One-pot three-component green synthesis of [1*H*-(1,2,3-triazol-5-yl)methylidene] heterocycles based on element-substituted propynals*

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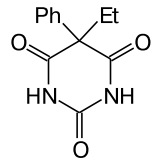
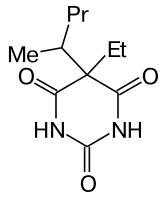
The one-pot three-component synthesis of polyfunctional bis-heterocyclic triazoles, namely, previously unknown 1*H*-1,2,3-triazolylmethylidenepyrimidines and -1,3-dioxanes, was performed for the first time in moderate or high yields starting from element-substituted propynals, trimethylsilyl azide, and heterocyclic CH-acids at room temperature in aqueous medium.

Key words: one-pot multicomponent synthesis, element-substituted propynals, barbituric acids, Meldrum´s acid, NH-1,2,3-triazolylmethylidenepyrimidines and 1,3-dioxanes, green chemistry.

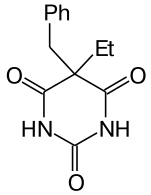
The barbituric acid derivatives (pyrimidine-2,4,6-triones) are widely used in medicine as tranquilizers (phenobarbital, nembutal) and hypnotic agents. Even minor structure modifications, especially variations of substituents at the carbon atom in position 5, can have a crucial influence on the biological activity of these compounds.[1,2]



Phenobarbital



Nembutal



5-Benzyl-5-ethylbarbituric acid

Owing to the presence of highly electrophilic double bond, alkylidene and arylmethylidene barbituric acid and Meldrum´s acid derivatives, including those generated *in situ*, are widely used in organic synthesis,[3,4] in asymmetric synthesis of the antibacterial agent (–)-PNU-286607,[5] and in the multicomponent assembly of various heterocycles.[6,7] The goal of the present study is to develop a synthetic route to previously unknown 1*H*-1,2,3-triazolylmethylidene derivatives based on heteroatom-substituted propynals, barbituric or *N*,*N*´-dimethylbarbituric acid, and Meldrum´s acid.

Results and Discussion

Accessible α,β-acetylenic aldehydes,[8] highly efficient ambident 1,3-bielectrophiles containing sterically unhindered aldehyde group and an activated triple bond, have been used previously for the cascade synthesis of polyfunctional heterocyclic compounds involving both reaction centers.[9—17] 1,2,3-Triazoles represent a practically important class of heterocycles used in biochemistry, medicinal chemistry, and agrochemistry and in the design of new materials.[18—22] Their practical value is caused by important properties of the triazole ring: chemical stability, high dipole moment, heteroaromatic nature, and the ability to form hydrogen bonds.[23—25] NH-1,2,3-Triazoles serve as ligands for the coordination materials used for the design of optoelectronic devices;[26,27] they are used as pharmaceuticals, *viz.,* as the antibacterial antibiotic cefatrizine, [28] which also has an anticancer activity;[29] antibiotic radezolid with a broad spectrum of activity,[30,31]

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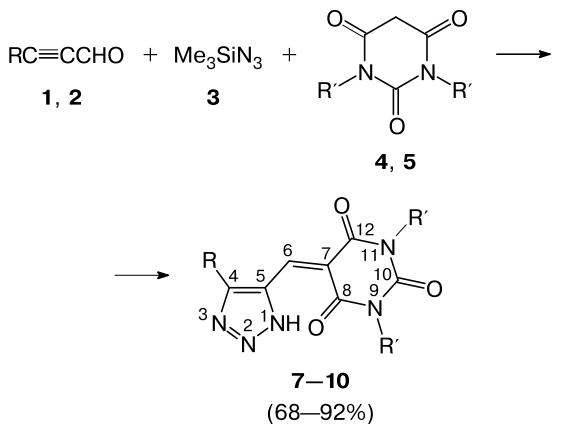
HIV protease inhibitors,[32] and neurokinin-1 antagonists.[33] A combination of two pharmacophores in one molecule is a well studied modern approach to the synthesis of more efficient drugs.[34] The preparation of dual-action hybrid molecules is a major route to the design of new effective drugs, including biologically important NH-1,2,3-triazoles.[28—33]

Recently, we have revealed high efficiency of water as the reaction medium for the synthesis of *N*-unsubstituted 1,2,3-triazolecarbaldehydes from substituted propynals in the absence of metal catalysts at room temperature[35,36] in comparison with the Huisgen thermal reaction in organic solvents.[37] Efficient green methods have been developed for the synthesis of new 4,5-disubstituted 1*H*-1,2,3-triazolylalkylidene derivatives by three-component reaction of substituted propynals with trimethylsilyl azide and malononitrile catalyzed by β-cyclodextrin in water at room temperature;[38] trimethylsilyl-1*H*-1,2,3-triazole-5-carbaldehyde oxime by the microwave (MW) assisted three-component reaction of trimethylsilylpropynal, trimethylsilyl azide, and hydroxylamine;[39] and NH-1,2,3-triazoleimines by MW-assisted three-component reaction in the absence of catalysts and solvents.[40]

As a continuation of these studies, we developed the first one-pot method for the synthesis of new, practically valuable 4,5-disubstituted 1*H*-1,2,3-triazolylmethylidene heterocycles from 3-trimethylsilyl(triethylgermyl)-2-propynals **1** and **2**, trimethylsilyl azide (**3**), and heterocyclic CH-acids (barbituric (**4**), *N*,*N*′-dimethylbarbituric (**5**), and Meldrum´s acids (**6**)) under green chemistry conditions, that is, in water at room temperature. The reactions with barbituric acids **4** and **5** proceed smoothly under these conditions at an equimolar reactant ratio to give the target NH-1,2,3-triazolebarbiturates **7—10** in high yields of 68—92% (Scheme 1).

Scheme 1



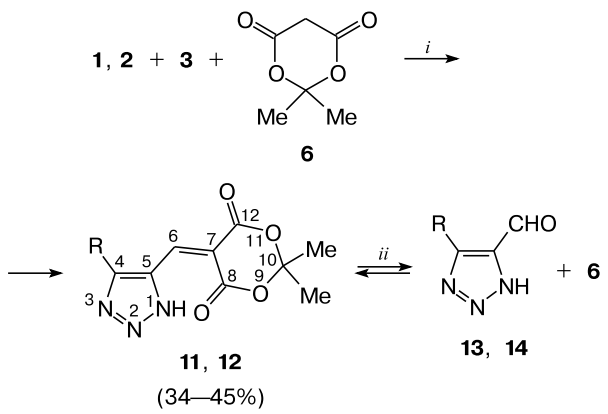
R = Me_3Si (**1**), Et_3Ge (**2**); R′ = H (**4**), Me (**5**);
R = Me_3Si, R′ = H (**7**); R = Et_3Ge, R′ = H (**8**);
R = Me_3Si, R′ = Me (**9**); R = Et_3Ge, R′ = Me (**10**)

Reagents and conditions: H_2O, 25 °C, 38 h.

The obtained compounds are colorless powders with m.p. 128—260 °C, poorly soluble in most organic solvents. Their structures were determined by IR spectroscopy and ^1H and ^{13}C NMR spectroscopy, and the compositions were confirmed by elemental analysis. According to ^1H NMR spectroscopy data, the reaction occurs as a domino process including 1,3-dipolar cycloaddition and Knoevenagel condensation. These reactions in water are facilitated by the formation of gem-diols of the initial propynals,[41] which increases the water solubility of propynals, decreases their volatility, and prevents resinification typical of their reactions.

Triazolylmethylidene derivatives **11** and **12** of Meldrum´s acid **6** were prepared under analogous conditions in satisfactory yields of 34—45% (Scheme 2). The relatively low yields of compounds **11** and **12** may be attributable to reversibility of the Knoevenagel condensation step.

Scheme 2



R = Me_3Si (**11**, **13**), Et_3Ge (**12**, **14**)

Reagents and conditions: *i*. H_2O, 25 °C, 38 h; *ii*. H_2O, 25 °C.

According to ^1H NMR spectroscopy, in the case of trimethylsilylpropynal **1**, the reaction mixture after 38 h contains 4-trimethylsilyl-1*H*-1,2,3-triazole-5-carbaldehyde (**13**) together with the target 2,2-dimethyl-5-(4-trimethylsilyl-1*H*-1,2,3-triazol-5-yl)methylidene-1,3-dioxane-4,6-dione (**11**), the **11** to **13** molar ratio being 42 : 58. In the reaction mixture isolated after 100 h, the content of intermediate triazolecarbaldehyde **13** has somewhat increased and the **11** to **13** molar ratio was 37 : 63 (^1H NMR data (DMSO-d_6)). The proton chemical shifts of triazoloalkylidene **11** (δ 8.18, s, 1 H (CH=C)) and triazole-5-carbaldehyde **13** (δ 10.13, s, 1 H (CHO)) served as the characteristic values.

Previously, we detected low reactivity of the triple bond of enyne $Me_3SiC{\equiv}CCH{=}C(CN)_2$ towards the cycloaddition of trimethylsilyl azide in water at room temperature,[38] caused by weak polarization of the triple bond. The considerable inertness of the triple bond of this Knoevenagel adduct towards the cycloaddition of 4-di-

methylaminophenyl azide under either thermal or click reaction conditions has been demonstrated earlier.[42]

The role of silicon and germanium in the biological activities of organic molecules is a topical issue for modern medicinal chemistry. It was shown that introduction of silicon into known drugs increases their lipophilicity in comparison with carbon analogs, which can be employed to increase their efficiency and reduce their toxicity.[43,44] Study of the C/Si/Ge bioisosterism of amino acids clearly indicates that the replacement of carbon in amino acids by silicon or germanium may serve as a useful tool for improving the biological properties of peptides.[45]

Thus, we developed a new, one-pot, atom-economic, green method for the synthesis of binuclear heterocycles, NH-1,2,3-triazoloalkylidenepyridines and -1,3-dioxanes, from element-substituted propynals, trimethylsilyl azide, and heterocyclic CH-acids. The benefits of the method include accessibility of the starting propynals, the absence of metal catalysts, the aqueous medium, room temperature, high or moderate yields, and no need for chromatographic purification of the target products. The previously unknown bis-heterocyclic triazoloalkylidenes, namely, polyfunctional *N*-unsubstituted 1,2,3-triazoles containing interrelated nucleophilic and electrophilic reaction centers, are promising biologically active compounds, ligands for metal complex catalysts, and platforms for the design of new polyfunctional 1,2,3-triazole derivatives, including hybrid molecules.

Experimental

IR spectra were recorded on a Bruker Vertex-70 instrument in KBr pellets or thin film. ^{1}H and ^{13}C NMR spectra were obtained on Bruker DPX-400 and Bruker AV-400 spectrometers (operating at 400.1 MHz (^{1}H) or 100.62 MHz (^{13}C)) in DMSO-d_6, with the residual DMSO signals serving as internal standards (δ_H 2.50, δ_C39.50). Elemental analysis of the reaction products was carried out on a Thermo Finnigan Flash EA 1112 analyzer. The melting points were determined on a Micro-Hot-Stage PolyTherm A instrument. The mixtures were analyzed and the product purity was checked by TLC on Silufol UV-254 plates in the chloroform—methanol (20 : 1) system; the spots were visualized by iodine vapor. 3-Trimethylsilyl-2-propynal (**1**) was prepared by a known procedure;[8] 3-triethylgermyl-2-propynal (**2**) was synthesized by a published procedure.[46] For ^{1}H NMR monitoring of the reaction, the aqueous phase of the reaction mixture (1 mL) was extracted with ethyl acetate (3×5 mL), the combined filtrate was washed with cold water and methanol (5 mL) and dried with $MgSO_4$. After removal of the solvents *in vacuo*, the residue was analyzed by ^{1}H NMR (DMSO-d_6).

One-pot three-component synthesis of NH-1,2,3-triazoloalkylidenes (7—12) (general procedure). Trimethylsilyl azide (1 mmol) was added dropwise to a mixture of propynal (1.0 mmol) and water (2 mL), and the mixture was stirred for 18 h at room temperature. Barbituric acid (or Meldrum´s acid) (1.0 mmol) was added, and the mixture was stirred for 20 h at room temperature. Water (2 mL) was added, and the precipitate was collected on a filter, washed with water and cold methanol, and dried at a reduced pressure.

5-[(4-Trimethylsilyl-1*H*-1,2,3-triazol-5-yl)methylidene]-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (7). Yield 0.19 g (68%). Colorless powder, m.p. >260 °C (decomp.). ^{1}H NMR (DMSO-d_6), δ: 0.41 (s, 9 H, Me_3Si); 8.25 (s, 1 H, CH=C); 11.48 (br.s, 2 H, NH(C=O)NH). ^{13}C NMR (DMSO-d_6), δ: –0.5 (Me_3Si); 119.9 (C(7)); 140.5 (C(4)); 143.0 (C(5)); 150.8 (C(10)=O); 163.3 (CH=C); 166.5 (C(12)=O); 170.2 (C(8)=O). IR (KBr), ν/cm^{-1}: 3187, 3066 (NH); 1716 (C=O); 1709 (C=O); 1688 (C=O); 1588 (CH=C); 1260, 848, 763 (Me_3Si); 1642, 1557, 1474, 1321, 1248 (triazole ring). Found (%): C, 43.21; H, 4.52; N, 25.14; Si, 10.13. $C_{10}H_{13}N_5O_3Si$. Calculated (%): C, 43.00; H, 4.69; N, 25.07; Si, 10.05.

5-[(4-Triethylgermyl-1*H*-1,2,3-triazol-5-yl)methylidene]-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (8). Yield 0.34 g (92%). Colorless powder, m.p. 184—186 °C. ^{1}H NMR (DMSO-d_6), δ: 0.99—1.12 (m, 15 H, Et_3Ge); 8.15 (s, 1 H, CH=C); 14.68 (br.s, 2 H, NH(C=O)NH). ^{13}C NMR (DMSO-d_6), δ: 4.9 (CH_2Ge); 9.1 (CH_3); 118.8 (C(7)); 140.4 (C(4)); 142.6 (C(5)); 150.8 (C(10)=O); 163.4 (CH=C); 168.9 (C(12)=O); 170.1 (C(8)=O). IR (KBr), ν/cm^{-1}: 3184, 3150 (NH); 1711 (C=O); 1620 (CH=C); 1650, 1550, 1463, 1327, 1234 (triazole ring). Found (%): C, 42.43; H, 5.11; Ge, 19.73; N, 19.20. $C_{13}H_{19}GeN_5O_3$. Calculated (%): C, 42.67; H, 5.23; Ge, 19.84; N, 19.14.

1,3-Dimethyl-5-[(4-trimethylsilyl-1*H*-1,2,3-triazol-5-yl)-methylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (9). Yield 0.22 g (71%). Colorless powder, m.p. 135—137 °C. ^{1}H NMR (DMSO-d_6), δ: 0.41 (s, 9 H, Me_3Si); 3.19 (s, 3 H, CH_3); 3.23 (s, 3 H, CH_3); 8.31 (s, 1 H, CH=C). ^{13}C NMR (DMSO-d_6), δ: –0.5 (Me_3Si); 28.4 (NMe); 29.0 (NMe); 98.4 (C(7)); 142.5 (C(4)); 144.9 (C(5)); 151.5 (C(10)=O); 162.5 (CH=C); 169.3 (C(12)=O); 169.6 (C(8)=O). IR (KBr), ν/cm^{-1}: 3147 (NH); 1691 (C=O); 1658 (CH=C); 1263, 854, 761 (Me_3Si); 1623, 1554, 1452, 1315, 1219 (triazole ring). Found (%): C, 46.50; H, 5.43; N, 22.51; Si, 9.20. $C_{12}H_{17}N_5O_3Si$. Calculated (%) C, 46.89; H, 5.57; N, 22.78; Si, 9.14.

1,3-Dimethyl-5-[(4-triethylgermyl-1*H*-1,2,3-triazol-5-yl)-methylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione (10). Yield 0.36 g (92%). Colorless powder, m.p. 128—129 °C. ^{1}H NMR (DMSO-d_6), δ: 0.97—1.12 (m, 15H, Et_3Ge); 3.23 (s, 6 H, $(CH_3)_2$); 8.22 (s, 1 H, CH=C). ^{13}C NMR (DMSO-d_6), δ: 4.9 (CH_2Ge), 9.1 (CH_3), 28.5 (NMe), 29.0 (NMe), 141.1 (C(4)); 143.3 (C(5)); 160.8 (CH=C), 151.6 (C(10)=O); 162.3 (C(12)=O), 162.6 (C(8)=O). IR (KBr), ν/cm^{-1}: 3146 (NH); 1691 (C=O); 1679 (C=O); 1625 (CH=C); 1660, 1554, 1450, 1310, 1243 (triazole ring). Found (%): C, 45.24; H, 5.69; Ge, 18.51; N, 17.25. $C_{15}H_{23}GeN_5O_3$. Calculated (%): C, 45.73; H, 5.88; Ge, 18.43; N, 17.78.

2,2-Dimethyl-5-[(4-trimethylsilyl-1*H*-1,2,3-triazol-5-yl)-methylidene]-1,3-dioxane-4,6-dione (11). Yield 0.1 g (34%). Colorless powder, m.p. 149—151 °C. ^{1}H NMR (DMSO-d_6), δ: 0.42 (s, 9 H, Me_3Si); 1.79 (s, 6 H, $(CH_3)_2$); 8.18 (s, 1 H, (CH=C); 15.52 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: –0.7 (Me_3Si); 27.56, 30.9 (2 CH_3); 104.7 (C(10)); 115.8 (C(7)); 141.5 (C(4)); 143.1 (C(5)); 144.3 (CH=C); 158.9 (C(12)=O); 162.1 (C(8)=O). IR (KBr), ν/cm^{-1}: 3150 (NH); 1711

(C=O); 1620 (CH=C); 1650, 1550, 1463, 1327, 1234 (triazole ring). Found (%): C, 48.50; H, 5.57; N, 14.17; Si, 9.65. $C_{12}H_{17}N_3O_4Si$. Calculated (%): C, 48.80; H, 5.80; N, 14.23; Si, 9.51.

2,2-Dimethyl-5-[(4-triethylgermyl-1*H*-1,2,3-triazol-5-yl)-methylidene]-1,3-dioxane-4,6-dione (12). Yield 0.17 g (45%). Colorless powder, m.p. 137—138 °C. ^{1}H NMR (DMSO-d_6), δ: 1.03—1.18 (m, 15 H, Et_3Ge); 1.80 (s, 6 H, $(CH_3)_2$); 8.08 (s, 1 H, CH=C); 15.46 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 4.7 (CH_2Ge); 8.9 (CH_3); 27.5 (2 CH_3); 104.5 (C(10)); 114.9 (C(7)); 141.5 (C(4)); 143.3 (C(5)); 145.0 (CH=C); 158.4 (C(12)=O); 162.7 (C(8)=O). IR (KBr), ν/cm^{-1}: 3147 (NH); 1691 (C=O); 1658 (CH=C); 1263, 854, 761 (Me_3Si); 1623, 1554, 1452, 1315, 1219 (triazole ring). Found (%): C, 47.04; H, 6.15; Ge, 19.27; N, 11.15. $C_{15}H_{23}GeN_3O_4$. Calculated (%): C, 47.16; H, 6.07; Ge, 19.02; N, 11.00.

The major results were obtained using the equipment of the Baikal analytical center for collective use (Irkutsk Scientific Center, Siberian Branch, Russian Academy of Sciences).

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