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Direct Synthesis of 1,5-Disubstituted-4-magnesio-1,2,3-triazoles, Revisited

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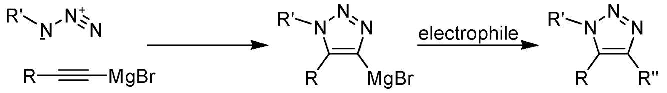
ABSTRACT



After revisiting earlier works reporting the regioselective synthesis of 1,5-disubstituted-1,2,3-triazoles via the addition of bromomagnesium acetylides to azides, much improved yields of the products were obtained for a wide array of azides and alkynes. The intermediates of that reaction can be trapped with different electrophiles to regioselectively form 1,4,5-trisubstituted 1,2,3-triazoles.

1,2,3-Triazoles are attractive constructs, which because of their unique chemical properties and structure should find many applications in organic, organometallic, and medicinal chemistry, as well as in materials chemistry. Not present in natural products, they are remarkably stable to metabolic transformations, such as oxidation, reduction, and both basic and acidic hydrolysis. Furthermore, 1,2,3-triazole moieties are emerging as powerful pharmacophores in their own right.[1] However, probably because of the lack of convenient direct methods for their synthesis, these aromatic heterocycles have not received as much attention as they deserve.

Known methods for the regioselective synthesis of 1,5-disubstituted- and 1,4,5-trisubstituted-1,2,3-triazoles include reactions of azides with active methylene compounds.[2] Functional groups may also be introduced to the existing 1,2,3-triazole ring by lithiation of the heterocycle followed by reaction with an electrophile.[3] One of the most attractive approaches to the synthesis of 1,2,3-triazoles are 1,3-dipolar cycloadditions of azides and alkynes.[4] Although there are known examples of influencing the regiochemistry of the addition by the electronic properties of the substrate, they are neither general nor reliable, usually requiring a strong electron-withdrawing substituent on the alkyne.[5] Metals, such as tin, germanium, or silicon, attached to the acetylenic carbon atom have been shown to give mainly 4-metalated 1,5-disubstituted triazoles.[6] Reactions of sodium, lithium, or magnesium acetylides with organic azides have also been reported.[7,8] 1,5-Disubstituted 1,2,3-triazoles are the major products of these reactions. The scope of this transformation was investigated by Akimova et al. in the late 1960s.[8] Extensive studies were presented, in which a wide variety of azides and lithium or magnesium acetylides were em-

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(1) (a) Bourne, Y.; Kolb, H. C.; Radić, Z.; Sharpless, K. B.; Taylor, P.; Marchot, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 1449. (b) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radić, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053.

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(3) (a) Holzer, W.; Ruso, K. *J. Heterocycl. Chem.* **1992**, *29*, 1203. (b) Ohta, S.; Kawasaki, I.; Uemura, T.; Yamashita, M.; Yoshioka, T.; Yamaguchi, S. *Chem. Pharm. Bull.* **1997**, *45*, 1140. (c) Uhlmann, P.; Felding, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1997**, 9177. (d) Felding, J.; Uhlmann, P.; Kristensen, J.; Vedsø, P.; Begtrup, M. *Synthesis* **1998**, 1181.

(4) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1−176.

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(6) Himbert, G.; Frank, D.; Regitz, M. *Chem. Ber.* **1976**, *109*, 370.

(7) (a) Fridman, S. G.; Lisovska, N. M. *Zap. Inst. Khim., Akad. Nauk U.R.S.R., Inst. Khim.* **1940**, *6*, 353. (b) Boyer, N. M.; Mack, C. H.; Goebel, N.; Morgan, L. R., Jr. *J. Org. Chem.* **1958**, *23*, 1051. (c) Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1965**, *1*, 2077.

(8) (a) Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1967**, *3*, 968. (b) Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1967**, *3*, 2241. (c) Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1968**, *4*, 389.

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Table 1. Synthesis of 1,5-Disubstituted-1,2,3-triazoles

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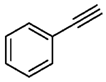
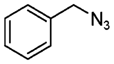
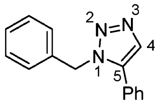
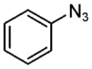
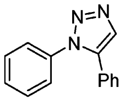
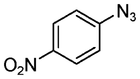
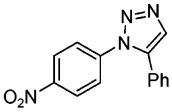
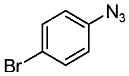
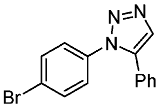
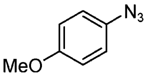
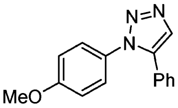
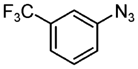
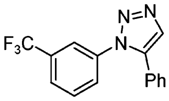
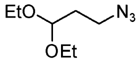
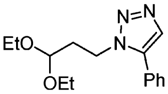
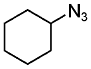
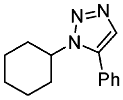
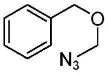
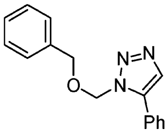
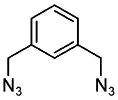
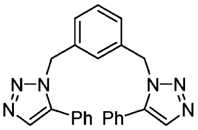
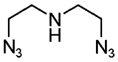
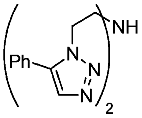
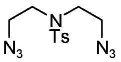
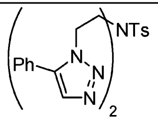
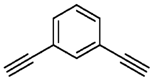
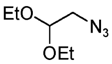
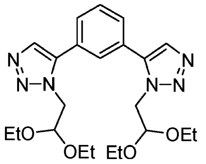
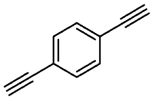
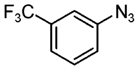
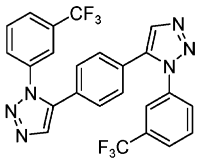
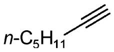
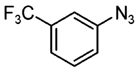
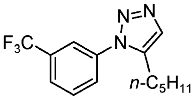
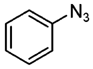
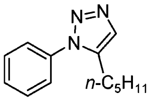
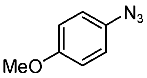
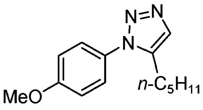
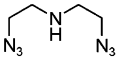
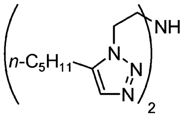
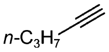
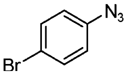
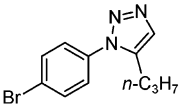
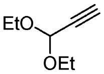
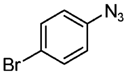
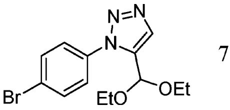
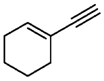
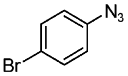
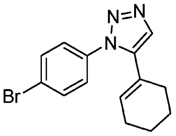
a				90
b				96 (40)
c				96 (75)
d				100 (57)
f				100
g				96
h				88
i				76
j				97
k				98
l				94
m				95
n				63[b]
o				81[c]
p				95
r				95
s				83[b]
t				87
u				94 (60)
v				78[b]
w				99

[a] Unless stated otherwise, the yields are crude; yields in parentheses are taken from the original papers.[8] [b] After flash chromatography. [c] After recrystallization.

ployed. Their proposed mechanism (Scheme 1) begins with the nucleophilic attack of the acetylide **1** on the terminal nitrogen atom of the azide **2**, followed by spontaneous closure of the linear intermediate **3** to the 4-metallotriazole species **4**. The reaction of the bromomagnesium acetylides with azides gave, after hydrolysis, preferentially the 1,5-disubstituted triazoles **5**; however, the yields were low. Formation of byproduct **7** was reported in some cases along with unreacted starting materials. On the other hand, the use of lithium acetylides favored further attack by intermediate **4** on a second molecule of azide, resulting upon hydrolysis, in the 4-triazene-substituted triazoles **7**, often in high yields.[8]

Finding the copper(I)-catalyzed route to 1,4-disubstituted-1,2,3-triazoles from azides and terminal alkynes[9] highlighted the need for a direct way to achieve the complementary union of the same reactants, namely, one giving the regioisomeric 1,5-triazole analogues. Although Akimova, et al. had studied such a process over 30 years ago,[8] a citation search turned

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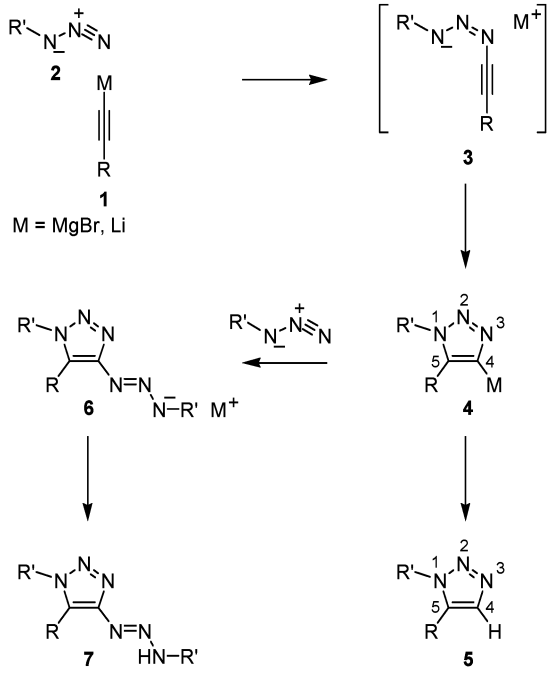
(9) Rostovtsev, V. V.; Green, L. G.; Fokin V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

Scheme 1. Proposed Mechanism for the Synthesis of 1,5-Disubstituted-1,2,3-triazoles



up no further uses of their nice one-step procedure, likely because of the poor to moderate yields they reported. In any case, we find that Akimova's procedure actually gives 1,5-disubstituted-1,2,3-triazoles in much better yields than originally reported (Table 1).[8]

Most reactions furnished 1,5-disubstituted-1,2,3-triazoles at room temperature overnight in almost quantitative yields, and the crude products required no purification.[10] Aliphatic acetylides are less reactive than their aryl counterparts. Electron-poor azides react much faster than the electron-rich ones, an observation consistent with the proposed nucleophilic attack of the acetylide on the azide (Scheme 1). For example, products **5c** and **5g** were formed almost instantly after mixing the reagents (concentration of 0.4 M), whereas the formation of product **5s**, from two of the least reactive components, required several days under the same conditions to reach completion.[11]

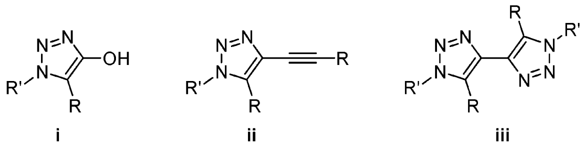
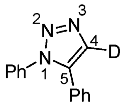
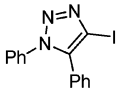
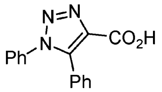
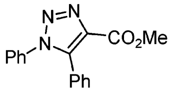
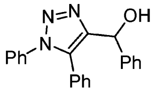
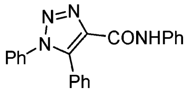
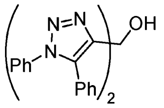
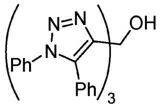
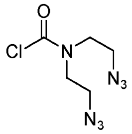
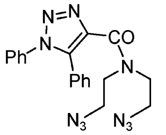


Figure 1. Reaction byproducts.[13]

Although the reaction is usually fast and clean, several types of trace byproducts can be observed (Figure 1). Long reaction times without strict exclusion of oxygen promote oxidative couplings, which result in the formation of structures such as **i**, **ii**, or **iii**. Byproducts can also include **7** (vide supra), but an excess of the azide over the acetylide as well as extended reaction times are required to form significant amounts of **7**. When bromomagnesium acetylides are used as substrates, trace amounts of 1,5-disubstituted-4-bromotriazoles are observed.[12] The presence of the 4-halo-

Table 2. Synthesis of Fully Substituted 1,2,3-Triazoles

entry	electrophile	product	yield
1	DCl/D_2O		95 98%D
2	I_2		84[a]
3	CO_2		76 (54)[b]
4	$ClCO_2Me$		42[c]
5	PhCHO		92[a]
6	PhNCO		77[d]
7	HCO_2Et		64[a]
8	$(CCl_3)_2CO_3$		58[c]
9			45[c]

[a] Yields after recrystallization. [b] Yield taken from the original paper.[8a] [c] Yields after flash chromatography; substantial amounts of 1,5-diphenyl-1,2,3-triazole were recovered. [d] Yield after trituration with Et_2O.

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(10) The reactions are carried out at concentrations ranging from 0.4 to 1.0 M on a 2−10 mmol scale. **Experimental Procedure.** To the dried flask containing a solution of EtMgBr or EtMgCl in dry THF under a nitrogen atmosphere, the terminal alkyne is added dropwise at room temperature. Good results are usually obtained using commercially available 1 M EtMgBr in THF and no extra solvent. After the alkyne is added, the solution is heated to 50 °C for 15 min and cooled to room temperature (if necessary can be diluted with dry THF). Neat azide (or a concentrated THF solution thereof) is added dropwise. The reaction is exothermic, and for the reactive, electron-poor azides (e.g., entries **c** and **g**, Table 1) over within 1 h as a result of self-heating or after 24 h in any case. Since there are no significant side reactions, elevated temperature (50 °C) can be applied in most cases, whereupon reactions are complete within 1 h. After quenching with aqueous NH_4Cl, the products are extracted using ethyl acetate or chloroform. Provided the azide-acetylide couple is reactive and there is no intention of in situ derivatization of the 4-magnesio-triazole, the reactions can even be performed on 2 mmol or larger scale with no special precautions concerning moisture or oxygen exclusion, in screw-capped vials. In the case of less reactive (electron-rich aromatic) azides and/or when further functionalization of the intermediate 4-halomagnesio triazoles is intended, maintaining complete dryness is crucial.

byproducts is eliminated by using chloromagnesium Grignard reagents to generate the magnesium acetylide reactant.

Of course, the 4-halomagnesiotriazole intermediates, instead of being hydrolyzed, can be trapped with electrophiles other than protons,[14] resulting in a regioselective formation of 1,4,5-trisubstituted 1,2,3-triazoles (Table 2). This option, noted previously but unexplored,[8a] becomes more attractive because of the high yields of the 4-magnesiotriazole intermediates. Table 2 highlights the results of quenching of the 4-chloromagnesio-1,5-diphenyl-1,2,3-triazole with nine different electrophiles.[15] The yields are usually good, but in cases where trace acid impurities are hard to avoid (e.g., entry 9), the product of protonation at C-4 is also formed.

Not all electrophilic compounds are suitable for this capture process. For example, the use of sulfamoyl and sulfonyl chlorides results in partial chlorination of the triazole ring at C-4. Although iodination with elemental iodine is an efficient process, the use of bromine promotes the formation of oxidatively coupled 4,4′-bis-triazoles of type **iii** in significant amounts, along with the 4-bromotriazole analogues. Because of the very strong basicity of 4-magnesiotriazoles, reactions with electrophiles, which also possess acidic C-H bonds usually fail as a result of competing protonation at C-4. Many of these drawbacks can be overcome by transmetalation prior to the coupling.[3d]

In summary, upon reexamination, the old process of Akimova et al.[8] is much better than was thought and should find many uses in the rapidly growing field of 1,2,3-triazole chemistry.

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(11) This particular compound was synthesized at the concentration of 2.0 M at room temperature in 4 h. The reaction times for less active azides (e.g., *p*-methoxyphenyl azide) can be shortened to about 1 h at 50 °C.

(12) Similar observations were made in the copper(I)-catalyzed reaction, described in ref 9.

(13) Structures tentatively assigned by mass spectrometry.

(14) However, it is important to note that labeling of the 4-position with the other isotopes of hydrogen, namely, deuterium (98% D incorporation, Table 2, entry 1) and tritium can be very useful for mechanistic and biological studies. Once attached to the carbon at the 4-position of the 1,5-disubstituted triazoles, the hydrogen atom is very difficult to remove (Begtrup, M., personal communication; ref 3b suggests that 5-lithiation of triazoles is strongly favored over 4-lithiation, even in the absence of a directing group at the 1-position).

(15) Reactions between phenyl azide and chloromagnesium phenylacetylide were performed on 6 mmol scale at 50 °C for 1 h, and then the electrophile (neat or as a concentrated THF solution) was added. For experimental procedure see ref 10.