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β-Cyclodextrin-catalyzed three-component synthesis of 4,5-disubstituted 1,2,3-(NH)-triazoles from propynals, trimethylsilyl azide and malononitrile in water

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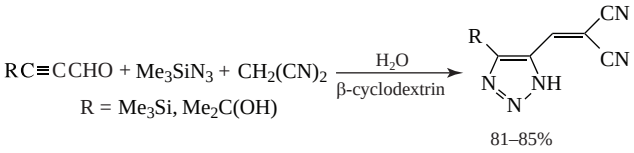
An efficient green method for the selective synthesis of new 4,5-disubstituted 1*H*-1,2,3-triazoloalkylidenes *via* the β-cyclodextrin-catalyzed three-component reaction between substituted propynals, trimethylsilyl azide and malononitrile in water at room temperature has been developed.



Despite the 1,2,3-triazoles do not occur in natural compounds, due to their versatile biological activity they have found a wide application in medicinal chemistry,[1] agrochemistry[2] and materials science.[3] Nowadays novel 1,2,3-triazole-based bis-heterocycles containing different pharmacophores have attracted considerable attention.[4] Conceptually new approach to the synthesis of functionalized triazoles *via* the copper-catalyzed azide-alkyne cycloaddition ('click' reaction) has become extremely popular for efficient and selective synthesis of 1,4-disubstituted 1,2,3-triazoles containing various functional groups.[5] This reaction has found numerous applications in many research fields including biochemistry and materials science.[6]

However, these methods tolerate only N-substituted 1,2,3-triazoles and terminal alkynes and just few protocols can be used for the synthesis of N-unsubstituted analogues from these alkynes. Many compounds containing the NH-triazole moiety are employed as antituberculosis, anti-HIV and anticancer agents, neurokinin-1 receptor antagonists, metallo-β-lactamase inhibitors[7] and ligands to produce remarkable coordination materials.[8]

Toxicity of copper compounds inducing metabolic disorders and oxidative damage in biological systems,[9] on the one hand, limits their application in click-chemistry, but, on the other hand, it stimulates the important development of new metal-free methods for triazole synthesis.

Recently, we have shown that water can be efficiently used as a solvent in the metal-free synthesis of N-unsubstituted 1,2,3-triazolecarbaldehydes from the substituted propynals[10] as compared to thermal Huisgen processes.[11] Available substituted α,β-acetylenic aldehydes[12] bearing sterically unhindered aldehyde group and the activated triple bond are promising 1,3-bielectrophiles for the cascade syntheses of heterocyclic compounds with the participation of both reaction sites.[13]

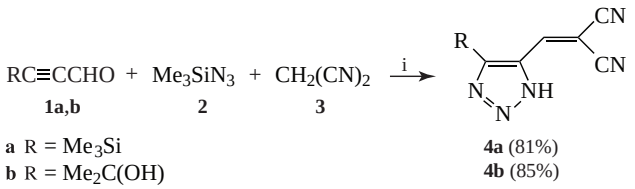
Multicomponent green syntheses are especially attractive for the preparation of NH-1,2,3-triazoles. Recently, we have obtained hardly accessible trimethylsilyl-1*H*-1,2,3-triazole-5-carbaldehyde oxime *via* MW-assisted three-component reaction between trimethylsilylpropynal, trimethylsilyl azide and hydroxylamine.[14] In continuation of our research devoted to the synthesis of polyfunctional N-unsubstituted 1,2,3-triazoles, we have implemented for the first time β-cyclodextrin-catalyzed three-component reaction of propynals, trimethylsilyl azide and malononitrile in water at ambient temperature to afford 4,5-disubstituted 1,2,3-(NH)-triazoles. Alkylidene- and arylidenemalononitriles are versatile synthons for the synthesis of structurally diverse 2,6-dicyanoanilines[15] and heterocyclic compounds with good pharmaceutical profiles[16] or fluorophores.[17]

Cyclodextrins (CDs) are cyclic oligosaccharides containing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high efficiency and selectivity. They promote the reactions by supramolecular catalysis involving reversible formation of host–guest complexation by noncovalent bonding as seen in enzymes, allowing its performance under biomimetic conditions.[18] Evidence for host–guest complexation of β-CD with hydrophobic trimethylsilyl propynal in aqueous phase was supported using ^{1}H NMR spectroscopy in our previous work.[19] This prompted us to carry out supramolecular synthesis of new highly functionalized 4,5-disubstituted 1*H*-1,2,3-triazoloalkylidenes from propynals catalyzed by β-CD in water.

The successful application of β-CD in the one-pot synthesis of heterocyclic compounds on the example of acetylenedicarboxylic esters was reported.[20] Recently, 1,4-disubstituted 1,2,3-triazoles were obtained from terminal alkynes by the β-CD-promoted 'click' reaction in water.[21] However, the reactions of ambident propynals catalyzed by β-CD were not described until now.

The reaction of the acetylenic aldehydes **1a**,**b**, trimethylsilyl azide and malononitrile was carried out upon simultaneous administration of the reactants in the presence of 1 equiv. of β-CD in water at room temperature for 4 h. Hitherto unknown products **4a**,**b** were isolated after column chromatography in 81 and 85% yields, respectively (Scheme 1).†

† ^{1}H and ^{13}C NMR spectra (400.13 and 100.61 MHz, respectively) were recorded on a Bruker DPX-400 spectrometer at ambient temperature in DMSO-d_6 and referenced to TMS as an internal standard. IR spectra were

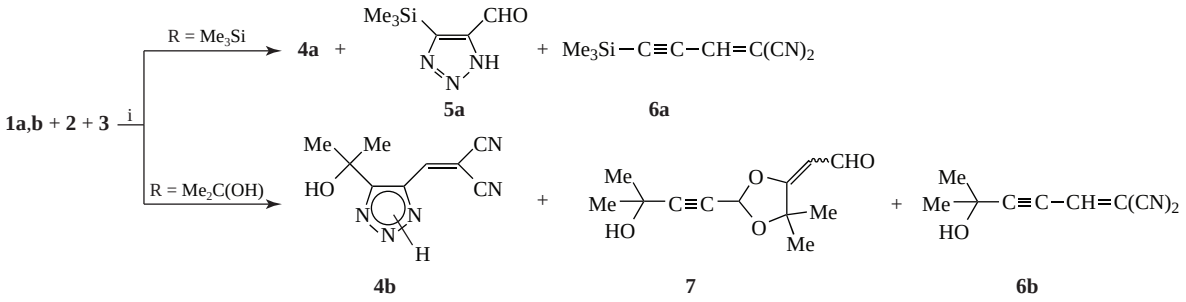


Scheme 1 *Reagents and conditions*: i, β-CD cat., H_2O, 25 °C, 4 h.

For comparison, the same reactions were carried out in the abscence of β-CD. According to the ^{1}H NMR data, the reactions proceeded in those cases non-selectively (Scheme 2).‡

Thus, in the case of ynal **1a** after 4 h the reaction mixture contained the target adduct **4a**, triazolecarbaldehyde **5a**, enyne **6a** and malononitrile in a molar ratio of 47 : 40 : 6 : 7, respectively (^{1}H NMR). The similar reaction of ynal **1b** gave, along with the target adduct **4b** (as a mixture of NH-tautomers in a 1:1 ratio), 1,3-dioxolane **7**, the product of the initial aldehyde dimerization, enyne **6b** and malononitrile in a molar ratio of 70 : 17 : 5 : 8. The higher content of the target adduct **4b** in this case compared to the case with **4a** can be explained by partial solubility of **1b** in water in contrast to hydrophobic trimethylsilylpropynal **1a**. We have found that dimerization of γ-hydroxy alkynals to acetylenic 1,3-dioxolanes of type **7** is catalyzed by amines.[22] Apparently, in this case, dimerization process is catalyzed in water by triazole **4b** as a weak base. Note, that low reactivity of the weakly polarized triple bond of enyne **6a** in the cycloaddition of 4-dimethylaminophenyl azide under thermal and 'click' reaction conditions is known.[23]

In the presence of β-CD, the content of the target products **4a**,**b** in the reaction mixture after 4 h was 90 (**4a**) and 93% (**4b**), the side products were not detected. These results clearly point to significant acceleration of the tandem process 1,3-dipolar cycloaddition/Knoevenagel condensation to afford dicyanovinyl-substituted NH-1,2,3-triazoles. Importantly, under these conditions, like to trimethylsilylpropynal, the regiospecific 1,3-dipolar cycloaddition of hydrazoic acid to ynal **1b** in the presence of



Scheme 2 *Reagents and conditions*: i, H_2O, 25 °C, 4 h.

recorded on a Bruker Vertex-70 spectrometer as KBr pellets. Elemental analysis was performed on a Thermo Finnigan FlashEA 1112 gas analyzer. Melting points were determined on a Micro Hot Stage PolyTherm A apparatus.

3-Trimethylsilyl-2-propyn-1-al and 4-hydroxy-4-methyl-2-pentynal were prepared by published procedure.[12] Column chromatography and TLC were carried out on kieselgel (Merck, type 60, 70–230 mesh, 60 Å), with chloroform–methanol (10:1) as an eluent.

Compounds **4a**,**b** (*general procedure*). β-CD (1 mmol) was dissolved in water (8 ml) by warming to 60 °C until a clear solution was formed. To this clear solution, acetylenic aldehyde **1a**,**b** (1 mmol) and trimethylsilyl azide (1.2 mmol) were added. After stirring for 10 min the solution of malononitrile (1 mmol) in H_2O (2 ml) was added and the mixture was stirred at room temperature for 4 h until completion of the reaction as indicated by ^{1}H NMR. ^{1}H NMR reaction control was made for selected portions (1 ml) every hour. The extract from reaction mixture with ethyl acetate was evaporated *in vacuo* and analyzed in DMSO-d_6. Then β-CD was filtered off, the aqueous phase was extracted with ethyl acetate (3x5 ml). The combined extracts were washed with 5 ml of water and dried over $MgSO_4$. The filtrate was evaporated *in vacuo*, and column chromatography of the residue afforded the target compounds. Visualization on TLC was made with iodine vapor.

*2-[(4-Trimethylsilyl-1*H*-1,2,3-triazol-5-yl)methylidene]malononitrile* **4a**. Yield 0.176 g (81%), colorless solid, mp 180−181 °C. ^{1}H NMR δ: 0.41 (s, 9 H, $SiMe_3$), 8.22 (s, 1H, CH=C), 15.49 (br. s, 1H, NH). ^{13}C NMR δ: −1.09 ($SiMe_3$), 80.2 [=*C*(C≡N)$_2$], 113.33 (C≡N), 114.64 (C≡N), 144.41 (C^4), 148.81 (CH=), 150.47 (C^5). IR (KBr, ν/cm^{-1}): 3260 (NH), 2240, 2226 (C≡N), 1607 (C=C), 1257, 855, 767 ($SiMe_3$); 1661, 1437, 1321, 1217 (triazole ring). Found (%): C, 49.35; H, 5.27; N, 32.42; Si, 12.96. Calc. for $C_9H_{11}N_5Si$ (%): C, 49.74; H, 5.10; N, 32.23; Si, 12.92.

*2-{[4-(1-Hydroxy-1-methylethyl)-1*H*-1,2,3-triazol-5-yl]methylidene}malononitrile* **4b**. Yield 0.173 g (85%), colorless crystals, mp 162−164 °C. ^{1}H NMR δ: 1.53 (s, 6 H, 2Me), 5.76 (br. s, 1H, OH), 8.54 (s, 1H, CH=), 15.63 (br. s, 1H, NH). ^{13}C NMR δ: 31.0 (2Me), 68.85 (COH), 79.34 [=*C*(C≡N)$_2$], 113.14 (C≡N), 114.72 (C≡N), 135.18 (C^5), 149.19 (CH=), 152.57 (C^4). IR (KBr, ν/cm^{-1}): 3440 (OH), 3260 (NH), 2274, 2234 (C≡N), 1610 (CH=C), 1633, 1532, 1463, 1305, 1232 (triazole ring). Found (%): C, 53.37; H, 4.32; N, 34.28. Calc. for $C_9H_9N_5O$ (%): C, 53.20; H, 4.46; N, 34.47.

‡ *Reactions* **1** + **2** + **3** *in the absence of β-CD*. A mixture of ynal **1a**,**b** (1 mmol), trimethylsilyl azide (1.2 mmol) and malononitrile (1 mmol) in H_2O (10 ml) was stirred at room temperature for 4 h. After extraction with ethyl acetate (3×5 ml), the combined extracts were washed with 5 ml of water and dried over $MgSO_4$. The volatiles were removed *in vacuo* and the residue was analyzed by ^{1}H NMR spectroscopy.

Reaction **1a** + **2** + **3**. The residue was an oily yellow solid (0.069 g). Along with **4a**, 4-trimethylsilyl-1*H*-1,2,3-triazole-5-carbaldehyde **5a**,[11] 2-(3-trimethylsilylprop-2-ynylidene)malononitrile **6a**[24] and malononitrile were detected in a molar ratio of 47 : 40 : 6 : 7, respectively. ^{1}H NMR data of compounds **5a** and **6a** were consistent with the literature ones.

Reaction **1b** + **2** + **3**. The residue was an oily yellow solid (0.083 g). According to ^{1}H NMR data, the product contained compound **4b** (two tautomers, 1:1), ^{1}H NMR δ: 1.54, 1.41 (s, 6 H, 2Me), 5.90 (br. s, 1H, OH), 5.57 (br. s, 1H, OH), 8.62 (s, 1H, CH=), 8.45 (s, 1H, CH=), 15.72, 15.59 (br. s, 1H, NH); *Z*,*E*-2-[2-(3-hydroxy-3-methylbut-1-ynyl)-5,5-dimethyl-1,3-dioxolan-4-yliden]acetaldehyde **7**,[22] 2-(4-hydroxy-4-methyl-2-pentynylidene)malononitrile **6b** and malononitrile in a ratio of 70 : 17 : 5 : 8, respectively.

2-(4-Hydroxy-4-methylpent-2-ynylidene)malononitrile **6b** *(independent synthesis)*. Malononitrile (0.264 g, 4 mmol) was added to a magnetically stirred solution of aldehyde **1b** (0.224 g, 2 mmol) in DMSO (2 ml) and the solution was stirred at room temperature for 8 h. Then a mixture was diluted with H_2O (4 ml), extracted with Et_2O (3×4 ml) and dried over $MgSO_4$. Evaporation of the volatiles *in vacuo* gave compound **6b** [0.163 g (51%)] as a yellow oily liquid. ^{1}H NMR ($CDCl_3$) δ: 1.60 (s, 6 H, 2Me), 3.2 (br. s, 1H, OH), 3.25 (br. s, 1H, OH),), 6.96 (s, 1H, CH=). ^{13}C NMR δ: 30.90 (2Me), 65.79 (COH), 96.42 [=*C*(C≡N)$_2$], 110.93 (C≡N), 111.93 (C≡N), 141.11 (CH=), 116.75 (HOC*C*≡C), 120.10 (C≡*C*CH=). Found (%): C, 67.37; H, 5.32; N, 17.28. Calc. for $C_9H_8N_2O$ (%): C, 67.49; H, 5.03; N, 17.49.

$CH_2(CN)_2$ occurs to furnish compound **4b**. We have shown earlier that the reaction between γ-hydroxyalkynals and trimethylsilyl azide in water proceeds to form 4-hydroxyalkyl-1*H*-1,2,3-triazole-5-carbaldehydes as a mixture of regioisomers.[10(*b*)]

The efficiency and selectivity of the β-CD-catalyzed multicomponent reaction can be explained by the decrease in volatility of propynals due to the complexation, an increase in water-solubility and reactivity of the formed complex to give the target polyfunctional 1*H*-1,2,3-triazoles under metal-free mild conditions.

In conclusion, we have accomplished for the first time the β-cyclodextrin-catalyzed green three-component synthesis of hitherto unknown 4,5-disubstituted 1*H*-1,2,3-triazoloalkylidenes in high yields from substituted propynals, trimethylsilyl azide and malononitrile in water at room temperature.

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