RESEARCH ARTICLE

Condition-based switching the multicomponent reactions of 5-amino-3-(methylthio)-1,2,4-triazole, aromatic aldehydes, and pyruvic acid

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Abstract: The multicomponent reactions of 5-amino-3-methylthio-1,2,4-triazole with aromatic aldehydes and pyruvic acid were studied using conventional thermal heating and ultrasonic activation at room temperature. Under conventional heating, dihydrotriazolopyrimidine derivatives were formed in both two- and three-component treatments. In the case of ultrasonic activation, the multicomponent reaction led to the formation of 7-hydroxytetrahydrotriazolopyrimidines.

Keywords: 5-amino-3-(methylthio)-1,2,4-triazole; multicomponent reaction; ultrasonication; pyruvic acid; heterocyclization.

Introduction

Pyrimidine derivatives and their sulfur analogs have attracted much attention because of their wide range of biological activities involving antibacterial [1], anti-inflammatory [2-3], analgesic [3], antitumour [4-5], antimicrobial [6], anti-infective [7] and antifungal [8-9] activities.

In our previous work, the multicomponent reactions of 3-amino-1,2,4-triazole with aromatic aldehydes and pyruvic acid (arylpurvic acids) were discussed from the viewpoints of their selectivity and molecular diversity. Different types of heterocycles depending on the structures of the reagents, the solvent, the temperature mode, and the activation method were formed [10-13]. In particular, the multicomponent approaches based on the reaction of 3-amino-1,2,4-triazole, aromatic aldehydes, and pyruvic acid were described for the synthesis of dihydrotriazolopyrimidine-5-carboxylic acids **I**, 7-hydroxytetrahydrotriazolopyrimidine-7-carboxylic acid **II**, benzotriazo-

looxadiazocine-5-carboxylic acids **III** and 3-hydroxytriazolyldihydropyrrolones **IV** (Scheme 1). The reaction conditions were found for the selective synthesis of each of these compounds (**I-IV**). Application of non-classical activation methods like ultrasonication and microwave irradiation have appeared as convenient tools for tuning the multicomponent treatments.

Scheme 1. Diversity of heterocyclizations of 3-amino-1,2,4-triazole with aldehydes and pyruvic acids.

Received: 04.11.2020
Revised: 12.11.2020
Accepted: 19.11.2020
Published online: 30.12.2020

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Scheme 2. Switchable heterocyclizations of 3-(methylthio)-1H-1,2,4-triazol-5-amine with aldehydes and pyruvic acids.

Some reactions involving sulfur-containing substituents in the 3rd position of 3-amino-1,2,4-triazole were described in the literature as well [14–19].

Results and Discussion

Here, we report the Doebner-type synthesis of undescribed 2-methylthiotetrahydrotriazolo[1,5-*a*]pyrimidine-7-carboxylic acids, and 2-methylthiodihydrotriazolo[1,5-*a*]pyrimidine-5-carboxylic acids. The type of final heterocycle forming in the multicomponent reaction between 3-(methylthio)-1H-1,2,4-triazol-5-amine, aromatic aldehydes and pyruvic acid depends on the reaction conditions – conventional heating or ultrasonication.

In particular, it was found that the three-component treatment of an equimolar mixture of 3-(methylthio)-1H-1,2,4-triazol-5-amine (**1**), aromatic aldehydes **2a-d**, and pyruvic acid (**3**) under conventional heating at reflux in glacial acetic acid for 4 hours selectively led to the formation of a dihydropyrimidine ring and thus 2-(methylthio)-7-aryl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-5-carboxylic acids **4a-d** were isolated as the only products of the interaction in satisfactory yields (Scheme 2, Method A, and Table 1).

On the other hand, the multicomponent reaction of the same starting materials **1**, **2a-d**, and **3** in glacial acetic acid under ultrasonication at room temperature for 2 hours led to the formation of 7-hydroxy-2-(methylthio)-5-aryl-4,5,6,7-tetrahydro-[1,2,4]triazolo-[1,5-*a*]pyrimidine-7-carboxylic acids **5a-d** (Scheme 2, Method B, and Table 1). Mechanical stirring at room temperature instead of ultrasonication led to the formation of compounds **5a-d** as well. However, this procedure required a longer reaction time (ca. 30 h) and the yield and purity of the products were significantly lower.

It should be noted, that dihydropyrazolopyrimidine carboxylic acids **4** were formed by sequential procedure as well. The linear pathway included two steps: the synthesis of arylidenpyruvic acids **6a,b** starting from appropriate aromatic aldehyde **2** and pyruvic acid **3**, and their further heterocyclization with 3-(methylthio)-1H-1,2,4-triazol-5-amine **1** in glacial acetic acid under conventional heating for 30 min gave dihydropyrazolopyrimidine carboxylic acids **4a,b** (Scheme 2, Method C). Thus, the final reaction products **4** were identical to the compounds isolated from the multicomponent reaction (Scheme 2, Method A) in similar yields (Table 1).

The structures of the heterocyclic carboxylic acids **4a-d** and **5a-d** were established by MS, ¹H and ¹³C NMR spectral data. The ¹H NMR spectra of 2-(methylthio)-7-aryl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-5-carboxylic acids **4a-d** show the following signals: a broad singlet for NH group (9.82–9.99 ppm), signals of aromatic H-atoms and terminal groups, a doublet for H-atom in position 7 of the heterocycle (6.12–6.30 ppm, *J* = 3.9 Hz), a doublet for ethylene H-atom at C-5 (5.72–5.77 ppm, *J* = 3.7 Hz), a singlet for methyl group (2.38–2.39 ppm). The ¹H NMR spectra of 7-hydroxy-2-(methylthio)-5-aryl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids **5a-d** show a broad signal for the pyrimidine NH at δ = 7.78–7.94 ppm, a singlet for methyl group (2.42–2.43 ppm), a multiplet for the CH group at C-5 at δ = 4.54–4.80 ppm, a multiplet for the CH₂ group at C-6 at δ = 2.03–2.41 ppm, and peaks for aromatic protons as well as signals for other substituents.

The structure of compounds **4a-d** and **5a-d** was additionally confirmed by the comparison of their ¹H NMR spectra with literature data for similar pyrimidines [10–12].

MS and ¹³C NMR are also in an agreement with the proposed structures.

Table 1. Synthesis of compounds **4a-d** and **5a-d**.

Entry	Starting materials		Reaction time (hours)	Pathway	Conditions Δ or US	Product	Yield (%)
	Compd.	R					
1	2a	C ₆ H ₅	4	A	Δ	4a	37
2	2b	4-Cl-C ₆ H ₄	4	A	Δ	4b	64
3	2c	4-CH ₃ O-C ₆ H ₄	4	A	Δ	4c	44
4	2d	4-COOCH ₃ -C ₆ H ₄	4	A	Δ	4d	43
5	2a	C ₆ H ₅	2	B	US	5a	67
6	2b	4-Cl-C ₆ H ₄	2	B	US	5b	40
7	2c	4-CH ₃ O-C ₆ H ₄	2	B	US	5c	69
8	2d	4-COOCH ₃ -C ₆ H ₄	2	B	US	5d	64
9	6a	4-Cl-C ₆ H ₄	0.5	C	Δ	4b	40
10	6b	4-CH ₃ O-C ₆ H ₄	0.5	C	Δ	4c	43

Conclusions

Thus, we showed that the multicomponent reactions involving 5-amino-3-methylthio-1,2,4-triazole, aromatic aldehydes, and pyruvic acid can be switched between two different pathways using either conventional thermal heating in acetic acid or ultrasonic activation at room temperature in the same solvent. Under conventional heating 2-(methylthio)-7-aryl-4,7-dihydro-[1,2,4]triazolo-[1,5-*a*]pyrimidine-5-carboxylic acids were formed both in the three-component treatment and in sequential two-step reaction *via* preliminary synthesis of arylidenpyruvic acid. In the case of ultrasonic activation the multicomponent reaction led to the formation of 7-hydroxy-2-(methylthio)-5-aryl-4,5,6,7-tetrahydro-[1,2,4]triazolo-[1,5-*a*]pyrimidine-7-carboxylic acids.

Experimental section

Melting points were determined with a Kofler apparatus and were uncorrected. The ¹H and ¹³C NMR spectra were recorded in DMSO-*d*₆ at 400 MHz (100 MHz for ¹³C NMR) with a Varian MR-400 spectrometer.

The mass spectra were measured Shimadzu GCMS-2020 instrument (70 eV ionizing energy) using the direct inlet (DI) method. Elemental analysis was performed on a Euro Vector EA-3000.

Ultrasound-assisted experiments were carried out using a standard ultrasound bath (SELDI, Ukraine) with a working frequency of 44.2 kHz.

Arylidenpyruvic acids **4a-b** were synthesized according to the literature procedure [20]. 3-(Methylthio)-1*H*-1,2,4-triazol-5-amine (**1**), 2-oxopropoic acid **2**, and substituted aldehydes **3a-d** were commercially available and were purchased from Merck.

General procedure for the preparation of compounds **5a-d**:

Method A: 100 mg (0.77 mmol) of 3-(methylthio)-1*H*-1,2,4-triazol-5-amine (**1**) were dissolved in glacial AcOH (2 mL), then pyruvic acid (**2**; 0.77 mmol) and the appropriate aldehyde (**2a-2d**; 0.77 mmol) were added. The mixture was refluxed for 4h, then it was cooled and allowed to stand overnight. After that, the resulting precipitate was collected by filtration and dried in air, yielding a colorless solid.

2-(methylthio)-7-phenyl-4,7-dihydro[1,2,4]triazolo-[1,5-*a*]pyrimidine-5-carboxylic acid (**4a**):

Yield: 27 mg, 37%; Colorless solid; mp 259-261 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.86 (s, 1H, NH), 7.15-7.42 (m, 5H, ArH), 6.18 (d, *J* 3.9 Hz, 1H), 5.77 (d, *J* 3.7 Hz, 1H), 2.39 (s, 3H, SCH₃). Anal. Calcd. for C₁₃H₁₂N₄O₂S: C, 54.16; H, 4.20; N, 19.43. Found C, 54.08; H, 4.27; N, 19.51. MS (EI, 70 eV) *m/z* (%) 288 (M⁺, 100), 243 (30), 211 (61), 193 (45), 165 (27), 115 (50), 77 (39).

7-(4-chlorophenyl)-2-(methylthio)-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-5-carboxylic acid (**4b**):

Yield: 76 mg, 64%; Colorless solid; mp 285-287 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.89 (s, 1H, NH), 7.20-7.46 (m, 4H, ArH), 6.22 (d, *J* 3.9 Hz, 1H, CH), 5.76 (d, *J* 3.7 Hz, 1H, CH), 2.39 (s, 3H, SCH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 163.7; 159.9; 150.6; 140.6; 133.9; 129.8; 129.7; 128.5; 106.9; 59.6; 14.4. Anal. Calcd. for C₁₃H₁₁ClN₄O₂S: C, 48.38; H, 3.44; N, 17.36. Found C, 48.25; H, 3.47; N, 17.39. MS (EI, 70 eV) *m/z* (%) 322 (M⁺, 30), 290 (11), 286 (18), 241 (18), 211 (65), 193 (56), 165 (52), 140 (60).

7-(4-methoxyphenyl)-2-(methylthio)-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-5-carboxylic acid (**4c**):

Yield: 106 mg, 44%; Colorless solid; mp 273-275 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.82 (s, 1H, NH), 6.87-

7.18 (m, 4H, ArH), 6.12 (d, J 3.9 Hz, 1H, CH), 5.75 (d, J 3.7 Hz, 1H, CH), 3.73 (s, 3H, OCH₃), 2.39 (s, 3H, SCH₃). Anal. Calcd. for C₁₄H₁₄N₄O₃S: C, 52.82; H, 4.43; N, 17.60. Found C, 52.72; H, 4.51; N, 17.65. MS (EI, 70 eV) m/z (%) 318 (M⁺, 89), 271 (65), 211 (34), 193 (40), 158 (100), 145 (72), 128 (50).

7-(4-(methoxycarbonyl)phenyl)-2-(methylthio)-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-5-carboxylic acid (4d):

Yield: 120 mg, 43%; Colorless solid; mp 255-257 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.99 (s, 1H, NH), 7.32-8.02 (m, 4H, ArH), 6.30 (d, J 3.9 Hz, 1H, CH), 5.78 (d, J 3.7 Hz, 1H, CH), 3.84 (s, 3H, OCH₃), 2.38 (s, 3H, SCH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.9; 162.7; 159.0; 149.8; 145.6; 129.8; 129.5; 127.6; 127.1; 105.8; 59.1; 52.2; 13.5. Anal. Calcd. for C₁₅H₁₄N₄O₄S: C, 52.02; H, 4.07; N, 16.18. Found C, 51.96; H, 4.16; N, 16.25. MS (EI, 70 eV) m/z (%) 346 (M⁺, 1), 211 (28), 165 (36), 140 (40), 128 (36), 119 (45), 115 (77).

The same compounds as **4b** and **4c** were obtained via two-component reaction (**Method C**) including appropriate arylidenpyruvic acids **6a-b** and 3-(methylthio)-1H-1,2,4-triazol-5-amine (**1**). 100 mg (0.77 mmol) of 3-(methylthio)-1H-1,2,4-triazol-5-amine (**1**) were dissolved in glacial AcOH (2 mL), then appropriate 2-oxo-4-arylbut-3-enoic acids were added. The mixture was refluxed for 30 min, then it was cooled and allowed to stand overnight. After that, the resulting precipitate was collected by filtration and dried in air, yielding a colorless solid.

Method B: 100 mg (0.77 mmol) of 3-(methylthio)-1H-1,2,4-triazol-5-amine (**1**) were dissolved in glacial AcOH (2 mL), then the appropriate aldehyde (**2a-d**; 0.77 mmol) and pyruvic acid (**3**; 0.77 mmol) were added. The mixture was put into the ultrasound bath for 120 min. Then the mixture was allowed to stand overnight. After that, the resulting precipitate was collected by filtration and dried in air, yielding a colorless solid.

7-hydroxy-2-(methylthio)-5-phenyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (5a):

Yield: 160 mg, 67%; Colorless solid; mp 152-154 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.84 (s, 1H, NH), 7.26-7.66 (m, 5H, ArH), 4.57-4.70 (m, 1H, CH), 2.42 (s, 3H, SCH₃), 2.04-2.32 (m, 2H, CH₂). Anal. Calcd. for C₁₃H₁₄N₄O₃S: C, 50.97; H, 4.61; N, 18.29. Found C, 50.87; H, 4.66; N, 18.32. MS (EI, 70 eV) m/z (%) 288 (M⁺-H₂O, 8), 243 (15), 211 (18), 130 (100).

5-(4-chlorophenyl)-7-hydroxy-2-(methylthio)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (5b):

Yield: 115 mg, 40%; Colorless solid; mp 169-171 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.79 (s, 1H, NH), 6.89-7.51 (m, 4H, ArH), 4.59-4.70 (m, 1H, CH), 3.06 (s, 3H, O-CH₃), 2.42 (s, 3H, SCH₃), 2.04-2.32 (m, 2H, CH₂). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 170.6; 159.4; 155.4; 133.1; 128.2; 114.4; 81.6; 55.6; 50.8; 42.4; 13.9. Anal. Calcd. for C₁₃H₁₃ClN₄O₃S: C, 45.82; H, 3.85; N, 16.44.

Found C, 45.76; H, 3.91; N, 16.52. MS (EI, 70 eV) m/z (%) 322 (M⁺-H₂O, 3), 211 (6), 165 (87), 137 (46), 130 (79).

7-hydroxy-5-(4-methoxyphenyl)-2-(methylthio)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (5c):

Yield: 180 mg, 69%; Colorless solid; mp 168-170 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.79 (s, 1H, NH), 6.88-7.41 (m, 4H, Ar), 4.54-4.63 (m, 1H, CH), 3.75 (s, 3H, OCH₃), 2.42 (s, 3H, SCH₃), 2.03-2.31 (m, 2H, CH₂). Anal. Calcd. for C₁₄H₁₆N₄O₄S: C, 49.99; H, 4.79; N, 16.66. Found: C, 50.07; H, 4.76; N, 16.71. MS (EI, 70 eV) m/z (%) 318 (M⁺-H₂O, 20), 271 (21), 151 (100), 133 (52), 130 (61).

7-hydroxy-5-(4-(methoxycarbonyl)phenyl)-2-(methylthio)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (5d):

Yield: 179 mg, 64%; Colorless solid; mp 159-161 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.74 (s, 1H, NH), 7.46-8.20 (m, 4H, Ar), 4.68-4.80 (m, 1H, CH), 3.90 (s, 3H, OCH₃), 2.43 (s, 3H, SCH₃), 2.13-2.41 (m, 2H, CH₂). Anal. Calcd. for C₁₅H₁₆N₄O₅S: C, 49.44; H, 4.43; N, 15.38. Found: C, 49.36; H, 4.51; N, 15.41. MS (EI, 70 eV) m/z (%) 346 (M⁺-H₂O, 3), 189 (67), 145 (40), 130 (100).

Notes

Acknowledgments and finances. The authors thank the National Academy of Sciences of Ukraine for financial support in the frame of the projects "Creation of modern bases for obtaining and analyzing substances and components of materials for pharmaceutical purposes" (0119U100727) and "Functional materials for biomedical purposes based on halogen-containing organic compounds" (0120U102660).

The authors declare no conflict of interest.

Author contributions. Ya. I. S.: synthesis of compounds, investigation, formal analysis, writing of the most part of the manuscript, editing. M. V. M.: synthesis of compounds, writing experimental section of the manuscript, formal analysis. N. V. C.: experimental section. M. A. K. and E. H. S.: mass experiments. S. M. D.: editing. M. V. I.: NMR correlation experiments. V. A. C. conceptualization, supervision, writing - review & editing.

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Переключаємі за рахунок умов багатоконпонентні реакції 5-аміно-3-(метилтіо)-1,2,4-триазолу, ароматичних альдегідів та піровиноградної кислоти

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Резюме: Вивчено багатоконпонентні реакції 5-аміно-3-метилтіо-1,2,4-триазолу з ароматичними альдегідами та піровиноградною кислотою із застосуванням звичайного термічного нагріву та при використанні ультразвукової активації при кімнатній температурі у тому ж самому розчиннику. При звичайному нагріванні в оцтовій кислоті утворювались 2-(метилтіо)-7-арил-4,7-дигідро-[1,2,4]триазоло-[1,5-а]піримідин-5-карбонові кислоти, як при трикомпонентній реакції, так і при послідовній двохкомпонентній реакції, шляхом попереднього синтезу ариліденпіровиноградних кислот. У випадку ультразвукової активації багатоконпонентна реакція в оцтовій кислоті за кімнатної температури приводила до утворення 7-гідрокси-2-(метилтіо)-5-арил-4,5,6,7-тетрагідро-[1,2,4]триазоло-[1,5-а]піримідин-7-карбонових кислот. Подальше вивчення особливостей утворення даних речовин має суттєве фундаментальне значення для детального розуміння механізмів формування азолазинових систем, що є важливим для цілеспрямованого синтезу гетероциклічних систем, які мають заздалегідь задані властивості. Показано перспективність синтезу нових гетероциклічних сполук цього класу, які прогнозовано мають широкий спектр біологічної активності.

Ключові слова: 5-аміно-3-(метилтіо)-1,2,4-триазол; багатоконпонентна реакція; ультразвук; піровиноградна кислота; гетероциклізація.