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One-Pot Synthesis of Alkyl 3-Aryl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoates

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Abstract—Reaction of 3-aryl-2-bromopropanoic acids esters, products of the Meerwein arylation, with sodium azide afforded alkyl 2-azido-3-arylpropanoates. The latter react with ethyl acetoacetate and phenylacetylene to form 1,2,3-triazole derivatives. A one-pot method for the synthesis of 3-aryl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-propanoic acid esters via a tricomponent reaction of alkyl 2-bromo-3-arylpropanoates, sodium azide, and phenylacetylene in the presence of CuI was developed.

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Many derivatives of 3-aryl-2-(1*H*-1,2,3-triazol-1-yl)propanoic acids have practically useful properties: peptidomimetics with 1,2,3-triazole rings instead of amide fragments [1], triazole peptides that are analogs of the Pro-Gly dipeptide [2], multi-sheeted dendrimers [3], and organic tectones [4]. A fragment of 3-aryl-2-(1*H*-1,2,3-triazol-1-yl)propanoic acids is present in the composition of compounds that are used in the cancer diagnostics [5], possess the anticancer activity [6], are inhibitors of histone deacetylase **8** [7], are studied as antidiabetic drugs [8].

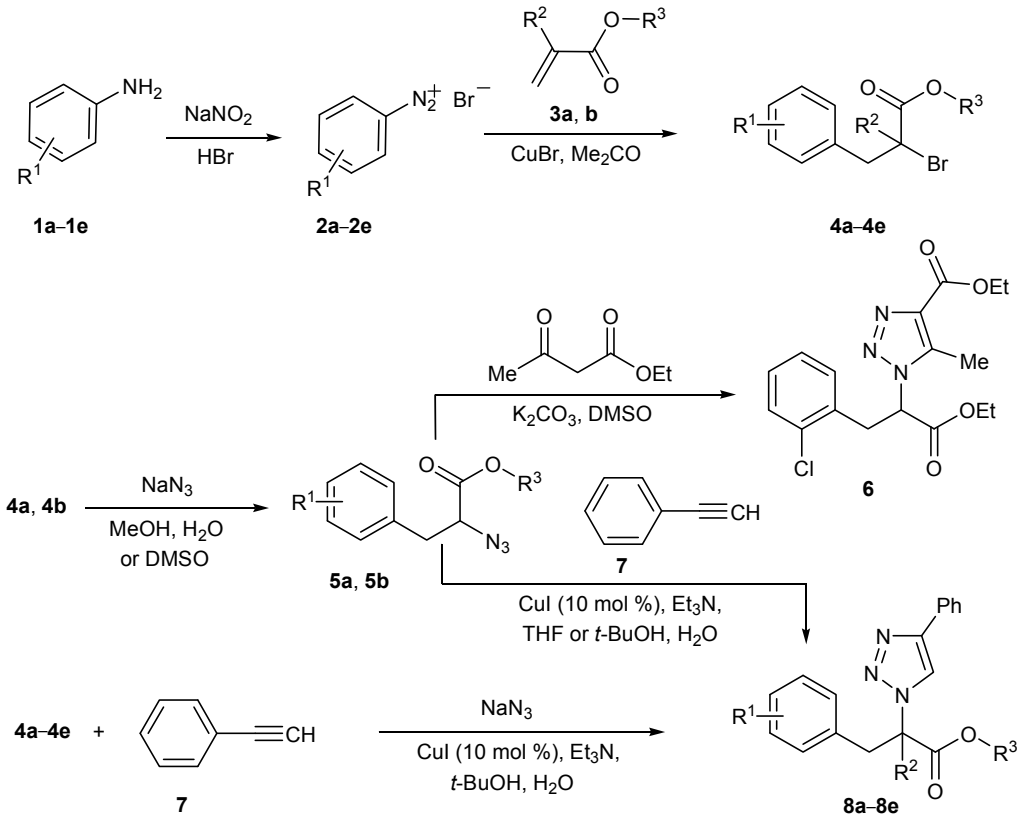
Convenient approaches to the construction of complex molecules with the 1,2,3-triazole ring proceeding from more accessible reagents are multicomponent reactions [9]. One of the strategies for multicomponent synthesis of 1,2,3-triazole derivatives is the preparation of the corresponding azides *in situ* that further react with an alkyne present in the reactor. This method makes it possible to carry out the reaction without isolation of explosive azides. The initial reagents for the azides generation *in situ* are often halo derivatives [10–14].

In this paper, we present a convenient method of the synthesis of 3-aryl-2-(1*H*-1,2,3-triazol-1-yl)propanoic acids derivatives proceeding from the products of acrylates bromoarylation with arenediazonium salts along Meerwein reaction. We showed previously that the esters of 3-aryl-2-bromopropionic acids obtained by reacting arenediazonium bromides with acrylates were convenient reagents for the preparation of thiazoles [15–18], selenazoles [19, 20], and benzo[*b*]-thiophenes [21]. In this work we used 3-aryl-2-bromopropionic acids esters to generate azides and to use them in cycloaddition reactions, in particular, in *click*-reactions without isolation.

Compounds **4a–4e** were obtained by the reaction of arenediazonium bromides **2a–2e** with methyl or ethyl acrylates **3a** and **3b** in the presence of a CuBr catalyst [18].

The nucleophilic substitution of bromine by the azido group in methyl (ethyl) 2-bromo-3-aryl-propionates **4** proceeds fairly smoothly in MeOH–H_2O or DMSO practically without a side-reaction of elimination with the formation of cinnamic acids. Compounds **4a** and **4b** react with sodium azide to form azides **5a** and **5b** in a quantitative yield.

Azide **5b** reacts with ethyl acetoacetate in a K_2CO_3 –DMSO system to form triazole **6** in a 68 % yield. Azides **5a** and **5b** also enter into the copper catalyzed cycloaddition reaction with phenylacetylene **7**. The reaction proceeds at room temperature, triazoles **8a** and **8b** are obtained in a good yield. The reaction course is significantly affected both by the choice of and the presence of a tertiary amine in the reaction medium. In the absence of triethylamine in a THF–H_2O medium, 2 : 1, within 48 h the triazoles **8a** and **8b** were obtained in 21 and 29% yields, respectively. At the use of triethylamine as a cocatalyst as well of



R^1 = 3-Me, R^2 = H, R^3 = Et (**a**); R^1 = 2-Cl, R^2 = H, R^3 = Et (**b**); R^1 = 4-Br, R^2 = H, R^3 = Et (**c**); R^1 = 3,4-Cl_2, R^2 = H, R^3 = Me (**d**); R^1 = 3-CF_3, R^2 = Me, R^3 = Me (**e**).

anhydrous THF we managed to increase the yields of compounds **8a** and **8b** to 61 and 70%. A similar result was obtained by carrying out the reaction in *t*-BuOH–H_2O system, 1 : 1 or 2 : 1. The ratio of solvents was selected for each azide separately, depending on its solubility. In *tert*-butanol the reaction proceeds four times faster than in tetrahydrofuran: the total conversion of the initial reagents is achieved after 12 hours, and with THF the reaction completes in 48 hours.

We also developed a multi-component *click*-reaction based on alkyl 2-bromo-3-aryl-propionates **4**. The reaction of compounds **4** with sodium azide within 12 hours at room temperature in the presence of phenylacetylene **7**, CuI, and triethylamine in *t*-BuOH–H_2O, 2 : 1, leads to the formation of triazoles **8a–8e** in ~ 70% yields.

Hence, we developed an effective one-pot method of the synthesis of alkyl 3-aryl-2-(4-phenyl-1,2,3-triazol-1-yl)propanoates by the tricomponent reaction of alkyl 2-bromo-3-arylpropionates, sodium azide, and phenylacetylene under mild conditions.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Varian UnityPlus 400 and Bruker Avance 500 at operating frequencies of 400 and 500 MHz, respectively, internal reference TMS. Elemental analysis was performed on an analyzer Carlo Erba 1106. Melting points were measured on a Boetius apparatus. Compounds **4a–4e** were obtained by procedures [15, 16].

Ethyl 2-azido-3-arylpropanoates 5a and 5b. To a solution of 0.01 mol of an appropriate ethyl 2-bromo-3-arylpropanoate **4a** and **4b** in 12 mL of methanol was added 2 mL of water and 0.78 g (0.012 mol) of sodium azide. The mixture was stirred for 2 h at 50–60 °C. Methanol was distilled off in a vacuum, and 30 mL of water was added to the residue. The azide was extracted with methylene chloride (2 × 15 mL), the extract was dried with Na_2SO_4. The solvent was distilled off in a vacuum to give the azide, which was used without further purification.

Ethyl 2-azido-3-(*meta*-tolyl)propanoate (5a). Yield 2.21 g (95%). Viscous liquid. ^{1}H NMR spectrum

(500 MHz, $CDCl_3$), δ, ppm: 1.30 t (3H, $\underline{CH_3}CH_2$, *J* 7.1 Hz), 2.37 s (3H, CH_3), 3.00 d.d (1H, CH_2, *J* 8.8, 13.8 Hz), 3.17 d.d (1H, CH_2, *J* 5.3, 13.8 Hz), 4.06 d.d (1H, CH, *J* 5.3, 8.8 Hz), 4.26 q (2H, $CH_3\underline{CH_2}$, *J* 7.0 Hz), 7.04–7.17 m ($3H_{arom}$), 7.24 t (1H, H^5_{arom}, *J* 7.3 Hz). Found, %: C 61.64; H 6.34; N 18.17. $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.79; H 6.48; N 18.01.

Ethyl 2-azido-3-(2-chlorophenyl)propanoate (5b). Yield 2.45 g (97%). Viscous liquid. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.29 t (3H, $\underline{CH_3}CH_2$, *J* 7.1 Hz), 3.11 d.d (1H, CH_2, *J* 9.0, 13.6 Hz), 3.38 d.d (1H, CH_2, *J* 5.5, 13.7 Hz), 4.18–4.30 m (3H, CH + $CH_3\underline{CH_2}$), 7.23–7.33 m ($3H_{arom}$), 7.37–7.42 m ($1H_{arom}$). Found, %: C 52.14; H 4.91; N 16.45. $C_{11}H_{12}ClN_3O_2$. Calculated, %: C 52.08; H 4.77; N16.56.

Ethyl [3-(2-chlorophenyl)-1-ethoxycarbonylethyl]-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (6). To a solution of 1.25 g (5 mmol) of azide and 0.64 mL (5 mmol) of ethyl acetocetate in 5 mL of DMSO at vigorous stirring was added 5 g of K_2CO_3 and the mixture was stirred for 48 hours at room temperature. The reaction mixture was diluted with water, extracted with the methylene chloride. The solvent was distilled off in a vacuum. Yield 1.24 g (68%). Viscous liquid. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.23 t (3H, CH_3CH_2, *J* 7.1 Hz), 1.40 t (3H, $\underline{CH_3}CH_2$, *J* 7.1 Hz), 2.25 s (3H, CH_3), 3.69 t (1H, CH_2, *J* 11.0 Hz), 3.97 d.d (1H, CH_2, *J* 4.5, 14.1 Hz), 4.25 q (2H, $CH_3\underline{CH_2}$, *J* 7.1 Hz), 4.39 q (2H, $CH_3\underline{CH_2}$, *J* 7.1 Hz), 5.36 d.d (1H, CH, *J* 4.6, 10.7 Hz), 6.92 d (1H, H^6_{arom}, *J* 7.5 Hz), 7.03 t (1H, H^5_{arom}, *J* 7.5 Hz), 7.16 t (1H, H^4_{arom}, *J* 7.5 Hz), 7.34 d (1H, H^3_{arom}, *J* 7.5 Hz). Found, %: C 55.61; H 5.34; N 19.59. $C_{17}H_{20}ClN_3O_4$. Calculated, %: C 55.82; H 5.51; N 11.49.

Triazoles (8a and 8b). An appropriate azide **5a** and **5b** (1 mmol) and 0.11 mL (1 mmol) of phenylacetylene **7** were dissolved in 5 mL of *tert*-butanol. To the solution water was added dropwise until an emulsion formed, after that 0.4 mL (2.8 mmol) of triethylamine and 0.05 g of CuI were added. The mixture was stirred for 12 hours at room temperature, 15 mL of water and 5 mL of concentrated ammonia solution were added. The product was extracted with methylene chloride (3 × 10 mL), the extract was dried with Na_2SO_4 and evaporated. If necessary, the product was recrystallized from ethanol.

Triazoles (8a–8e). In 5 mL of *t*-butanol 1 mmol of the corresponding alkyl 2-bromo-3-arylpropanoate **4a–4e**, 0.08 g (1.2 mmol) of sodium azide, and 0.11 mL (1 mmol) of phenylacetylene **7** was dissolved. To the solution, water was added dropwise until the emulsion was formed, 0.4 mL of triethylamine and 0.05 g of CuI was added. The mixture was stirred for 12 hours at room temperature, 15 mL of water and 5 mL of concentrated ammonia solution was added. The product was extracted with methylene chloride (3 × 10 mL), the extract was dried with Na_2SO_4 and evaporated, the residue was recrystallized from ethanol if necessary.

Ethyl (*meta*-tolyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoate (8a). Yield 0.23 g (69%), mp 96–97°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6 + CCl_4), δ, ppm: 1.17 t (3H, $\underline{CH_3}CH_2$, *J* 7.1 Hz), 2.21 s (3H, CH_3), 3.47 d.d (1H, CH_2, *J* 6.0, 14.3 Hz), 3.59 d.d (1H, CH_2, *J* 5.7, 14.2 Hz), 4.19 q (2H, $CH_3\underline{CH_2}$, *J* 7.0 Hz), 5.83 d.d (1H, CH, *J* 5.8, 6.0 Hz), 6.99–7.10 m ($4H_{arom}$), 7.34 t ($1H_{arom}$, *J* 7.3 Hz), 7.45 t ($2H_{arom}$, *J* 7.5 Hz), 7.82 d (2H, $H^{2,6}_{Ph}$, *J* 7.4 Hz), 8.69 s ($1H_{triazole}$). Found, %: C 71.85; H 6.09; N 12.44. $C_{20}H_{21}N_3O_2$. Calculated, %: C 71.62; H 6.31; N 12.53.

Ethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3-(2-chlorophenyl)propanoate (8b). Yield 0.23 g (65%), mp 99–100°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.18 t (3H, $\underline{CH_3}CH_2$, *J* 7.1 Hz), 3.62 d.d (1H, CH_2, *J* 5.9, 14.1 Hz), 3.80 d.d (1H, CH_2, *J* 6.0, 14.0 Hz), 4.21 q (2H, $CH_3\underline{CH_2}$, *J* 7.0 Hz), 5.88 d.d (1H, CH, *J* 5.9, 6.0 Hz), 7.19–7.46 m ($7H_{arom}$), 7.84 d (2H, $H^{2,6}_{Ph}$, *J* 7.4 Hz), 8.81 s ($1H_{triazole}$). Found, %: C 63.93; H 4.95; N 11.93. $C_{19}H_{18}ClN_3O_2$. Calculated, %: C 64.13; H 5.10; N 11.81.

Ethyl 3-(4-bromophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoate (8c). Yield 0.28 g (70%) mp 89–90°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.18 t (3H, $\underline{CH_3}CH_2$, *J* 7.1 Hz), 3.54 d.d (1H, CH_2, *J* 6.1, 14.5 Hz), 3.62 d.d (1H, CH_2, *J* 5.5, 14.0 Hz), 4.20 q (2H, $CH_3\underline{CH_2}$, *J* 7.0 Hz), 5.91 d.d (1H, CH, *J* 5.5, 6.0 Hz), 7.20 d (2H, $H^{2,6}_{Ar}$, *J* 8.5 Hz), 7.35 t (1H, H^4_{Ph}, *J* 7.5 Hz), 7.43–7.48 m (4H, $H^{3,5}_{Ar}$ + $H^{3,5}_{Ph}$), 7.84 d (2H, $H^{2,6}_{Ph}$, *J* 7.5 Hz), 8.76 s($1H_{triazole}$). Found, %: C 57.20; H 4.40; N 10.59. $C_{19}H_{18}BrN_3O_2$. Calculated, %: C 57.01; H 4.53; N 10.50.

Methyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3-(3,4-dichlorophenyl)propanoate (8d). Yield: 0.27 g (72%), mp 102–103°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6 + CCl_4), δ, ppm: 3.50–3.61 m (1H, CH_2), 3.66 d.d (1H, CH_2, *J* 4.8, 14.3 Hz), 3.74 s (3H, CH_3), 5.99 d.d (1H, CH, *J* 5.0, 6.0 Hz), 7.18 d ($1H_{arom}$, *J* 7.5 Hz), 7.35 d ($1H_{arom}$, *J* 7.2 Hz), 7.39–7.50 m

($3H_{arom}$), 7.55 c ($1H_{arom}$), 7.82 d ($2H_{arom}$, *J* 7.1 Hz), 8.72 s (1H, $H_{triazole}$). Found, %: C 57.65; H 4.13; N 10.95. $C_{18}H_{15}Cl_2N_3O_2$. Calculated, %: C 57.46; H 4.02; N 11.17.

Methyl 2-methyl-3-(3-trifluoromethylphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoate (8e). Yield 0.23 g (59%), mp 107–108°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.79 s (3H, CH_3), 3.55 d (1H, CH_2, *J* 13.7 Hz), 3.77 d (1H, CH_2, *J* 13.7 Hz), 3.77 s (3H, CH_3), 7.17 s (1H, H^2_{arom}), 7.26 d ($1H_{arom}$, *J* 7.4 Hz), 7.35 t (1H, H^5_{arom}, *J* 7.4 Hz), 7.43–7.64 m ($5H_{arom}$), 7.86 d ($1H_{arom}$, *J* 7.4 Hz), 8.72 s (1H, $H_{triazole}$). Found, %: C 61.50; H 4.43; N 10.65. $C_{20}H_{18}F_3N_3O_2$. Calculated, %: C 61.69; H 4.66; N 10.79.

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