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CHEMISTRY

Synthesis of 1,3-Dioxacyclan-2-yl-Substituted 1,2,3-Triazoles

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Abstract—A new method for preparing 4-(1,3-dioxacyclan-2-yl)-5-phenyl-1,2,3-triazoles in 30–75% yields has been developed on the basis of azide–alkyne cycloaddition to 2-phenylethinyl-1,3-dioxacyclanes. It has been shown that the best results are achieved when the reaction is carried out at 150–155°C in DMSO.

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The compounds of triazole series show distinct biological activity, which causes its efficient application as chemical weed and pest killers [1–5]. Triazole derivatives containing 1,3-dioxocyclane fragments are of intrinsic interest, in particular, Etaconazole and Propiconazole, which find an application as systemic fungicides for crop protection [2, 6]. We developed new methods for the synthesis of triazoles containing 1,3-dioxacyclane substituents in the side chain. These compounds can be used as herbicides and chemicals in the previously developed syntheses of polyfunctional reagents [7, 8].

Preparatively available 1-phenyl-3,3-diethoxyprop-1-yne **1** [9] was converted into phenylpropynal **2**, which was transformed by reacting with sodium azide into heterocyclic aldehyde **3** followed by its cyclization with glycols **4a**–**4e** into target 1,3-dioxacycloalkanes **5a–5e**. The yields of the products were within 20–25%.

An alternative method for preparation of the latter compounds consisted in the transacetalization of compound **1** with glycols **4a**–**4e** followed by the treatment of 1,3-dioxacycloalkanes **6a**–**6e** with sodium azide to give target compounds **5a–5e** (yield 30–75%) (Scheme 1).

The comparison of the two competitive synthetic routes showed that the second route is more efficient because the reaction of heterocyclic aldehyde **3** with diols **4a**–**4e** in the first case is accompanied by tar formation, which decreases yield and hampers isolation of the target substituted triazoles **5a–5e**.

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The structure of the obtained compounds was proved by mass spectrometry and ^{1}H NMR.

The mass spectra (electron impact, 70 eV) of compounds **5a–5e** show the peaks of molecular ions $[M]^{+\cdot}$ and $[M-H]^+$, whose intensity varies within 60–100%. The general direction of molecular ions decomposition is the cleavage of C–O bonds of 1,3-dioxacyclane moiety resulting in emergence of peaks with *m/z* 189 (Scheme 2).

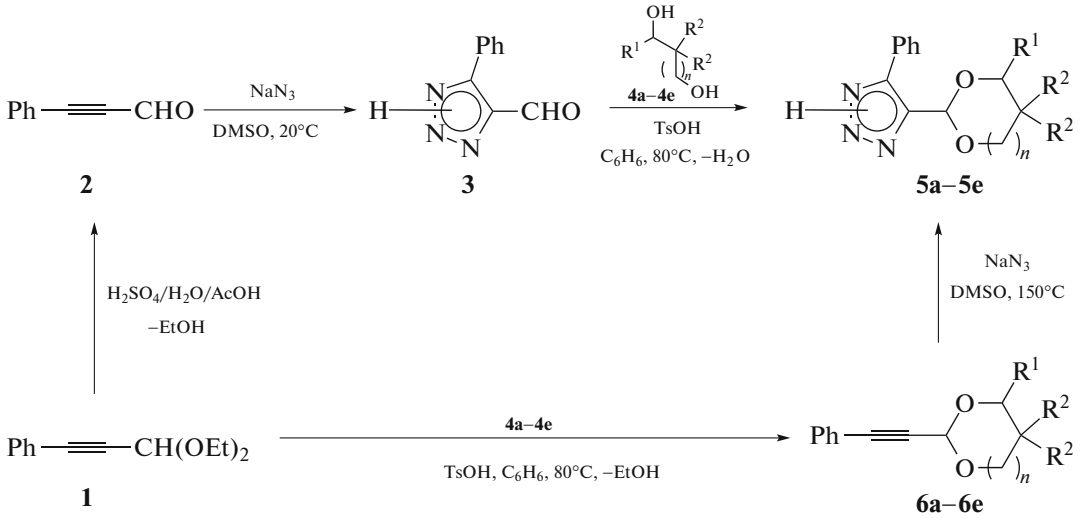
Further decomposition leads to formation of peaks with *m/z* = 172 and 144. The elimination of N_2 and HCN molecules typical for degradation of 1,2,3-triazole ring is the final stage of fragmentation [10].

The ^{1}H NMR spectra of triazoles **5a–5e**[1] show characteristic proton signals of CH_2 groups of dioxacyclane ring at δ_H = 3.6–4.2 ppm and a signal at δ_H = 6 ppm corresponding to the proton of the methine group (H^2). The spectrum of compound **5e** displays two singlets at δ_H = 0.80 and 1.30 ppm corresponding to the protons of axial and equatorial CH_3 groups, respectively, which indicates the rigid conformation of this ring.

The protons of alkyl groups R^1 (δ_H = 0.8–2 ppm) and dioxacyclane ring in compounds **5b**–**5d** give a series of multiplets. It was difficult to assign unambiguously the signals to one or another diastereomer and perform their strict integration. Two singlets in the region δ_H = 6.1–6.3 ppm correspond to the protons of methine groups (H^2) of two diastereomers.

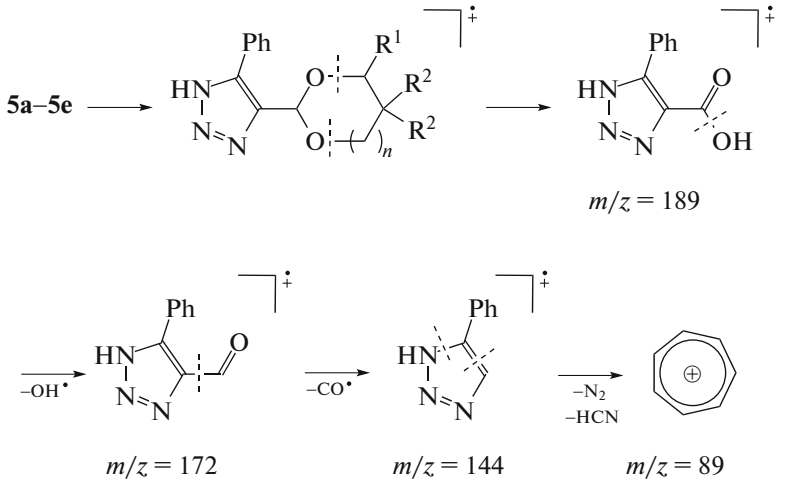
The spectra of all triazoles **5a–5e** include typical broadened singlet (br s) (δ_H = 10–11.6 ppm) of the proton of 1,2,3-triazole ring.

[1] 1,3-Dioxolanes **5b** and **5c** were isolated as mixtures of *cis* and *trans* isomers.



$R^1 = R^2 = H$, $n = 0$ (**a**); $R^1 = Me$, $R^2 = H$, $n = 0$ (**b**); $R^1 = Pr$, $R^2 = H$, $n = 0$ (**c**);
$R^1 = Me$, $R^2 = H$, $n = 1$ (**d**); $R^1 = H$, $R^2 = Me$, $n = 0$ (**e**)

Scheme 1.



Scheme 2.

Thus, we have developed a new method of synthesis of previously unknown 4-(1,3-dioxacyclan-2-yl)-5-phenyl-1,2,3-triazoles, which are of interest as potentially useful biologically active compounds.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (operating at 300 and 75 MHz, respectively) in $CDCl_3$ solutions using Me_4Si as an internal reference. Mass spectra at electron impact were recorded on a Shimadzu GCMS 2010 Ultra chromatograph coupled with mass spectrometer (Rtx-5MS capillary column) at ionizing voltage 70 eV. Reaction course and individuality of the obtained compounds were monitored by TLC on Sorbfil plates (using EtOAc : petroleum ether = 1 : 3 as an eluent) and by gas chromatography on a Kristallyuks 4000M chromatograph with a flame ionization detector and a ZB-1capillary column (50 m × 0.25 mm, stationary phase 100% PDMS, film thickness 0.5 μm). Melting points were measured in open capillary tubes and were not corrected.

Chemical used were commercially available sodium azide, diols, and solvents. DMSO was dried prior to use with 3 Å molecular sieves. Linear acetal **1**

and phenylpropynal **2** were obtained by the previously developed procedure [11], the physicochemical characteristics of heterocyclic aldehyde **3** agree well with the literature data [12]. The preparation of cyclic acetals **6a–6e** is described by us in the work [9].

Procedure for the preparation of 1-phenyl-3,3-diethoxyprop-1-yne (1) [11]**.** A solution of 24.5 g (0.24 mol) of phenylacetylene in 50 mL of ether was added to a solution of 0.26 mol of EtMgBr (from 6.34 g of Mg and 28.3 g of EtBr) in 250 mL of anhydrous diethyl ether on cooling with water. The reaction mixture was heated under reflux for 4–5 h, 39 g (0.26 mol) of triethyl orthoformate was added, and the mixture was heated under reflux for additional 7–8 h. The complex was decomposed by addition of 100 mL of saturated NH_4Cl solution dropwise on cooling, next the organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The organic layer and the ethereal extracts were combined and dried with Na_2SO_4, the solvent was removed, and the residue was distilled in a vacuum. Yield 90%, bp 144–148°C (12 mmHg) (bp 144–145°C (14 mmHg).

Procedure for the preparation of phenylpropynal (2) [11]**.** A mixture of 0.05 mol of acetal **1**, 10 mL of 5% aqueous solution of H_2SO_4, and 7.5 mL of AcOH was heated on stirring (70–80°C) for 1 h, while distillate was distilled off under slightly reduced pressure. The reaction mixture after cooling and distillate were treated with crystalline $NaHCO_3$ to pH 6–7 and combined, the product was extracted with ether (3 × 30 mL). The extract was dried with Na_2SO_4, the ether was removed, and the residue was distilled in a vacuum under nitrogen atmosphere. Yield 92%, bp 118–121°C (40 mmHg).

General procedure for the preparation of acetylene dioxacyclanes (6a–6e) [9]**.** A solution of 0.05 mol of acetal **1**, 0.055 mol of diol **4a–4e**, and 100 mg of toluenesulfonic acid in 50 mL of benzene was heated under reflux, while a fraction containing benzene and ethyl alcohol was distilled off. As distillate was distilled off, fresh solvent was added to the boiling solution. The distillation was carried out until the absence of ethanol in distillate according to gas-liquid chromatography. The reaction mixture was cooled, washed with $NaHCO_3$ solution, dried with Na_2SO_4, benzene was removed, and the residue was distilled in a vacuum.

Synthesis of 4-(1,3-dioxacyclan-2-yl)-5-phenyl-1,2,3-triazoles (5a–5e). (A) From aldehyde **3**. Toluenesulfonic acid (100 mg) was added to a solution of 3.1 g (0.018 mol) aldehyde **3** and 1.5 g (0.024 mol) of ethylene glycol **4a** in 20 mL of benzene and the mixture was heated under reflux using a Dean–Stark distilling trap until water evolution ceased. The reaction mixture was cooled, washed with $NaHCO_3$ solution, dried with Na_2SO_4 and the solvent was removed in a vacuum. Compound **5a** was isolated by chromatography on silica gel (EtOAc : petroleum ether = 1 : 1). Yield 0.88 g (23%).

(B) From 1-phenyl-3,3-diethoxyprop-1-yne **1**. An appropriate compound of **6a–6e** series (5 mmol) was added to a solution of 0.34 g (5.25 mmol) of NaN_3 in 10 mL of dry DMSO. The solution was heated at 150–155°C for 8–10 h until complete transformation of compounds **6a–6e** (control by TLC), and then the solvent was removed in a vacuum. The solid residue was washed on a filter with 10 mL of dry benzene and dried in air for 10–15 min. Ten milliliters of water and next HCl (1 : 1) was added to the obtained salt to pH 4–5. The product was extracted with diethyl ether (3 × 15 mL), the extract was dried with Na_2SO_4, the solvent was removed in a vacuum, and the residue was kept at 20–25 mmHg for 1–1.5 h.

4-(1,3-Dioxolan-2-yl)-5-phenyl-1,2,3-triazole (5a). Yield 24% (procedure A), 70% (procedure B). Colorless powder, mp 56–57°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 3.80–4.20 (m, 4H, $H^{4,5}$), 6.16 (s, 1H, H^2), 7.13–7.64 (m, 3H, H^{Ar}), 7.13–7.95 (m, 2H, H^{Ar}), 10.17 (br s, 1H, NH). MS (*m*/*z* (I_{rel}, %)): 216 (100) $[M-1]^+$, 189 (43), 172 (46), 130 (13), 117 (22), 102 (20), 89 (30), 73 (78), 63 (15), 51 (17).

For $C_{11}H_{11}N_3O_2$ anal. calcd. (%): C, 60.82; H, 5.10. Found (%): C, 60.57; H, 5.19.

4-(4-Methyl-1,3-dioxolan-2-yl)-5-phenyl-1,2,3-triazole (5b). Yield 20% (procedure A), 30% (procedure B). Colorless viscous oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.14–1.36 (m, Me), 3.47–3.70 (m, $H^{4,5}$), 4.09–4.14 (m, $H^{4,5}$), 4.30–4.50 (m, $H^{4,5}$), 6.14 (s, H^2), 6.29 (s, H^2), 7.32–7.46 (m, H^{Ar}), 7.75–7.78 (m, H^{Ar}), 7.93–7.97 (m, H^{Ar}), 10.88 (br s, NH). MS (*m*/*z* (I_{rel}, %)): 230 (60) $[M-1]^+$, 189 (52), 172 (100), 158 (12), 144 (10), 130 (15), 117 (19), 103 (17), 87 (43), 77 (19), 59 (35), 51 (10).

For $C_{12}H_{13}N_3O_2$ anal. calcd. (%): C, 62.33; H, 5.67. Found (%): C, 62.46; H, 5.77.

4-(4-Propyl-1,3-dioxolan-2-yl)-5-phenyl-1,2,3-triazole (5c). Yield 23% (procedure A), 54% (procedure B). Colorless viscous oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 0.84–0.98 (m, Pr), 1.21–1.76 (m, Pr), 3.49–3.70 (m, $H^{4,5}$), 4.06–4.35 (m, $H^{4,5}$), 6.16 (s, H^2), 6.28 (s, H^2), 7.28–7.48 (m, H^{Ar}), 7.71–7.84 (m, H^{Ar}), 7.96–7.99 (m, H^{Ar}), 11.58 (br s, NH). MS (*m*/*z* (I_{rel}, %)): 259 (65) $[M]^+$, 189 (62), 172 (100), 158 (21), 145 (5), 115 (20), 103 (15), 89 (13), 77 (12), 69 (61).

For $C_{14}H_{17}N_3O_2$ anal. calcd. (%): C, 64.85; H, 6.61. Found (%): C, 64.71; H, 6.43.

4-(4-Methyl-1,3-dioxan-2-yl)-5-phenyl-1,2,3-triazole (5d). Yield 24% (procedure A), 61% (procedure B). Colorless viscous oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.22–1.35 (m, Me), 1.50–1.54 (m, Me), 1.83–1.97 (m, $H^{4,5,6}$), 3.50–3.57 (m, $H^{4,5,6}$), 3.90–4.07 (m, $H^{4,5,6}$), 4.25–4.30 (m, $H^{4,5,6}$), 5.90(s, H^2), 6.29 (s, H^2), 7.35–7.46 (m, H^{Ar}), 7.81–7.90 (m, H^{Ar}), 11.57 (br s, NH).MS (*m*/*z* (I_{rel}, %)): 245 (65) $[M]^+$, 189 (100), 172

(77), 144 (15), 117 (25), 101 (22), 89 (28), 77 (18), 56 (11), 55 (67).

For $C_{13}H_{15}N_3O_2$ anal. calcd. (%): C, 63.66; H, 6.16. Found (%): C, 63.28; H, 6.09.

4-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-phenyl-1,2,3-triazole (5e). Yield 25% (procedure A), 73% (procedure B). Colorless platelet crystals, mp 125–127 °C. ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 0.80 (s, 3H, CH_3^{eq}), 1.30 (s, 3H, CH_3^{ax}), 3.69 (d, 2H, $H^{4(6)eq}$, $^2J_{HH}$ 11.4), 3.86 (d, 2H, $H^{4(6)ax}$, $^2J_{HH}$ 11.4), 5.80 (s, 1H^2), 7.37–7.50 (m, 3H, H^{Ar}), 7.84 (dd, 2H, H^{Ar}, J 8.6, 2.0), 11.74 (s, 1H, NH). MS (m/z (I_{rel}, %)): 259 (68), 189 (8), 173 (100), 145 (16), 117 (23), 89 (22), 77 (11), 69 (45), 45 (12), 41 (25).

For $C_{14}H_{17}N_3O_2$ anal. calcd. (%): C, 64.85; H, 6.61. Found (%): C, 64.72; H, 6.70.

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