stage method for the synthesis of disubstituted 4-chloro-, 4-bromo-, and 4-iodo-1,2,3-triazoles from terminal alkynes and organic azides is proposed.

Keywords: 4-halo-1,2,3-triazoles, organomagnesium compounds, 1,3-dipolar cycloaddition.

1,2,3-Triazoles are a well-studied class of heterocyclic compounds. They find wide use to create dyes,[1] polymers,[2] energetic materials,[3] as well as in organic synthesis and homogeneous catalysis.[4] 1,2,3-Triazoles are most intensively studied in medicinal chemistry,[5,6] as they exhibit antitumor,[7] antiparasitic,[8] and antiviral[9] activity. A powerful impetus in the development of the chemistry of 1,2,3-triazoles was the discovery of a highly effective synthesis method, the 1,3-dipolar cycloaddition of terminal alkynes to azides catalyzed by copper.[10] However, this approach makes it possible to obtain only 1,4-disubstituted triazoles, while the creation of 1,4,5-trisubstituted derivatives present a more difficult task.

Since one of the effective approaches to the functionalization of heterocyclic compounds is employing the cross-coupling reactions, the creation of various halo-substituted triazoles becomes an important and urgent task. Earlier, we already proposed an effective approach to the synthesis of 5-halo derivatives[11] which were successfully used in the Suzuki–Miyaura reaction,[12] but the issue of the effective creation of various 4-halo-1,2,3-triazoles remained open. It is known that 4-bromo derivatives can be easily obtained by decarboxylation of triazolecarboxylic acids in bromine water,[13] however, more complex methods of synthesis are often used to create 4-chloro- or 4-iodotriazoles,[14,15] and analogous decarboxylation methods are not described at all.

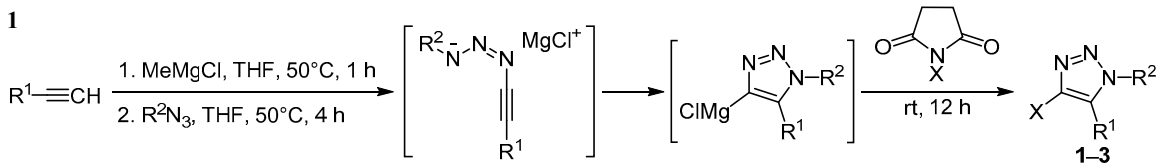
Our attempts to use this approach have shown that the action of elemental iodine, chlorine, as well as *N*-chloro- and *N*-iodosuccinimides, potassium iodide and chloride, sodium hypochlorite, cyanuric chloride, sodium dichloroisocyanurate, and *t*-BuOCl on various triazolecarboxylic acids does not lead to the production of target products.

As a result, we decided to use the reaction of non-catalytic 1,3-dipolar cycloaddition of magnesium acetylides to azides for the creation of 4-haloazoles, first described by Akimova as a method for the synthesis of 1,5-disubstituted triazoles.[16,17] The mechanism of this reaction has not been studied in detail, but it is assumed that at first a nucleophilic attack of acetylide at the terminal nitrogen atom of the azide group takes place (Scheme 1). The resulting linear intermediate then closes to form 4-halomagnesium-1,2,3-triazoles, which give 1,5-disubstituted derivatives during hydrolysis, as well as react with electrophilic agents.[17]

Surprisingly, we found that this approach had not previously been utilized to synthesize 4-halotriazoles, and the use of iodine, shown only in one example,[18] turned out to be ineffective. In our work, we investigated the possibility of using other electrophiles and showed that the use of *N*-halosuccinimides is the most effective (for 4-chloro derivatives, perchloroethane with subsequent hydrolysis can also be used).

To carry out the reaction, the desired acetylene was subjected to the action of methylmagnesium chloride, after

Scheme 1



1a–c X = Cl, R^2 = Ph **2a,b** X = Br, R^1 = Ph **3a–c** X = I

1a R^1 = *n*-Pr (82%) **2a** R^2 = *p*-$MeOC_6H_4$ (84%) **3a** R^1 = *n*-Pr, R^2 = Ph (52%)

1b R^1 = Ph (89%) **2b** R^2 = *o*-$MeOC_6H_4$ (88%) **3b** R^1 = Ph, R^2 = *p*-$MeOC_6H_4$ (67%)

1c R^1 = *t*-Bu (56%) **3c** R^1 = Ph, R^2 = *o*-$MeOC_6H_4$ (61%)

which the corresponding aryl azide was introduced into the reaction mixture, followed by the corresponding electrophile (Scheme 1). With this approach, no separation of intermediate products is required, and the resulting solutions of organomagnesium derivatives can be separated and used to synthesize several different chloro-, bromo-, and iodotriazoles **1**–**3**. The method is demonstrated with 8 examples, all compounds were obtained with good yields.

It should be noted that the reaction requires strict following of the temperature regime. Thus, the reaction of acetylides with azides requires some heating, while the addition of electrophiles requires cooling, since otherwise a mixture of by-products will form leading to a decrease in yield. It is interesting to note that similar reactions leading to the formation of 1,5-disubstituted 1,2,3-1*H*-triazoles have also been described for lithium derivatives,[17] but an attempt to carry out the proposed conversion using lithium acetylides has led to a mixture of unidentifiable products.

To conclude, we have obtained a library of new halo-substituted triazoles with various substituents. It was shown that the nature and position of the substituents in the aromatic azide practically do not influence the yield of the reaction, while the replacement of aromatic acetylenes with aliphatic, as well as bromine and chlorine with iodine, leads to a decrease in the yield.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance III spectrometer (700 and 176 MHz, respectively) in $CDCl_3$, with TMS signal or the residual solvent signal (7.27 ppm for ^{1}H and 77.2 ppm for ^{13}C) used to assign chemical shifts. Elemental analysis was performed on a Thermo Flash-EA 200 Elemental Analyzer. Melting points were determined on an SMP 30 apparatus and are uncorrected. Reagents were supplied by Acros Organics and were used without additional purification. Solvents were freshly distilled before use. All operations with moisture sensitive substances were performed using Schlenk techniques under dry argon atmosphere.

The aryl azides were derived from monosubstituted anilines by the diazotization reaction, followed by the replacement of the diazo group by the azide.[19,20]

Synthesis of 4-halo-1*H*-1,2,3-triazoles 1a–c, 2a,b, 3a–c (General method). The corresponding terminal alkyne (10 mmol) was dissolved in anhydrous THF (30 ml); then 3 M methylmagnesium chloride solution in diethyl ether (3 ml, 12 mmol) was added to the obtained solution dropwise over 5 min. The obtained mixture was heated to 50°C and kept at this temperature for 1 h, then cooled to room temperature, and the corresponding azide (11.0 mmol) in anhydrous THF (5 ml) was added dropwise over 5 min. The mixture was once more heated to 50°C and kept at this temperature for 4 h. It was cooled to 0°C, and *N*-halosuccinimide (20 mmol) was added in small portions with vigorous stirring, then the mixture was kept at room temperature for 12 h. Then distilled water (30 ml) was added, the mixture stirred and extracted with ethyl acetate (3×50 ml). The organic extracts were combined, washed with saturated aqueous NaCl (2×35 ml), and dried over anhydrous Na_2SO_4. The solvent was evaporated on the rotary evaporator, the residue purified by column chromatography on silica gel (eluent hexane–EtOAc, 5:1) and recrystallized from ethanol.

4-Chloro-1-phenyl-5-propyl-1*H*-1,2,3-triazole (1a).[11] Yield 1.82 g (82%), white crystals, mp 80–82°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.86 (3H, t, ^3J = 7.4, $CH_2CH_2C\underline{H_3}$); 1.53 (2H, sex, ^3J = 7.5, $CH_2C\underline{H_2}CH_3$); 2.64–2.74 (2H, m, $C\underline{H_2}CH_2CH_3$); 7.39–7.47 (2H, m, H Ph); 7.52–7.62 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.3 ($CH_2CH_2\underline{C}H_3$); 20.9 ($CH_2\underline{C}H_2CH_3$); 24.2 ($\underline{C}H_2CH_2CH_3$); 125.0; 129.4; 129.8; 133.6; 133.9; 136.1. Found, %: C 59.53; H 5.48; N 19.04. $C_{11}H_{12}ClN_3$. Calculated, %: C 59.60; H 5.46; N 18.95.

4-Chloro-1,5-diphenyl-1*H*-1,2,3-triazole (1b).[11] Yield 2.27 g (89%), white crystals, mp 102–105°C. ^{1}H NMR spectrum, δ, ppm: 7.22–7.29 (2H, m, H Ph); 7.29–7.34 (2H, m, H Ph); 7.35–7.47 (6H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 124.7; 124.9; 128.8; 129.4; 129.5 (2 signals); 129.7; 132.9; 134.3; 136.4. Found, %: C 65.81; H 3.88; N 16.45. $C_{14}H_{10}ClN_3$. Calculated, %: C 65.76; H 3.94; N 16.43.

5-*tert*-Butyl-4-chloro-1-phenyl-1*H*-1,2,3-triazole (1c). Yield 1.32 g (56%), white crystals, mp 77–80°C. ^{1}H NMR spectrum, δ, ppm: 1.28 (9H, s, *t*-Bu); 7.34–7.38 (2H, m, H Ph); 7.49–7.53 (2H, m, H Ph); 7.54–7.58 (1H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 30.1 ($C(\underline{C}H_3)_3$); 32.0 ($\underline{C}(CH_3)_3$); 127.8; 129.0; 130.5; 132.7; 138.9; 140.4. Found, %: C 61.22; H 5.93; N 17.81. $C_{12}H_{14}ClN_3$. Calculated, %: C 61.15; H 5.99; N 17.83.

4-Bromo-1-(4-metoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole (2a). Yield 2.77 g (84%), white crystals, mp 112–115°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.83 (3H, s, OCH_3); 6.90 (2H, d, ^3J = 9.0, H Ar); 7.23 (2H, d, ^3J = 9.0, H Ar); 7.29 (2H, dd, ^3J = 8.0, ^4J = 1.5, H Ph); 7.37–7.43 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 55.5 (OCH_3); 114.4; 120.8; 125.4; 126.2; 128.7; 129.3; 129.5; 129.6; 135.3; 160.1. Found, %: C 54.80; H 3.61; N 12.71. $C_{15}H_{12}BrN_3O$. Calculated, %: C 54.56; H 3.66; N 12.73.

4-Bromo-1-(2-metoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole (2b). Yield 2.90 g (88%), white crystals, mp 123–125°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.46 (3H, s, OCH_3); 6.90 (1H, d, ^3J = 8.7, H Ar); 7.08 (1H, td, ^3J = 7.6, ^4J = 1.2, H Ar); 7.26–7.29 (2H, m, H Ar); 7.31–7.37 (3H, m, H Ar); 7.42–7.46 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.3 (OCH_3); 112.2; 119.8; 120.9; 125.3; 126.0; 128.2; 128.3; 128.5; 129.3; 131.7; 137.0; 153.3. Found, %: C 54.50; H 3.60; N 12.80. $C_{15}H_{12}BrN_3O$. Calculated, %: C 54.56; H 3.66; N 12.73.

4-Iodo-1-phenyl-5-propyl-1*H*-1,2,3-triazole (3a).[21] Yield 1.61 g (52%), white crystals, mp 133–136°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (3H, t, ^3J = 7.4, $CH_2CH_2C\underline{H_3}$); 1.44–1.54 (2H, m, $CH_2C\underline{H_2}CH_3$); 2.64–2.72 (2H, m, $C\underline{H_2}CH_2CH_3$); 7.38–7.44 (2H, m, H Ph); 7.52–7.59 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 13.6 ($CH_2CH_2\underline{C}H_3$); 21.7 ($CH_2\underline{C}H_2CH_3$); 25.5 ($\underline{C}H_2CH_2CH_3$); 90.1 (CI); 125.4; 129.6; 130.0; 136.3; 140.2. Found, %: C 42.14; H 3.83; N 13.50. $C_{11}H_{12}IN_3$. Calculated, %: C 42.19; H 3.86; N 13.42.

4-Iodo-1-(4-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole (3b). Yield 2.53 g (67%), white crystals, mp 120–124°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.82 (3H, s, OCH_3); 6.87–6.90 (2H, m, H Ar); 7.19–7.22 (2H, m, H Ar); 7.27 (2H, dd, ^3J = 8.0, ^4J = 1.5, H Ar); 7.37–7.44 (3H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.5 (CH_3); 90.5 (CI); 114.4; 126.2; 126.3; 128.7; 129.3; 129.6; 129.8; 139.4; 160.2. Found, %: C 47.80; H 3.23; N 11.10. $C_{15}H_{12}IN_3O$. Calculated, %: C 47.77; H 3.21; N 11.14.

4-Iodo-1-(2-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole (3c). Yield 2.30 g (61%), white crystals, mp 153–155°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.46 (3H, s, OCH_3); 6.88 (1H, d, ^3J = 8.7, H Ar); 7.05 (1H, td, ^3J = 7.7, ^4J = 1.1, H Ar); 7.26 (2H, dd, ^3J = 8.1, ^4J = 1.6, H Ar); 7.30–7.36 (3H, m, H Ar); 7.39–7.44 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.2 (OCH_3); 89.0 (CI); 112.0; 120.7; 125.2; 126.5; 128.1 (2 signals); 128.7; 129.1; 131.5; 140.8; 153.3. Found, %: C 47.73; H 3.22; N 11.19. $C_{15}H_{12}IN_3O$. Calculated, %: C 47.77; H 3.21; N 11.14.

Supporting information file containing ^{1}H and ^{13}C NMR spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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References

1. Duan, T.; Fan, K.; Fu, Y.; Zhong, C.; Chen, X.; Peng, T.; Qin, J . *Dyes Pigm.* **2012**, *94*, 28.
2. Wang, Z.; Tao, Y.; Wang, Z.; Yan, J. *Polym. Chem.* **2016**, *7*, 3172.
3. Lee, D.-H.; Kim, K. T.; Jang, Y.; Lee, S.; Jeon, H. B.; Paik, H.-J.; Min, B. S.; Kim, W. *J. Appl. Polym. Sci.* **2014**, *131*, DOI:10.1002/app.40594.
4. Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848.
5. Miura, S.; Izuta, S. *Curr. Drug Targets* **2004**, *5*, 191.
6. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
7. Pokhodylo, N.; Shyyka, O.; Matiychuk, V. *Sci. Pharm.* **2013**, *81*, 663.
8. Maurya, S. K.; Gollapalli, D. R.; Kirubakaran, S.; Zhang, M.; Johnson, C. R.; Benjamin, N. N.; Hedstrom, L.; Cuny, G. D. *J. Med. Chem.* **2009**, *52*, 4623.
9. Wen, Y.; Zhang, Z.; Liu, N.-N.; Andrei, G.; Snoeck, R.; Xiang, Y.-H.; Schols, D.; Chen, X.; Zhang, Z.-Y.; Zhang, Q.-S.; Wu, Q.-P. *Med. Chem.* **2017**, *13*, 453.
10. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
11. Gribanov, P. S.; Topchiy, M. A.; Karsakova, I. V.; Chesnokov, G. A.; Smirnov, A. Yu.; Minaeva, L. I.; Asachenko, A. F.; Nechaev, M. S. *Eur. J. Org. Chem.* **2017**, 5225.
12. Gribanov, P. S.; Chesnokov, G. A.; Topchiy, M. A.; Asachenko, A. F.; Nechaev, M. S. *Org. Biomol. Chem.* **2017**, *15*, 9575.
13. Afanas'ev, O. I.; Tsyplenkova, O. A.; Seliverstov, M. Y.; Sosonyuk, S. E.; Proskurnina, M. V.; Zefirov, N. S. *Russ. Chem. Bull., Int. Ed.* **2015**, *64*, 1470. [*Изв. АН, Сер. хим.* **2015**, 1470.]
14. Pérez, J. M.; Crosbie, P.; Lal, S.; Díez-González, S. *ChemCatChem* **2016**, *8*, 2222.
15. McIntosh, M L.; Johnston, R. C.; Pattawong, O.; Ashburn, B. O.; Naffziger, M. R.; Cheong, P. H.; Carter, R. G. *J. Org. Chem.* **2012**, *77*, 1101.
16. Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1965**, *1*, 2077.
17. Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1968**, *4*, 389.
18. Krasiński, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237.
19. Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4217.
20. Maddani, M. R.; Moorthy, S. K.; Prabhu, K. R. *Tetrahedron* **2010**, *66*, 329.
21. Kawamoto, H.; Ito, S.; Satoh, A.; Nagatomi, Y.; Hirata, Y.; Kimura, T.; Suzuki, G.; Sato, A.; Ohta, H. Eur. Patent 1764362.