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SYNTHESIS OF 1-(R-PHENYL)-5-(R-METHYL)-1*H*-1,2,3-TRIAZOLE-4-CARBOXYLIC ACIDS BY ONE-POT TANDEM REACTION

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Substituted 1H-1,2,3-triazole-4-carboxylic acids were synthesized by a three-component reaction of arylazides, ethyl 4-chloro-3-oxobutanoate, and either O- or S-nucleophiles in the presence of a base catalyst. The reaction most probably proceeded as a [3 + 2] cyclocondensation reaction between arylazide and ethyl 4-chloro-3-oxobutanoate with the further nucleophilic substitution of chlorine in the chloromethyl group. Reaction optimization was performed to carry out the reaction with an O-nucleophile. Conditions were found under which diethyl 2,5-dihydroxyterephthalate (the product of self-condensation of two molecules of ethyl 4-chloro-3-oxobutanoate with the further oxidation by azide) was obtained.

Keywords: Azides; cyclocondensation; multicomponent reactions; 1*H*-1,2,3-triazoles

INTRODUCTION

Multicomponent reactions are an attractive synthetic strategy for rapid and efficient library generation because the products are formed in one step and diversity can be achieved simply by changing the reaction components.[1,2] Unfortunately, such a strategy is rarely applied to 1,2,3-triazole derivative synthesis. On the other hand, 1,2,3-triazoles are an important class of heterocycles because of their range of applications as drugs (or their precursors) and for technical purposes.[3–5] In recent years, triazole-forming reactions have received much attention, and new conditions of 1,3-dipolar cycloaddition reaction between alkynes and azides (especially in click chemistry strategy) have been developed.[6] Base catalyst reactions of azides with methylenic compounds are less studied. Therefore, we report our efforts toward the development of facile, solution-phase, parallel, three-component reactions of 1,2,3-triazole synthesis using base-catalyzed reactions of azides with methylenic compounds.

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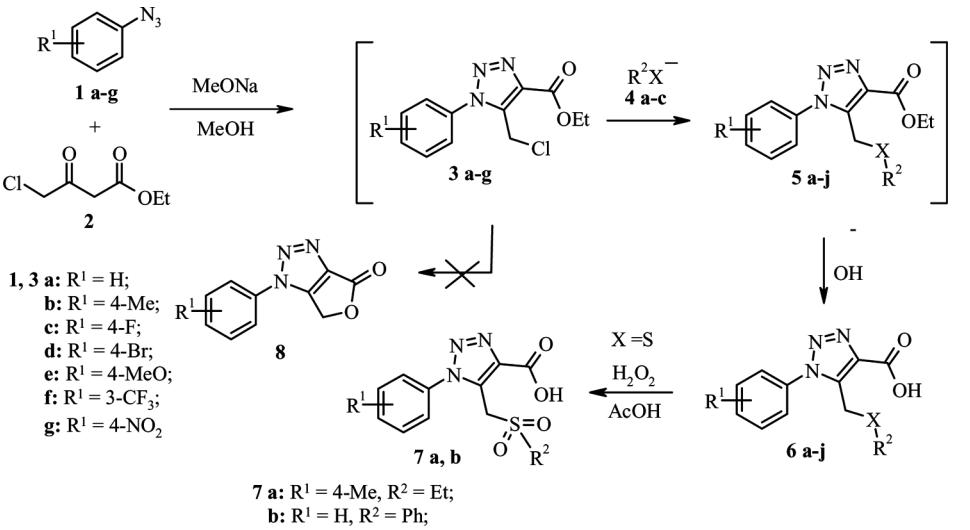
RESULTS AND DISCUSSION

It is well known that organic azides undergo base-catalyzed condensation reactions with activated methylenic compounds.[4] The first step of the reaction is the carbanion attack on the azido moiety to form triazenyl anions, which can then be trapped with internal electrophiles and cyclized to triazoles.[5] In the current article, reactions of arylazides with ethyl 4-chloro-3-oxobutanoate and nucleophiles are reported. The starting materials are commercially available compounds that provide a variety of triazoles. Rapid formation of the triazole ring is a perfect model of the reaction described. Obviously, if azide slowly reacts with carbanion in position 2 of ethyl 4-chloro-3-oxobutanoate, another molecule of this ester can be potentially attacked. In such case, the product of alkylation is obtained. It is theoretically possible to expect the formation of less stabilized carbanion in position 4 of ethyl 4-chloro-3-oxobutanoate (as a competition reaction), which can react with azides to yield ethyl (4-chloro-1-phenyl-1*H*-1,2,3-triazol-5-yl)acetate.

Only one example of ethyl 4-chloro-3-oxobutanoate reaction with azides has been reported previously.[7] By the reaction of 3-azido-2-amino-1,2,5-oxadiazole with ethyl 4-chloro-3-oxobutanoate and excess of the appropriate amine (piperidine, diethylamine, pyrrolidine), functionalized [1,2,3]triazoles were synthesized. Amines were used as base and N-nucleophiles. To preclude the purification of the reactive chloromethyl intermediate, [1,2,3]triazoles were prepared by a one-pot procedure.[7] In general, reactivity of azides is insufficiently studied.

Our findings on azide reactions with ethyl 4-chloro-3-oxobutanoate demonstrate that if the reaction occurs in a sodium methoxide–methanol system, S-nucleophiles rapidly react with the chloromethyl group. 5-(R-Sulfanyl)methyl-1*H*-1,2,3-triazoles **6h–j** were obtained in excellent yields (74–84%) at different temperatures. On the other hand, the reaction of compounds **1** with **2** and O-nucleophile (methylate anion) was



Scheme 1. Synthesis of 1-(R-phenyl)-5-(R-methyl)-1*H*-1,2,3-triazole-4-carboxylic acids.

Table 1. Synthesis of acids **6a–j**

Entry	Compound	R^1	R^2X	Yield[a] (%)
1	**6a**	H	MeO	43
2	**6b**	4-Me	MeO	37
3	**6c**	4-F	MeO	56
4	**6d**	4-Br	MeO	55
5	**6e**	4-MeO	MeO	40
6	**6f**	3-CF_3	MeO	67
7	**6g**	4-NO_2	MeO	65
8	**6h**	H	EtS	74
9	**6i**	4-Me	EtS	77
10	**6j**	H	PhS	84

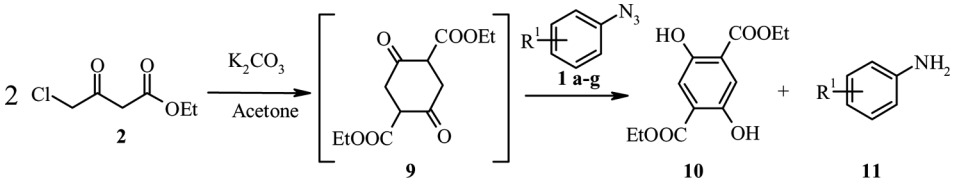
[a]Isolated yields of acids **6a–j** when the reaction occurred in a boiling solution.

carried out under strict control of temperature to avoid undesirable reactions, and yields of triazoles **6a–g** were moderate (Scheme 1, Table 1).

From the results summarized in Table 1, the correlation between yields and substituent in arylazide can be noted. Arylazides with electron-withdrawing groups in the aromatic ring under the sodium methoxide–methanol system conditions formed triazoles **6c, d, f,** and **g** in moderate (55–67%) yields. In contrast, arylazides with electron-donating groups under the same conditions gave poor yields of triazoles **6a, b,** and **e** (37–43%).

The use of methanol as a reaction medium was indispensable when the reaction occurred with methoxide nucleophile. Apparently, a weak concentration of methoxide ions in equilibrium was necessary to promote the reaction. No cyclization occurred when the reaction was carried out in the absence of a base. In addition, when the reaction occurred in acetone and potassium carbonate was selected as a base catalyst, the main product of the reaction was diethyl 2,5-dihydroxyterephthalate **10** (Scheme 2). Moreover, no triazole derivatives were found when the reaction was carried out in morpholine or pyridine solution at 100 °C.

Considerable improvements of yields were achieved under strict control of the temperature. It was found that the reaction of azides **1** with ethyl 4-chloro-3-oxobutanoate occurred slowly at −10 °C. Yields of triazoles were less than 5%, and in some cases triazoles were not even isolated. At 5 °C and by intensive interfusion, triazole yields increased but still were incidental (<10%). At room temperature and by rapid addition of reagents, triazole yields increased (20–30%), and the



Scheme 2. Concurred reaction of the diethyl 2,5-dihydroxyterephthalate formation.

Table 2. Temperature optimization for the reaction outlined in Scheme 1

		Yield[a] (%)			
Entry	R	–10 °C, 14d	+5 °C, 7d	25 °C, 1d	67 °C,[b] 1 h
1	H	—	5	19	43
2	Me	—	6	18	37
3	Br	4	9	30	55

Note. Conditions: sodium (0.25 g, 11 mmol); 5 mmol of azide **1**, ester **2**, and nucleophile **4**; MeOH (20 mL).

[a]Isolated yields of acids **6a, b,** and **d**.

[b]Boiling solution.

greatest yields (37–67%) were observed under intensive stirring of reagents at methanol boiling temperature (65 °C) (Table 2).

In case of arylazides with electron-withdrawing groups, yields of triazoles **6** were high in all temperature modes. The reaction occurred as an exothermic process. At all temperatures, compound **10**, amines **11**, and polymeric component were identified as by-products of the reaction. In addition, ethyl (4-chloro-1-aryl-1*H*-1,2,3-triazol-5-yl)acetates or products of their hydrolysis, along with possible products of nucleophilic substitution of chlorine in position 4 of triazole, were not detected. Furthermore, we expected a possible lactonization of the intermediate **3**. However, compounds **8** or products of their hydrolysis were not found in the reaction mixture.

The diversification of compounds **6i** and **j** was reached by oxidation of the sulfide to the sulfone moiety using hydrogen peroxide. The obtained sulfones **7a** and **b**, containing an activated methylene group, allowed prolongation of the system by various types of condensation.

Various substituted 1,2,3-triazole acids were obtained in good yields. They represent a category of versatile synthetic intermediates that provide miscellaneous building blocks in the parallel synthesis of druglike molecule libraries.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury 400 (400-MHz) and Bruker 500 (500-MHz) instruments. The ^{1}H chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) or the deuterated solvent as an internal reference. Mass spectra were run using an Agilent 1100 series liquid chromatography/mass spectra (LC/MS) instrument with an atmospheric pressure chemical ionization (APCI) mode. Low-resolution electron impact mass spectra (EIMS) were obtained on a 7683B LC/MS instrument (Agilent Technology), m/z (relative intensity in percentages, %), with an ionization energy of 70 eV. The evolution of the reactions and purity of the synthesized compounds were monitored chromatographically on Silufol UV-254 plates. Azides **1a–g** were prepared from corresponding amines.[8] In ^{1}H NMR spectra, the chemical shift of the carboxylic proton (compounds **6a, b, d, f–h**) is not observed, probably because of exchange with water in dimethylsulfoxide (DMSO-d_6).

General Procedure for the Synthesis of 1*H*-1,2,3-Triazole-4-carboxylic Acids 6a–j

Sodium (0.5 g, 0.022 mol) was added to 20 mL of absolute methanol. The appropriate azide **1** (0.01 mol) (0.01 mol of mercaptane in case of **6h–j** synthesis) was added to the obtained sodium methylate solution. (Caution! Hazardous manipulations with azides! Azides are known to decompose explosively.) The solution was heated under reflux, and 0.7 mL (0.01 mol) of ethyl 4-chloro-3-oxobutanoate **2** was quickly added with intensive stirring. The reaction mixture was heated under reflux for 1 h. The solid precipitated. Hot water was added to dissolve the sediment (50 mL); if necessary, the solution of sodium hydroxide can be added to pH 11–12 and heated under reflux for 1 h. The hot solution was poured to 10 mL of concentrated HCl and left to be crystallized. The obtained solid was filtered, washed with water twice, and crystallized from ethanol.

5-(Methoxymethyl)-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid 6a. Yield: 43% as a white solid; mp 153–154 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.28 (3H, s, Me), 4.73 (2H, s, CH_2), 7.57–7.68 (5H, m, H_{Ph}); MS (*m*/*z*): 234 ($M^+ + 1$). Anal. calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.81; H, 4.68; N, 18.11.

5-(Methoxymethyl)-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid 6b. Yield: 37% as a white solid; mp 167–168 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.42 (3H, s, Me), 3.20 (3H, s, Me), 4.71 (2H, s, CH_2), 7.44 (2H, d, ^3J 8.3, H_{Ar}-3,5), 7.55 (2H, d, ^3J 8.3, H_{Ar}-2,6); MS (*m*/*z*): 248 ($M^+ + 1$). Anal. calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.01; H, 5.25; N, 16.89.

1-(4-Fluorophenyl)-5-(methoxymethyl)-1*H*-1,2,3-triazole-4-carboxylic acid 6c. Yield: 56% as a white solid; mp 136–137 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.20 (3H, s, Me), 4.73 (2H, s, CH_2), 7.49 (2H, t, ^3J 8.8, H_{Ar}-3,5), 7.74 (2H, dd, $^3J_{HH}$ 8.8, $^4J_{HF}$ 4.9, H_{Ar}-2,6), 13.53 (1H, br.s, COOH); MS (*m*/*z*): 252 ($M^+ + 1$). Anal. calcd. for $C_{11}H_{10}FN_3O_3$: C, 52.59; H, 4.01; N, 16.73. Found: C, 52.24; H, 4.28; N, 16.61.

1-(4-Bromophenyl)-5-(methoxymethyl)-1*H*-1,2,3-triazole-4-carboxylic acid 6d. Yield: 55% as a white solid; mp: 167–168 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.30 (3H, s, Me), 4.76 (2H, s, CH_2), 7.65 (2H, d, ^3J 8.8, H_{Ar}-3,5), 7.78 (2H, d, ^3J 8.8, H_{Ar}-2,6); MS (*m*/*z*): 313 ($M^+ + 1$). Anal. calcd. for $C_{11}H_{10}BrN_3O_3$: C, 42.33; H, 3.23; N, 13.46. Found: C, 42.19; H, 3.04; N, 13.34.

5-(Methoxymethyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid 6e. Yield: 40% as a white solid; mp 214–215 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.51 (3H, s, Me), 3.21 (3H, s, Me), 4.76 (2H, s, CH_2), 7.73 (4H, br.s, H_{Ar}), 13.55 (1H, br.s, COOH); MS (*m*/*z*): 264 ($M^+ + 1$). Anal. calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.43; H, 5.07; N, 16.05.

5-(Methoxymethyl)-1-[3-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazole-4-carboxylic acid 6f. Yield: 67% as a white solid; mp 111–112 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.31 (3H, s, Me), 4.78 (2H, s, CH_2), 7.85–7.93 (2H, m, H_{Ar}-4,5), 8.02 (1H, d, ^3J 8.8, H_{Ar}-6), 8.05 (1H, s, H_{Ar}-2); MS (*m*/*z*): 302 ($M^+ + 1$).

Anal. calcd. for $C_{12}H_{10}F_3N_3O_3$: C, 47.85; H, 3.35; N, 13.95. Found: C, 47.42; H, 3.57; N, 13.74.

5-(Methoxymethyl)-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid 6g. Yield: 65% as a white solid; mp 161–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.31 (3H, s, Me), 4.85 (2H, s, CH_2), 8.03 (2H, d, ^3J 8.8, H_{Ar}-3,5), 8.47 (2H, d, ^3J 8.8, H_{Ar}-2,6); MS (*m*/*z*): 279 ($M^+ + 1$). Anal. calcd. for $C_{11}H_{10}N_4O_5$: C, 47.49; H, 3.62; N, 20.14. Found: C, 47.76; H, 3.44; N, 20.36.

5-[(Ethylsulfanyl)methyl]-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid 6h. Yield: 74% as a white solid; mp 109–110 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (3H, t, ^3J 7.8, Me), 2.37 (3H, q, ^3J 7.8, CH_2), 4.11 (2H, s, CH_2), 7.62 (5H, br.s, H_{Ph}) MS (*m*/*z*): 264 ($M^+ + 1$). Anal. calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.58; H, 4.74; N, 16.06.

5-[(Ethylsulfanyl)methyl]-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid 6i. Yield: 77% as a white solid; mp 161–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (3H, t, ^3J 7.8, Me), 2.39 (3H, q, ^3J 7.8, CH_2), 2.47 (3H, s, Me), 4.08 (2H, s, CH_2), 7.41 (2H, d, ^3J 7.8, H_{Ar}-3,5), 7.49 (2H, d, ^3J 7.8, H_{Ar}-2,6). 13.12 (1H, br.s, COOH); MS (*m*/*z*): 278 ($M^+ + 1$). Anal. calcd. for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.51; H, 5.39; N, 15.00.

1-Phenyl-5-[(phenylsulfanyl)methyl]-1*H*-1,2,3-triazole-4-carboxylic acid 6j. Yield: 84% as a white solid; mp 147–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.52 (2H, s, CH_2), 7.12–7.23 (5H, m, H_{Ar}), 7.46–7.59 (5H, m, H_{Ar}), 13.10 (1H, br.s, COOH); MS (*m*/*z*): 312 ($M^+ + 1$). Anal. calcd. for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.84; H, 4.25; N, 13.37.

Other Conditions

The mixture of appropriate azide **1** (0.01 mol), ethyl 4-chloro-3-oxobutanoate **2** (0.7 mL, 0.01 mol), and potassium carbonate (0.01 mol) was heated under reflux for 6 h. Water was added to dissolve the sediment, and the solution was poured to 10 mL of concentrated HCl and left to be crystallized. The obtained solid was filtered and crystallized. Diethyl 2,5-dihydroxyterephthalate **10** was isolated in 37% yield as white needles. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (6H, t, ^3J 6.8, Me), 4.40 (4H, q, ^3J 6.8, CH_2), 7.30 (2H, s, H_{Ar}-3,6), 9.89 (2H, s, HO), EIMS: 254 (M^+, 32), 208 (100), 180 (25), 162 (75), 134 (16), 107 (10), 79 (7), 53 (9), 29 (4).

Oxidation of Sulfides 6i and j to Sulfones 7a and b

Appropriate sulfides **6i, j** (0.017 mol) were dissolved in 15 mL of acetic acid during heating. The solution was cooled to 50 °C and 50 mL (approx. 0.05 mol) of a 30% solution of hydrogen peroxide was added dropwise during 5 min keeping the temperature below 75 °C. At the end of addition the solution was left for 3 h at 85 °C. The reaction mixture was cooled, the precipitated crystals were filtered, washed with methanole and dried.

5-[(Ethylsulfonyl)methyl]-1-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxylic acid 7a. Yield: 77% as a white solid; mp 161–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (3H, t, ^3J 7.8, Me), 2.47 (3H, s, Me), 3.03 (3H, q, ^3J 7.8, CH_2), 4.83 (2H, s, CH_2), 7.49 (2H, d, ^3J 8.0, H_{Ar}-3,5), 7.50 (2H, d, ^3J 8.0, H_{Ar}-2,6). 13.12 (1H, br.s, COOH); MS (m/z): 310 ($M^+ + 1$). Anal. calcd. for $C_{13}H_{15}N_3O_4S$: C, 50.47; H, 4.89; N, 13.58. Found: C, 50.28; H, 4.81; N, 13.70.

1-Phenyl-5-[(phenylsulfonyl)methyl]-1*H*-1,2,3-triazole-4-carboxylic acid 7b. Yield: 88% as a white solid; mp 177–178 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.08 (2H, s, CH_2), 7.45–7.58 (9H, m, H_{Ar}), 7.64–7.70 (1H, m, H_{Ar}), 13.10 (1H, br.s, COOH); MS (m/z): 345 ($M^+ + 1$). Anal. calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 55.83; H, 3.76; N, 12.08.

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