Tetrahedron 73 (2017) 3979–3985

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Microwave assisted solvent- and catalyst-free three-component synthesis of NH-1,2,3-triazoloimines

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ARTICLE INFO

Article history:
Received 30 January 2017
Received in revised form
12 May 2017
Accepted 23 May 2017
Available online 25 May 2017

Keywords:
Multicomponent
Microwave-assisted synthesis
Imino-NH-1,2,3-triazoles
Trimethylsilyl(triethylgermyl) propynals
Metal-free 1,3-dipolar cycloaddition

ABSTRACT

Highly efficient microwave-assisted solvent- and catalyst-free multicomponent synthesis of 5-R-imino-[4-trialkylsilyl(germyl)]-1*H*-1,2,3-triazoles from Si/Ge-substituted propynals, trimethylsilyl azide and functionalized primary amines has been developed. In the case of 2-aminoethanethiol, 4-element substituted 5-(1,3-thiazolan-2-yl)-1*H*-1,2,3-triazoles have been obtained. Their heterolysis by MeOH at room temperature leads to the corresponding triazoloimines in high yield.

1. Introduction

The 1,2,3-triazoles are an important class of heterocycle utilized in biological science, medicinal chemistry, material science[1] and a broad range of industrial applications.[2] A combination of important properties of the triazole ring such as high chemical stability, large dipole moment, heteroaromatic character, and ability of the H-bonding is efficiently employed in organic synthesis for the design of biologically active molecules[3] and new materials.[4] The synthesis of functionalized triazoles *via* the copper-catalyzed azide-alkyne cycloaddition "click" reaction (CuAAC) has become extremely popular as a highly efficient and selective method for the synthesis of 1,4-disubstituted 1,2,3-triazoles from substituted azides and terminal alkynes under mild conditions,[5] but the toxicity of copper compounds, inducing metabolic disorders and oxidative damage in biological systems,[6] is an limiting factor for their broader applications in bio-material chemistry and chemical biology. On the other hand, these limitations stimulate the design of copper complexes using available ligands for execution CuAAC reaction inside living cells[7] and important development of new metal-free methods for the synthesis of triazoles including N-unsubstituted ones.

NH-1,2,3-triazoles are also valuable compounds, which are widely used in organic and pharmaceutical chemistry. For example, among them are the antibacterial antibiotic Cefatrizine,[8] which also induces endoplasmic reticulum (ER) stress in breast cancer cells,[8b] antibiotic Radezolid, effective against serious multi-drug–resistant infections[9] (Fig. 1). Many 1,2,3-triazoles having *N*-unsubstituted moiety are found to be biologically active and useful as inhibitors of tuberculosis,[10] HIV-protease[11] and metallo-β-lactamase,[12] neurokinin-1 receptor antagonists[13] and ligands to produce remarkable coordination materials for optoelectronic applications.[14]

The main methods for the synthesis of NH-1,2,3-triazoles include the copper-catalyzed azide-alkyne cycloaddition,[15] palladium catalyzed synthesis of 1,2,3-triazoles from alkenyl halides and sodium azides,[16] the rearrangement of propargyl azide (Banert cascade),[17] thermal azide-alkyne Huisgen cycloaddition of hydrazoic acid,[18a] sodium azide,[18b] trimethylsilyl azide[18c-d] or at room temperature in water.[19] Alternate methods for the synthesis of 4-aryl-NH-1,2,3-triazoles based on the *p*-TsOH 1,3-dipolar cycloaddition of nitroolefins with sodium azide[20] or three-component reaction of aldehydes, nitroalkanes, and sodium azide,[21] enamines with highly electrophilic azides[22] have been developed over the last years. However, these methods are not applicable for the selective synthesis of the silicon or germanium substituted NH-1,2,3-triazoles.

Multicomponent methodology[23] was successfully used for the

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http://dx.doi.org/10.1016/j.tet.2017.05.077
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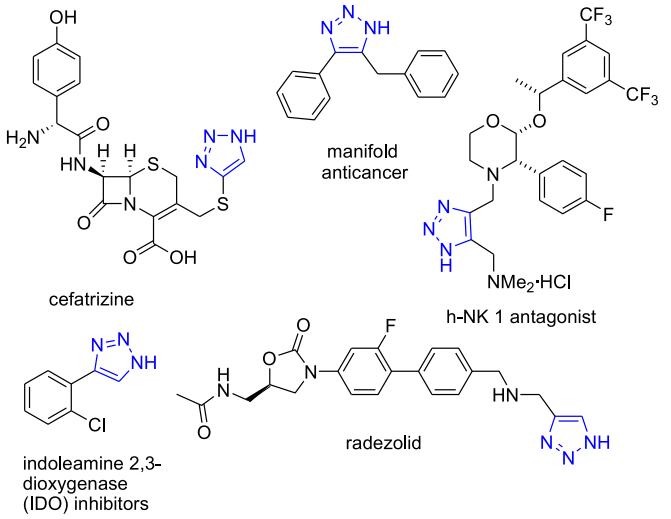

Fig. 1. Some biologically important NH-1,2,3-triazoles.

three-component copper(I)-catalyzed synthesis of 2-hydroxymethyl-2*H*-1,2,3-triazoles by cycloaddition of alkynes with sodium azide and formaldehyde, followed by removal of hydroxymethyl group under relatively harsh conditions to give NH-1,2,3-triazoles,[15a] 4,5-disubstituted NH-1,2,3-triazoles were prepared via one-pot three-component assembling from acid chlorides, terminal acetylenes, and sodium azide under ultrasonication-promoted Sonogashira coupling-1,3-dipolar cycloaddition.[15b] Metal- and alkyne-free methods for the three-component synthesis of 4-aryl-NH-1,2,3-triazoles involve the cycloaddition reactions of aldehydes, nitroalkanes and sodium azide,[21] the combination of enolizable ketones, nitrophenyl azide and NH_4OAc.[24]

NH-1,2,3-triazoles are served as key synthetic intermediates for the synthesis of new functionalized triazoles. Among them are the $FeCl_3$-catalyzed triazole propargylation of substituted propargyl alcohols,[25] synthesis of N-vinyl-1,2,3-triazoles via an Au(I) catalyzed NH-1,2,3-triazoles addition to non-activated alkyne,[26] asymmetric transannulation of NH-1,2,3-triazoles with olefins catalyzed by chiral dirhodium (II) complex in one-pot synthesis of 2,3-dihydropyrroles,[27] regioselective catalytic N-2 alkylation[28] and N-2 arylation.[29] Cascade assembling of organic paramagnetics 1,2,3-triazolyl-substituted nitronyl nitroxides was realized from the corresponding Me_3Si- or Et_3Ge-containing heterocyclic aldehydes and vicinal di(*N*-hydroxyamine) with followed by oxidation.[30]

Available substituted α,β-acetylenic aldehydes[31] bearing sterically unhindered aldehyde group and the activated triple bond are promising 1,3-biselectrophiles for the cascade syntheses of functionalized heterocyclic compounds with the participation of both reaction sites. Element-substituted propynals play a special role in the chemistry of α,β-acetylenic aldehydes. The presence of silicon and germanium heteroatoms at the triple bond of a propynal stabilizes the molecule of the aldehyde and the forming adducts, upon subsequent demetallation under mild reaction conditions, can afford analogs with the terminal triple bond.[32] This advantage of trialkylsilylpropynals is used in the synthesis of natural cytostatics – forboxazoles,[33] inhibitor of thrombocyte aggregation – xemilofibane.[34] An important role of silicon and germanium in comparison with carbon analogs in biological activity of organic molecules has been investigated in modern medicinal chemistry. Thus, the optimization of the therapeutic potential of drugs by the incorporation of silicon bioisosteres into known drug scaffolds due to the increased lipophilicity of organosilicon molecules is a modern strategy to improve biological activity and reduce toxicity of drugs.[35] A study on C/Si/Ge bioisosterism of amino acids clearly demonstrate that sila- and germa-substitution of amino acids may be a useful tool to improve the biological properties of peptides.[36]

We have shown that element-substituted propynals[31] can be successfully employed in the cascade assembling of polyfunctional N-[37] and O-[38] containing heterocycles via, *inter alia*, multicomponent reactions[39] involving both reaction sites. Recently, we have developed new efficient methods for the metal-free synthesis of *N*-unsubstituted 1,2,3-triazole carbaldehydes from the substituted propynals in water proceeding at room temperature[19] in contrast to thermal Huisgen processes.[18d] Also, MW-assisted three-component reaction between trimethylsilylpropynal, trimethylsilyl azide and hydroxylamine to afford trimethylsilyl-1*H*-1,2,3-triazole-5-carbaldehyde oxime[39d] and β-cyclodextrin-catalyzed three-component synthesis of 4,5-disubstituted 1*H*-1,2,3-triazoloalkylidenes *via* the reaction between substituted propynals, trimethylsilyl azide and malononitrile in water at room temperature have been elaborated.[39e]

In continuation of our research devoted to the metal-free synthesis of polyfunctional N-unsubstituted 1,2,3-triazoles, we have implemented for the first time microwave (MW)-assisted three-component reaction of propynals, trimethylsilyl azide and primary amines under solvent-free conditions to afford 4,5-disubstituted NH-1,2,3-triazoloimines and element-substituted 5-(1,3-thiazolan-2-yl)-1*H*-1,2,3-triazoles. The investigations of multicomponent reactions, application of microwave activation, and studies of solvent- and catalyst-free processes in fine organic synthesis are the trends in development of modern "green" chemistry.[40]

Schiff bases are very important compounds in pharmaceutics and medicine. Noteworthy, the imine group, present in such compounds, is shown to be critical to their biological activities.[41] Several derivatives of N-substituted 1,2,3-triazoles, containing quinoline and Schiff base moieties, exert a broad spectrum of antimicrobial and antifungal activity.[42] Schiff base ligands attract considerable attention due to their ability to produce stable complexes with a large number of transition metal ions.[43]

2. Results and discussion

Bifunctional heteronucleophiles 2-aminoethanol **3**, as well as well-known pharmacophore heterocylic amines 2-amino-5-methylthiazole **4**, 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one (4-aminoantipyrine) **5** and 2-aminoethanethiol **6** are employed as nucleophilic reagents (Fig. 2) in the multicomponent synthesis of NH-1,2,3-triazoloimines.

MW-assisted reaction between 3-trimethylsilyl-2-propyn-1-al **1a**, trimethylsilyl azide **2** and 2-aminoethanol **3** proceeds under solvent-free conditions to give 2-[[(*E*)-[1*H*-1,2,3-triazol-5-yl]methylidene]amino]-1-ethanol **7a** in 83% yield (Table 1, entry 1). The *E* configuration of the compound **7a** is indicated by the 1-*J*(CH) value of 156 Hz for the azomethine fragment.[44] Heterolysis of the $Si-C^2_{sp}$ bond is probably catalyzed by 2-aminoethanol as a base. In the case of 3-triethylgermyl-2-propyn-1-al **1b**, under analogous reaction conditions, 2-[[(*E*)-[4-(triethylgermyl)-1*H*-1,2,3-triazol-5-yl]methylidene]amino]-1-ethanol **7b** (entry 2) is prepared in 88%

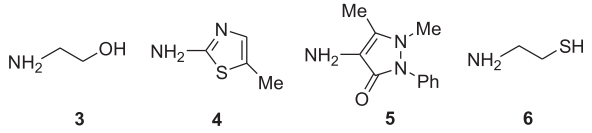

Fig. 2. Nucleophilic reagents.