DOI 10.1007/s10593-019-02414-8

Chemistry of Heterocyclic Compounds **2019**, *55*(1), 28–30

HETEROCYCLES
IN FOCUS

Recent methods for the synthesis of NH-1,2,3-triazoles (microreview)

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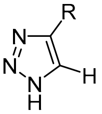
Published in Khimiya Geterotsiklicheskikh Soedinenii,
2019, *55*(1), 28–30

Submitted October 1, 2018
Accepted December 26, 2018



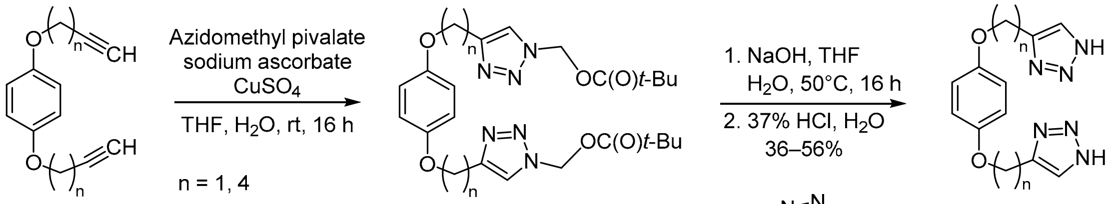
Microreview summarizes the latest examples on *N*H-unsubstituted 1,2,3-triazole synthesis. The described methods are categorized according to the used starting materials.

Introduction

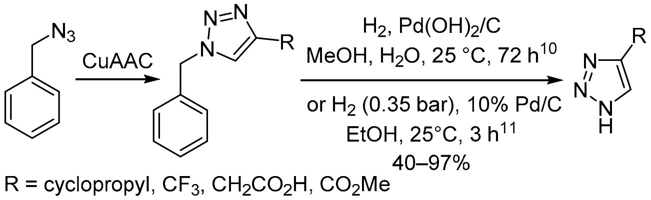
In the last decade, 1,2,3-triazoles have found wide application in many different fields.[1–6] A large number of 1,2,3-triazoles have recently been discovered to have remarkable bioactivity, such as IDO1 inhibitors, antiviral agents, Src kinase and HDAC inhibitors.[7] This review is devoted to the recent methods for *N*H-unsubstituted 1,2,3-triazole synthesis including catalytic, solid-phase, and microwave-assisted ones.

CuAAC reaction followed by deprotection

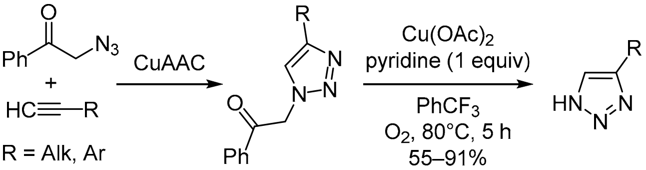
Copper(I)-catalyzed azide–alkyne [3+2] cycloaddition (CuAAC) reaction is one of the most popular and frequently used methods for the synthesis of 1,2,3-triazoles.[8] *N*(1)H-Unsubstituted 1,2,3-triazoles were obtained in good yields *via* cycloaddition of acetylenes with azidomethyl pivalate under standard CuAAC conditions. The pivalate protecting group was then removed by treatment with bases, followed by acidification.[9]



It has been shown that benzyl group at the first position of 1,2,3-triazole ring also can be removed by hydrogenation under various conditions.[10,11]



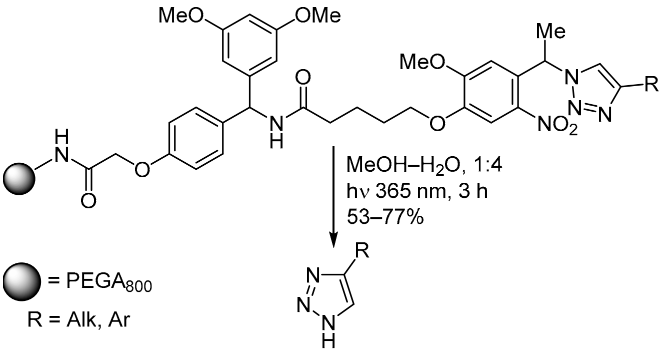
Hyojin Cha et al. recently developed new approach for the synthesis of 4-substituted NH-1,2,3-triazoles utilizing copper-catalyzed aerobic oxidative C–N bond cleavage reaction.[12] This method is also based on the CuAAC reaction and requires the use of $Cu(OAc)_2$ as a catalyst, pyridine as an additive, and trifluorotoluene as a solvent.



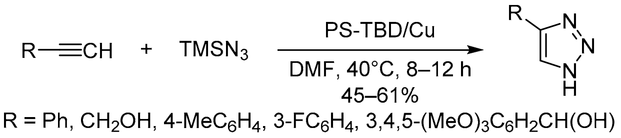
Efimov Ilya V. received his engineer degree in 2010 from the Ural Federal University named after the first President of Russia B. N. Yeltsin in Yekaterinburg. He obtained PhD at the same university under supervision of Prof. Vasiliy Bakulev in 2015 and subsequently became a postdoctoral fellow. In 2018, he has started his postdoctoral fellowship at the RUDN University in the group of Prof. Leonid Voskressensky. His scientific interests include cycloaddition reactions of azides and enamines, as well as reactions of isoquinolines.

Solid-phase synthesis

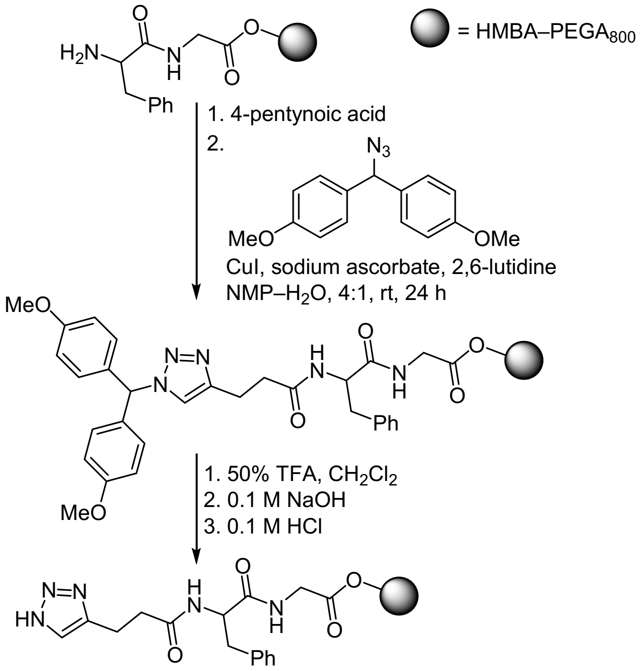
Attractive method for the synthesis of NH-1,2,3-triazoles applying CuAAC reaction was reported by Katrine Qvortrup and Thomas E. Nielsen.[13] The reaction of solid-supported photolabile azido linker and alkynes gave 4-substituted 1,2,3-triazoles which can easily release the desired *N*H-unsubstituted 1,2,3-triazoles upon UV irradiation under very mild conditions.



New supported catalysts for the Huisgen's azide–alkyne [3+2] cycloaddition have been prepared by immobilization of copper species on commercially available polymeric matrices incorporating the 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) template.[14] The use of this catalyst allowed to synthesize *N*H-unsubstituted 1,2,3-triazoles by the CuAAC reaction of trimethylsilyl azide and 1-alkynes. Since TMS ion is a good leaving group, the desired *N*H-unsubstituted 1,2,3-triazoles were efficiently obtained without any additional manipulations.

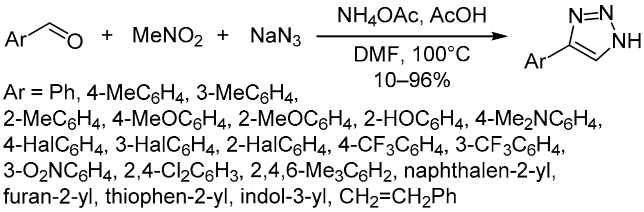


Another solid-phase synthesis of NH-1,2,3-triazoles using 4,4'-(azidomethylene)bis(methoxybenzene) building block was developed by A. Emil Cohrt et al.[15] The 4-(hydroxymethyl)-benzoic acid (HMBA) linker was coupled to the poly-[acryloylbis(aminopropyl)polyethylene glycol] (PEGA) resin using *N*,*N*,*N*',*N*'-tetramethyl-*O*-(benzotriazol-1-yl)-uronium tetrafluoroborate (TBTU) as the coupling reagent, followed by attachment of FmocGlyOH using 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT) for the esterification. FmocPheOH and 4-pentynoic acid were subsequently attached to provide an alkyne handle for the CuAAC reaction.



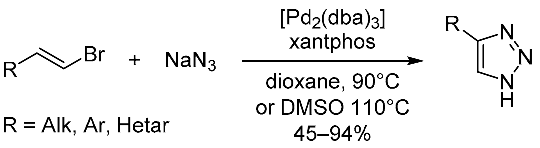
Three-component reaction of aldehydes, $MeNO_2$, and NaN_3

Another attractive synthetic method toward NH-1,2,3-triazoles is based on the one-pot three-component reaction of aldehydes, nitromethane, and NaN_3.[16] The described approach is general and allows synthesis of 4-aryl-, 4-hetaryl-, and 4-alkenyl-1,2,3-triazoles.



Reaction of alkenyl bromides with NaN_3

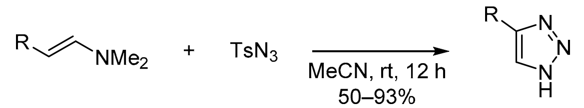
Palladium-catalyzed reaction of β-bromostyrenes with sodium azide provides NH-1,2,3-triazoles in high yields (up to 94%).[17] The substituent on the aromatic ring had no influence on the reaction outcome. The reaction was tolerant to sensitive functional groups such as methoxycarbonyl or nitrile, as well as *ortho* substituent on the aromatic ring. The chemoselectivity of the reaction is noteworthy, as the presence of a halide (bromide or chloride) substituent on the aromatic ring provides the triazole as the sole reaction product.



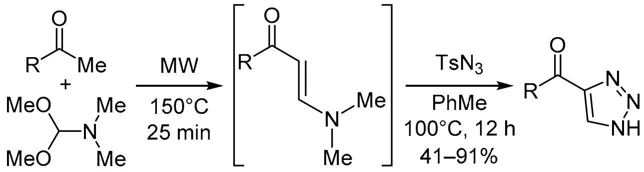
Reaction of enamines with TsN_3

Synthesis of rare 4-azolyl-1,2,3-triazoles was described by Ilya Efimov et al.[18] It was shown that the reactions of β-azolylenamines with tosyl azide in acetonitrile provide 1*H*-4-(azol-5-yl)-1,2,3-triazoles in yields ranging from 50 to 93%. β-Benzoylenaminones and β-nitroenamine were also suitable reagents to form the corresponding products, thus showing the versatility and efficiency of the method. Acetylenes were not advisable dipolarophiles for similar transformation.

Another interesting protocol was developed by Wim Dehaen et al.[19] Starting enamines were generated *in situ* from methyl ketones and DMF-DMA. Subsequent interaction of thus formed enamines with tosyl azide gave final NH-1,2,3-triazoles.



R = 1,2,3-thiadiazol-5-yl, isoxazol-5-yl, 1,2,3-triazol-5-yl, NO_2, ArCO



R = Alk, Ar, Hetar

This article was prepared with financial support from RUDN 5-100 program and from Russian Foundation for Basic Research and Moscow city Government according to the research project № 18-31-70021.

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