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Efficient Synthesis of 2-Substituted-1,2,3-triazoles

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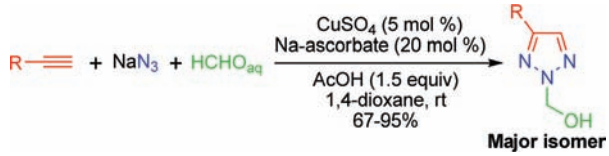
ABSTRACT



In this three-component reaction, alkynes undergo a copper(I)-catalyzed cycloaddition with sodium azide and formaldehyde to yield 2-hydroxymethyl-2*H*-1,2,3-triazoles, which are useful intermediates that can be readily converted to polyfunctional molecules. The hydroxymethyl group can also be removed, providing convenient access to N*H*-1,2,3-triazoles. The reaction is experimentally simple and readily scalable.

The 1,3-dipolar cycloaddition of organic azides and alkynes, a direct route to 1,2,3-triazoles,[1] is usually slow and not regioselective. Catalytic azide-alkyne cycloaddition methods for the synthesis of 1,4- (copper(I)-catalyzed)[2] or 1,5-disubstituted (ruthenium(II)-catalyzed)[3] 1,2,3-triazoles provide reliable means for the assembly of diversely substituted 1,2,3-triazoles under mild conditions and with excellent regioselectivity. However, a general, simple, and scalable method for the synthesis of the 2*H*-isomers is still not available.

Although 2-substituted-2*H*-1,2,3-triazoles can be obtained by alkylation of N*H*-1,2,3-triazoles with suitable electrophilic reagents, a mixture of the isomeric products is often produced.[4] Another common route to the 2*H*-1,2,3-triazoles, the oxidative cyclization of bishydrazones or bissemicarbazones, is limited to the synthesis of 2-aryl-substituted 1,2,3-triazoles.[5] In 2002, Yamamoto and co-workers reported an elegant three-component Pd-catalyzed synthesis of 2-allyl-1,2,3-triazoles.[6] The proposed mechanism involves the initial formation of a 1-allylpalladium-1,2,3-triazole complex, which may subsequently rearrange to the 2*H* isomer. Similar behavior was observed by Iddon et al. during the hydrolysis of a mixture of 1*H*- and 2*H*- MOM-alkylated 4,5-dibromo-1,2,3-triazoles, where only the 2-hydroxymethyl isomer was obtained.[7] These results suggest that the 2-hydroxymethyl derivative of 4,5-dibromo-1,2,3-triazole is thermodynamically more stable than its 1-substituted isomer and that there is a dynamic equilibrium between the *N*-hydroxymethyl triazole, formaldehyde, and the N*H*-triazole.[8]

Here we present a three-component, one-pot synthesis of 2-hydroxymethyl-2*H*-1,2,3-triazoles.[9] These compounds are versatile intermediates that can be used for the preparation of 2-chloromethyl-2*H*-1,2,3-triazoles and N*H*-1,2,3-triazoles,

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(5) Krivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev.* **2005**, *74*, 339.
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(7) Iddon, B.; Nicholas, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1341.
(8) *N*-Hydroxymethyl derivatives of other heterocycles are known to rearrange: (a) Katritzky, A. R.; Perumal, S.; Savage, G. P. *J. Chem. Soc. Perkin Trans. 2* **1990**, 921. (b) Alkorta, I.; Elguero, J.; Jagerovic, N.; Fruchier, A.; Yap, G. P. A. *J. Heterocycl. Chem.* **2004**, *41*, 285.
(9) (a) Ladyzhnikova, T. D.; Manuél, D. V.; Altukhov, K. V. *Russ. J. Org. Chem.* **1993**, *29*, 1249. (b) Quiclet-Sire, B.; Zard, S. Z. *Synthesis* **2005**, 3319.

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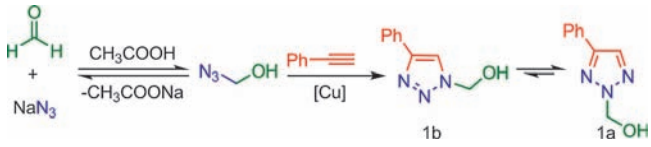
an important class of heterocycles with pharmacophoric properties.[10]

In our method, formaldehyde, sodium azide, and a terminal alkyne react in a one-pot two-reaction sequence under slightly acidic (pH = 6.5) conditions. Azidomethanol (HO-CH_2-N_3), formed in situ from protonated formaldehyde and sodium azide, is a likely intermediate.[11] Its subsequent copper(I)-catalyzed reaction with the alkyne provides the 1-hydroxymethyl-1*H*-1,2,3-triazole product. However, the instability of this derivative and its equilibrium with the N*H*-triazole and formaldehyde results in the rearrangement of the 1-hydroxymethyl triazole to the thermodynamically more stable 2-hydroxymethyl isomer.[12] Thus, the net result of a sequence that begins with phenylacetylene, formaldehyde, and sodium azide is the regioisomeric mixture of 1- and 2-hydroxymethyl-4-phenyl-1,2,3-triazole products **1**(**a**+**b**) (Scheme 1).

Scheme 1. Synthesis of 2-Substituted-2*H*-1,2,3-triazoles

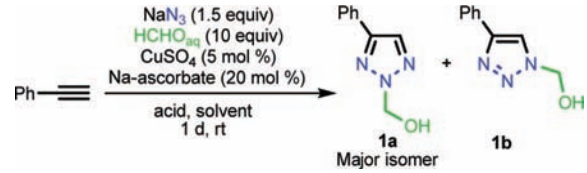


Examination of different reaction parameters (Table 1) revealed that the best yields of the triazole were obtained under slightly acidic conditions (entries 1−3). Due to the toxic and explosive nature of the hydrazoic acid, we opted to use the relatively weak acetic acid to conduct the reaction (CH_3COOH, $pK_a(H_2O) = 4.76$, $pK_a(DMSO) = 12.3$ cf. HN_3, $pK_a(H_2O) = 4.72$, pK_a (DMSO) = 7.9). The best results were obtained using a formalin/1,4-dioxane (1:1) mixture as the solvent system, which provided **1**(**a**+**b**) in 92% yield (entry 6). The reaction was successfully scaled up to 1 mol, and the product **1**(**a**+**b**) was isolated by simple extractive workup in 92% yield (157 g). The structure of **1a** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).

The scope of the one-pot method was then tested on a gram scale using several alkynes.[13] As shown in Table 2, mixtures of the 1- and 2-hydroxymethyl triazole products were obtained with yields ranging from 67% to 95%.

In all cases, the 2-substituted product was formed predominantly, as confirmed by the characteristic ^{13}C NMR chemical shift of the hydroxymethylene carbon. The identity of the minor

Table 1. One-Pot Synthesis of *N*-Hydroxymethyl-1,2,3-triazoles



entry	AcOH (equiv)	solvent[a]	yield (%)[b]
1	none	H_2O	none
2	0.6	H_2O	10
3	1.5	H_2O	48
4	1.5	H_2O/DMSO (1:1)	84
5	1.5	H_2O/DMF (1:1)	92
6	1.5	H_2O/dioxane (1:1)	92
7	1.5	H_2O[c]/dioxane (1:1)	1.3[c]

[a] A 37% solution of formaldehyde in water was used. [b] Combined yield of **1a** and **1b**. [c] No formaldehyde was added; N*H*-triazole **1c** was the product.

product as the 1,4-disubstituted-1,2,3-triazole was determined by HMQC and HMBC experiments. As demonstrated for the

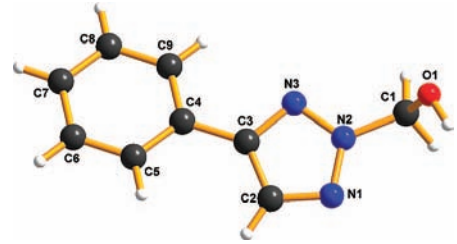


Figure 1. X-ray structure of **1a**.

product mixture **12**(**a**+**b**), the heteronuclear correlation experiments showed a strong interaction between the protons of the methylene group of the minor isomer with the C-5 carbon of the triazole ring, which was expected for the 1,4-isomer (see Supporting Information for details).

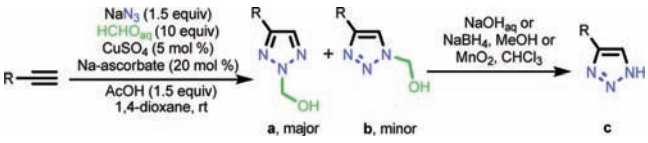
(10) (a) Woerner, F. P.; Reimlinger, H. *Chem. Ber.* **1970**, *103*, 1908. (b) Journet, M.; Cai, D.; Kowal, J. J.; Larsen, R. D. *Tetrahedron Lett.* **2001**, *42*, 9117. (c) Kallander, L. S.; Lu, Q.; Chen, W.; Tomaszek, T.; Yang, G.; Tew, D.; Meek, T. D.; Hofmann, G. A.; Schulz-Pritchard, C. K.; Smith, W. W.; Janson, C. A.; Ryan, M. D.; Zhang, G. F.; Johanson, K. O.; Kirkpatrick, R. B.; Ho, T. F.; Fisher, P. W.; Mattern, M. R.; Johnson, R. K.; Hansbury, M. J.; Winkler, J. D.; Ward, K. W.; Veber, D. F.; Thompson, S. K. *J. Med. Chem.* **2005**, *48*, 5644.

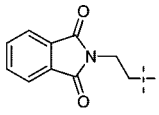
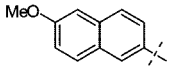
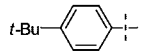
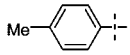
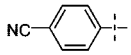
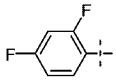
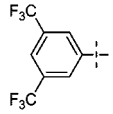
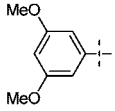
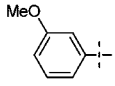
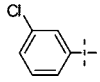
(11) We also considered the possibility of the Cu(I)-catalyzed cycloaddition of HN_3 and phenylacetylene to give the N*H*-triazole, which could subsequently react with formaldehyde (cf. Scheme 4). However, when H_2O was used instead of 37% formaldehyde solution (Table 1, entry 7), only N*H*-triazole **1c** was obtained in low 1.3% yield.

(12) Deprotection of the *O*-benzyl derivative of **1b** led to a mixture of **1a** and N*H*-triazole **1c** (see Suporting Information).

(13) General experimental procedure as exemplified for the synthesis of **1**. *CAUTION: any experiments that may result in the formation of hydrazoic acid should be performed in a well-ventilated fume hood and behind a blast shield. Sodium azide should not be mixed with strong acids.* A mixture of 37% $HCHO_{aq}$ (736 mL, 9.8 mol, 10 equiv), glacial AcOH (84 mL, 1.47 mol, 1.5 equiv), and 1,4-dioxane (736 mL) was stirred for 15 min, and NaN_3 (95.6 g, 1.47 mol, 1.5 equiv) was added, followed by phenylacetylene (100 g, 0.98 mol). At this point the pH of the reaction mixture was 6.5. After an additional 10 min of stirring, sodium ascorbate (38.8 g, 0.196 mol, 20 mol %) was added, followed by $CuSO_4$ solution (7.8 g, 0.049 mol, 5 mol %) in 40 mL of H_2O. *CAUTION: the reaction was exothermic, and although it achieved maximum temperature of 56 °C after 15 min without cooling, the use of an ice−water bath is recommended.* The mixture was stirred for 18 h at rt and then diluted with H_2O (3000 mL) and extracted using $CHCl_3$ (3 × 500 mL). Combined organic layers were filtered through Celite to remove solids, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator to give yellowish solid (157.5 g, 91.8%). The crude product was sufficiently pure to be used without further purification. The analytically pure sample was obtained as white solid (mp = 115−116 °C) by recrystallization from $CHCl_3$ or EtOAc/hexanes (1:1).

Table 2. Synthesis of *N*-Hydroxymethyl-1,2,3-triazoles and N*H*-1,2,3-Triazoles



product	R	yield **a**+**b** (%)	**a**:**b**[a]	^{13}C NMR **a**; **b** (ppm)[b]	yield of **c** (%)
1		92	84:16	76.0; 72.1	95[c] 86[d] 71[e]
2		73	86:14	75.5; 71.7	57[d] 57[e]
3		82	88:12	75.8; 72.1	85[c]
4		95	88:12	76.0; 72.1	96[c]
5		67	85:15	75.9; 72.0	99[c]
6		82	86:14	75.9; 72.0	97[c]
7		95	91:9	76.3; 72.3	84[d]
8		70	72:28	76.2; 72.1	87[c]
9		84	76:24	76.4; 72.5	97[c]
10		85	84:16	76.0; 72.1	83[c]
11		85	85:15	76.0; 72.1	88[c]
12		67	72:28	76.2; 72.2	83[c]
13		76	83:17	76.1; 72.2	98[c]

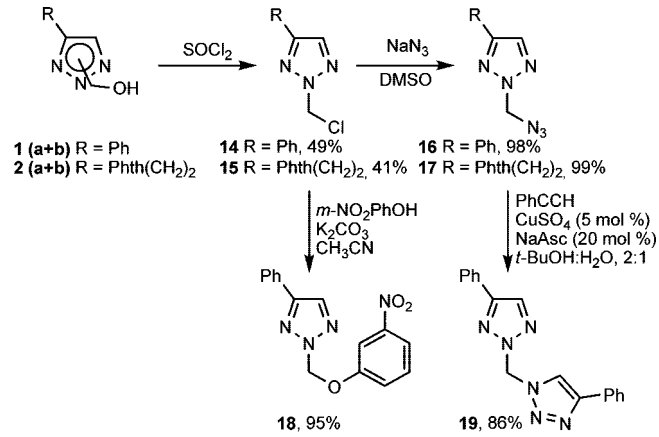
[a] Ratio of isomers was determined by integration of the triazole proton. [b] Hydroxymethylene carbon signals; all ^{13}C NMR spectra were recorded in d_6-DMSO. [c] NaOH. [d] $NaBH_4$. [e] MnO_2.

Basic hydrolysis of *N*-hydroxymethyl derivatives of various heterocycles is generally facile and leads to the parent N*H*-compounds.[14] Additionally, *N*-hydroxymethyl triazoles can be deprotected under reductive[15] or oxidative conditions. Therefore, isomeric mixtures of products **1**−**13**(**a**+**b**) can serve as precursors for the corresponding N*H*-triazoles. Therefore, basic hydrolysis with sodium hydroxide, reduction with sodium borohydride, and oxidation with manganese dioxide provide three complementary routes to the N*H*-triazoles. As illustrated in Table 2, all 13 N*H*-triazole products could be obtained in good yield using at least one of these reagents.

Existing syntheses of N*H*-triazoles usually use an azide with a suitable protecting group, which is removed after the 1,2,3-triazole heterocycle is assembled.[16] In our approach, azidomethanol serves as a "protected" azide which is formed in situ from inexpensive and readily available reagents, formaldehyde and sodium azide. The reaction can be readily performed on multigram scale (for example, 123 g of **1c** was obtained using this protocol).

To illustrate other facets of the reactivity and utility of *N*-hydroxymethyl triazoles, two representative compounds **1(a+b)** and **2(a+b)** were converted to the corresponding 2*H*-chloromethyl derivatives **14**[17] and **15**[18] (Scheme 2). Their electrophilic properties are revealed by reactions with nucleophiles, such as phenoxides and sodium azide. For example, they could be readily converted to aryl ethers **18** or to 2-azidomethyl-1,2,3-triazoles **16** and **17**.

Scheme 2. Synthesis of 2-Substituted-2*H*-1,2,3-triazoles



Additional proof that *N*-chloromethyl-1,2,3-triazole **14** and *N*-azidomethyl derivative **16** are 2*H* isomers comes from the Pd-catalyzed arylation of the bistriazole **19** with bromobenzene using a method recently developed by Gevorgyan and co-workers.[19] The di- and monoarylated products (**20** and **21**) were obtained in 24% and 60% yields, respectively (Scheme 3). The preferred formation of the monoarylated product **21** suggests that the 2,4-disubstituted triazole is less reactive in the Pd-catalyzed arylation than the 1,4-isomer.

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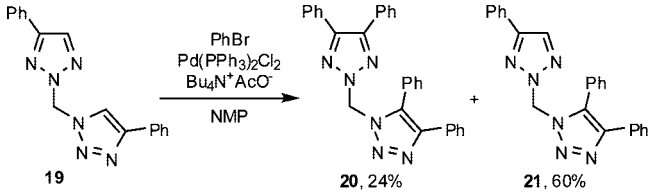
(15) For example, reaction of the 1*H*-hydroxymethyl benzotriazole with $NaBH_4$ provides exclusively 1*H*-benzotriazole: Gaylord, N. G.; Kay, D. J. *J. Org. Chem.* **1958**, *23*, 1574.

(16) (a) Shainyan, B. A.; Meshcheryakov, V. I. *Russ. J. Org. Chem.* **2001**, *37*, 1797. (b) Jin, T.; Kamijo, S.; Yamamoto, Y. *Eur. J. Org. Chem.* **2004**, 3789. (c) Kamijo, S.; Huo, Z.; Jin, T.; Kanazawa, C.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 6389. (d) Loren, J. C.; Krasiński, A.; Fokin, V. V.; Sharpless, K. B. *Synlett* **2005**, 2847. (e) Yap, A. H.; Weinreb, S. M. *Tetrahedron Lett.* **2006**, *47*, 3035.

(17) 1-(Chloromethyl)-4-phenyl-1*H*-1,2,3-triazole was obtained as a side product in 21% yield.

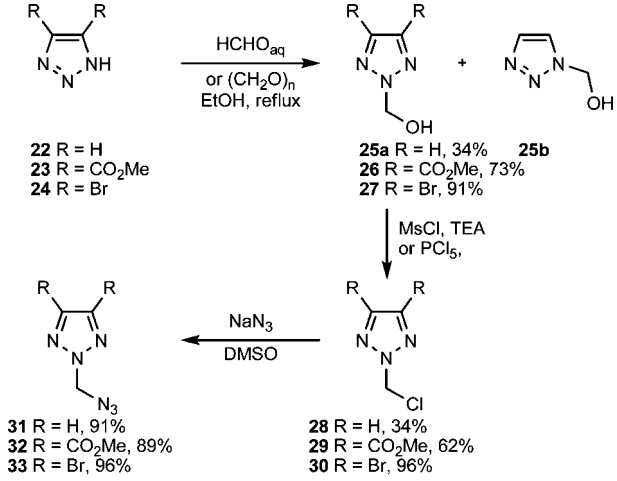
(18) NH-triazole **2c** (50%) accounts for the mass balance.

Scheme 3. Pd-Catalyzed Arylation of Bistriazole **19**



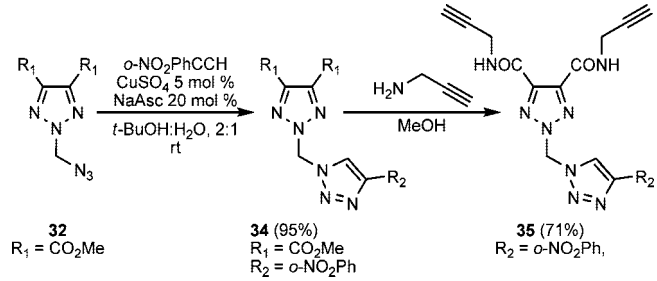
Synthesis of *N*-hydroxymethyl 1,2,3-triazoles can also be accomplished by the reaction of the N*H*-triazoles with paraformaldehyde or formaldehyde. Thus, the simplest parent N*H*-triazole **22** gave a mixture of 2*H*- and 1*H*-derivatives **25a** and **25b** in a 7:3 ratio (Scheme 4). In an earlier account,[20] only formation of the 2*H*-isomer was reported, possibly an artifact of insufficient ^{1}H NMR resolution. Nevertheless, the reaction of the regioisomeric mixture of **25(a**+**b)** and methanesulfonyl chloride gave, after distillation, pure 2*H*-chloromethyl derivative **28**. The scope of the method was probed using 4,5-dimethyl dicarboxylate- (**23**) and 4,5-dibromo-1,2,3-triazole

Scheme 4. Hydroxymethylation of N*H*-1,2,3-Triazoles



(**24**) as starting materials. The reactions of **23** and **24** with formaldehyde proceeded smoothly at room temperature leading exclusively to symmetrical 2*H*-hydroxymethyl products **26** and **27**, respectively (Scheme 4). Chlorination of the hydroxyl group of **26** and **27** was successfully achieved using PCl_5 on up to 60 g scale. 2*H*-chloromethyl-1,2,3-triazoles **28**, **29**, and **30** are versatile electrophiles. Their reaction with NaN_3 gives 2*H*-azidomethyl derivatives **31**, **32**, and **33**. 2*H*-Azidomethyl derivatives **32** and **33** can be readily functionalized at all three positions using known methods. For example, 2*H*-azidomethyl triazole **32** reacted with 1-ethynyl-2-nitrobenzene to form bistriazole derivative **34** in 95% yield (Scheme 5). Subsequent aminolysis of methyl esters with propargylamine gave bis(propargyl) amide **35**, a substrate poised to undergo a next round of alkyne transformations.

Scheme 5. Transformations of Azidomethyl Triazole **32**



In conclusion, 2*H*-hydroxymethyl-1,2,3-triazoles are now readily accessible from sodium azide, formaldehyde, and alkynes using a simple one-pot process. Alternatively, they can be prepared by hydroxymethylation of N*H*-triazoles with formaldehyde. Hydroxymethyl triazoles are versatile precursors to a broad variety of 2*H*- substituted 1,2,3-triazoles as well as N*H*-triazoles, which are important classes of heterocycles in medicinal chemistry and materials science.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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