Microwave-Assisted and Ultrasonic-Assisted Three-Component Heterocyclization of 4-Amino-5-carboxamido-1,2,3-triazole, Thiopyran-3-one-1,1-dioxide, and Aromatic Aldehydes

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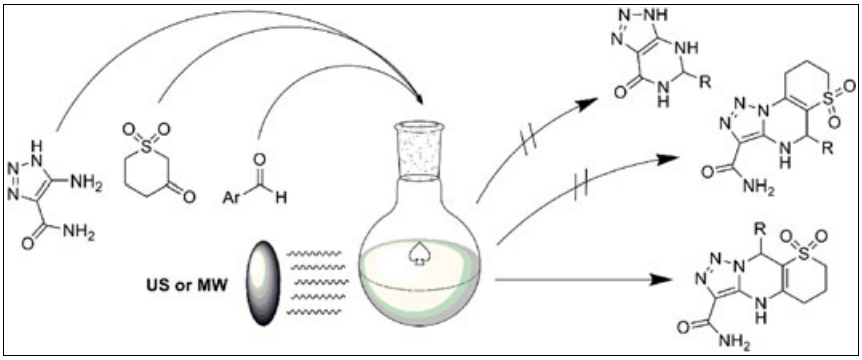
Received April 8, 2011
DOI 10.1002/jhet.1503
Published online 2 April 2013 in Wiley Online Library (wileyonlinelibrary.com).



Three-component heterocyclization of 4-amino-5-carboxamido-1,2,3-triazole, thiopyran-3-one-1,1-dioxide, and aromatic aldehydes under ultrasonic and microwave irradiation was studied. Regardless of the reaction parameters, 5,6,7,9-tetrahydro-4*H*-thiopyrano[3,2-*d*][1,2,3]triazolo[1,5-*a*]pyrimidine-8,8-dioxides were isolated as sole reaction products whose structures were proven with help of NMR data and X-ray analysis.

J. Heterocyclic Chem., **50**, E189 (2013).

INTRODUCTION

Highly substituted partially hydrogenated azolopyrimidines belong to an important class of organic compounds because of their known biological activities, for example, as cardiovascular vasodilators, calcium channel blocking agents, and potassium channel inhibitors and openers [1]. The most facile and widespread method for synthesis of these heterocycles is the reaction of aminoazoles with α,β-unsaturated ketones [2] or with their precursors – carbonyl containing CH acids and aldehydes [3]. The multicomponent procedures are considered more efficient and attract the attention of scientists. For instance, diverse azolopyrimidines were synthesized by such reactions involving numerous active methylene compounds such as acetoacetic acid derivatives, β-diketones, and pyruvic acids [2–4]. Perspective building blocks for multicomponent heterocyclizations, from the viewpoint of biological activity of the final heterocycles, are cyclic β-ketosulfones [5]. α-Sulfonyl and α-keto groups are good activators for CH_2 reaction center, allowing participation of β-ketosulfones not only in multicomponent treatments as active methylene components but also in other processes, for example, in β-alkylation of unsaturated carbonyl compounds [6].

However, in the most cases reported, 3-amino-1,2,4-triazoles, 5-aminotetrazole, 2-aminoimidazoles, and 2-aminobenzimidazole have been used as aminoazole component, whereas application of 4-amino-1,2,3-triazole has not been practically described for the above-mentioned multicomponent cyclocondensations. There are only a few examples of heterocyclizations involving 4-amino-1,2,3-triazoles: with β-diketones [4a, 7a], with *N*-cyanomethane imidates [7b], with isocyanates [7c], with chalcones [7d], and with acetoacetamides [4a]. It should be additionally noted that in some cases, participation in the heterocyclization of both carboxamide and NH_2 groups was observed [8].

In the present article, we disclose the results of our studies of the multicomponent heterocyclization between 4-amino-5-carboxamido-1,2,3-triazole, thiopyran-3-one-1,1-dioxide, and aromatic aldehydes under ultrasonic and microwave irradiation. In several of our recent publications [4f,g, 9], it was shown that the direction of the similar treatments can greatly depend on the reaction parameters including activation method, temperature, and type of the reaction medium.

RESULTS AND DISCUSSION

It was found that three-component cyclocondensation of 4-amino-5-carboxamido-1,2,3-triazole (**1**), thiopyran-3-one-1,1-dioxide (**2**), and the appropriate aromatic aldehyde **3a–e** under microwave irradiation (MeOH, 120°C, 15 min, method i) or under ultrasonication (HOAc, 35°C, 90 min, method ii) led to the formation of 5,6,7,9-tetrahydro-4*H*-thiopyrano[3,2-*d*][1,2,3]triazolo[1,5-*a*]pyrimidine-8,8-dioxides **4a–e** as sole reaction products (Scheme 1, Table 1).

The same compounds were obtained when the conditions of this reaction were varied. For example, microwave-assisted treatment of the starting materials in acetic acid or in methanol containing catalytic amounts of HCl as well as their ultrasonication in methanol (pure or containing HCl) always gave heterocycles **4a–e**, although in yields lower than under optimal conditions.

Similar situation was observed when the temperature of the treatment was changed within 20–45°C for ultrasonication and within 120–140°C for microwave-assisted synthesis.

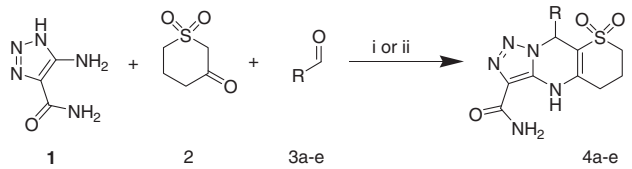
In the most cases, yields of the three-component reactions studied were higher for the ultrasonic-promoted procedures (Table 1). However, in the case of 4-Br-benzaldehyde **3d** under ultrasonication, the target reaction product was isolated with significant amount (up to 30%) of imine **6**. Microwave-assisted synthesis gave better result that allowed the improvement of the yield of compound **4d** up to 55% and avoided formation of azomethine. It should be noted that the reaction involving 4-Cl-benzaldehyde under ultrasonication yielded only imine **6** while corresponding fused pyrimidine **4** was not detected at all.

Alternative angular thiopyrano[2,3-*e*][1,2,3]triazolo-[1,5-*a*]pyrimidine-3-carboxamide-6,6-dioxides (**5**), whose content was inspected in ultrasonic-assisted synthesis at 35°C via formation of imines **6**, as it had been reported for similar reactions [4g, 9], were not found. Heterocyclic compounds **7**, whose analogues had also been described earlier [8], were not isolated as well.

These conclusions were made on the basis of physicochemical, spectral, and X-ray analysis data. For example, mass spectra and elemental analysis, showing a presence of fragments of all starting materials in equimolar ratio, allowed us to exclude structure **7**.

^{1}H NMR spectra of the main reaction products exhibited the following signals: characteristic resonances for the aromatic rings (6.9–7.3 ppm), a singlet for Ar–CH proton (6.6–6.9 ppm), a broad singlet for pyrimidine NH and amido group (7.4–10.0 ppm), complicated signals for $(CH_2)_3$ fragment (2.2–3.3 ppm), and signals for terminal substituents. This set of signals can correspond to both linear (compounds **4**) and angular (compounds **5**) heterocycles. However, our earlier experience with similar compounds demonstrated a distinct dependence of the chemical shift of the pyrimidine NH group in the ^{1}H NMR spectrum on its position in the dihydroazine fragment [4f,g, 9a, 10]. Linear structures such as **4** exhibit a signal for this proton at 9.5–10.5 ppm, whereas in the case of compounds such as **5**, it usually strong-field

Scheme 1



i - MeOH, MW, 120 °C, 15 min;
ii - HOAc, US, 35 °C, 90 min.

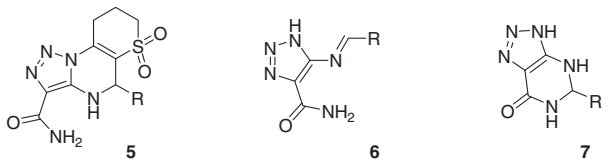


Table 1

Synthesis of compounds **4a–e**.

Entry	R	Yield, % (MW)	Yield, % (US)
4a	C_6H_5	35	63
4b	4-$CH_3OC_6H_4$	25	71
4c	2-$CH_3OC_6H_4$	15	77
4d	4-BrC_6H_4	55	16
4e	4-$CH_3C_6H_4$	41	56

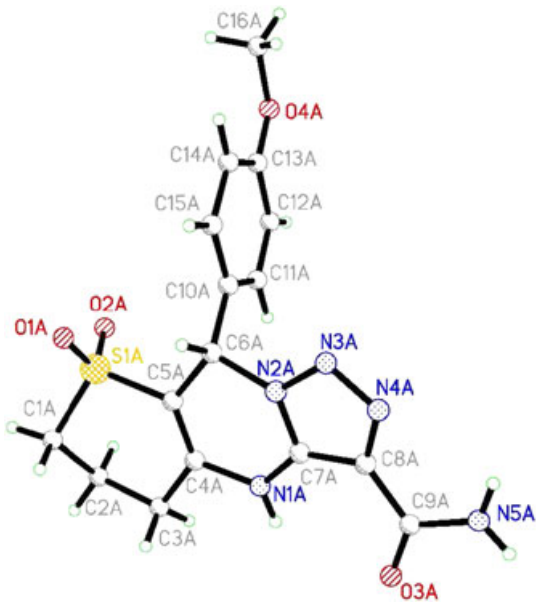


Figure 1. Molecular structure (X-ray diffraction data) of 5-(4-methoxyphenyl)-5,7,8,9-tetrahydro-4*H*-thiopyrano[2,3-*e*][1,2,3]triazolo-[1,5-*a*]pyrimidine-3-carboxamide-6,6-dioxide (**4b**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

shifted by 2–3 ppm. As a further confirmation of structure **4**, NOE and COSY correlations were not found between the CH and NH groups in the pyrimidine moiety.

Ultimately, the structure of heterocycles **4** was established by X-ray diffraction study carried out for a single crystal of compound **4b** (Figure 1).

CONCLUSION

Thus, under microwave or ultrasonic irradiation three-component heterocyclization of 4-amino-5-carboxamido-1,2,3-triazole, thiopyran-3-one-1,1-dioxide, and aromatic aldehydes regardless of other reaction parameters led to the formation of earlier undescribed 5,6,7,9-tetrahydro-4*H*-thiopyrano[3,2-*d*][1,2,3]triazolo[1,5-*a*]pyrimidine-8,8-dioxides. Application of ultrasonication in the most case gave better results from the viewpoint of yields.

EXPERIMENTAL

Melting points of all compounds synthesized were determined with a Gallenkamp melting point apparatus (Germany) in open capillary tubes. Analytical HPLC was performed on Merck RP-18 (Merck, Germany) column (250 × 4.1 mm) using gradient or isocratic elution by acetonitrile–water mixture (UV detection at 254 nm). The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 400 MHz (100 for ^{13}C) using Jeol Lambda 400 spectrometer (JEOL Ltd., Tokyo, Japan) or at 200 MHz using Varian Mercury VX-200 spectrometer. Low resolution mass spectra were measured on a GC–MS Varian 1200L (Varian Inc., USA, California, Palo Alto) (ionizing voltage 70 eV) instrument. Elemental analysis was realized on a EuroVector EA-3000 (EuroVector SpA, Milan, Italia). TLC analyses were performed on precoated (silica gel 60 HF_{254}) plates.

Ultrasonication was carried out with the help of standard ultrasonic bath, producing irradiation at 44.2 kHz in round-bottom flasks equipped with a condenser.

Microwave experiments were performed using Emrys Initiator reactors from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in sealed microwave process vials using high absorbance level settings and IR temperature monitoring. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

Solvents and chemicals were obtained from standard commercial vendors and were used without any further purification.

Starting aminoazole **1** and β-ketosulfone **2** were obtained by known methods [11,12].

X-ray diffraction data. The colorless crystals of **4b** 2 ($C_{16}H_{17}N_5O_4S$)·H_2O are triclinic. At 293 K, $a = 8.6210(2)$, $b = 14.3580(4)$, $c = 14.6850(5)$ Å, $\alpha = 106.528(3)°$, $\beta = 93.530(2)$, $\gamma = 90.368(2)°$, $V = 1738.8(1)$ Å^3, Mr = 768.83, $Z = 2$, space group $P_{\bar{1}}$, $d_{calc} = 1.468$ g/cm^3, $\mu(MoK\alpha) = 0.223$ mm^{-1}, $F(000) = 804$. Intensities of 12,247 reflections (6101 independent, $R_{int} = 0.149$) were measured on the "Xcalibur-3" diffractometer (Varian Inc., Palo Alto, CA) (graphite monochromated MoKα radiation, CCD detector, ω-scanning, $2\Theta_{max} = 50°$).

The structure was solved by direct method using SHELXTL package [13]. Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with $U_{iso} = nU_{eq}$ of the carrier atom ($n = 1.5$ for methyl group and $n = 1.2$ for other hydrogen atoms). Full-matrix least-squares refinement of the structures against F^2 in anisotropic approximation for nonhydrogen atoms using 5966 reflections was converged to $wR_2 = 0.104$ ($R_1 = 0.050$ for 1209 reflections with $F > 4\sigma(F)$, $S = 0.523$). The final atomic coordinates and crystallographic data for molecule **4b** have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition number CCDC 808028.

Procedure for the synthesis of 5-phenyl-5,7,8,9-tetrahydro-4*H*-thiopyrano[2,3-*e*][1,2,3]triazolo[1,5-*a*]-pyrimidine-3-carboxamide-6,6-dioxide (4a)

Method i (microwave-assisted). A mixture of 1.27 g (10 mmol) of 4-amino-5-carboxamido-1,2,3-thriazole (**1**), 1.48 g (10 mmol) of thiopyran-3-one-1,1-dioxide (**2**), and 1.06 g (10 mmol) of benzaldehyde (**3a**) in 3 mL of methanol in 5 mL closed MW vial was irradiated in the reactor for 15 min at 120°C. The reaction mixture was cooled down (5°C), and the precipitate formed was filtered off and washed with methanol. Recrystallization from DMF–methanol (1:3) afforded 1.21 g (35%).

Method ii (ultrasonic-assisted). A mixture of 1.27 g (10 mmol) of 4-amino-5-carboxamido-1,2,3-thriazole (**1**), 1.48 g (10 mmol) of thiopyran-3-one-1,1-dioxide (**2**), and 1.06 g (10 mmol) of benzaldehyde (**3a**) in 10 mL of glacial acetic acid were ultrasonicated in ultrasonic bath at 35°C for 90 min. The reaction mixture was mixed with 5 mL of water, and precipitated solid was filtered off and washed with small amount of cold methanol. Yield is 2.20 g (63%).

Colorless crystals, mp 304–305°C; ^{1}H NMR (DMSO-d_6): δ 2.26 (m, 2H, CH_2), 2.68 (m, 1H, CH_2), 2.94 (m, 1H, CH_2), 3.25 (m, 2H, CH_2), 6.72 (s, 1H, 9-H), 7.33 (m, 5H, Ar), 7.42 (bs, 1H, NH_2), 7.78 (bs, 1H, NH_2), 9.98 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 18.1, 26.0, 49.9, 54.9, 106.1, 123.4, 127.2, 128.7, 128.8, 135.2, 139.8, 141.6, 162.3 ppm; MS (EI): *m/z* 346 (M + 1), 307, 289; *Anal.* Calcd for $C_{15}H_{15}N_5O_3S$: C, 52.16; H, 4.38; N, 20.28; S, 9.28%. Found: C, 52.22; H, 4.30; N, 20.35; S, 9.29%.

5 - (4 -Methoxyphenyl) - 5,7,8,9- tetrahydro -4*H*-thiopyrano [2,3 -*e*][1,2,3]triazolo[1,5-*a*]pyrimidine -3- carboxamide - 6,6 - dioxide (4b). Colorless crystals, mp 300–301°C; ^{1}H NMR (DMSO-d_6): δ 2.27 (m, 2H, CH_2), 2.67 (m, 1H, CH_2), 2.93 (m, 1H, CH_2), 3.27 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 6.68 (s, 1H, 9-H), 6.91 (d, 2H, Ar), 7.26 (d, 2H, Ar), 7.41 (bs, 1H, NH_2), 7.77 (bs, 1H, NH_2), 9.93 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 18.1, 26.0, 50.0, 54.5, 55.1, 106.3, 114.0, 123.3, 128.6, 131.9, 135.1, 141.4, 159.4, 162.3 ppm; MS (EI): *m/z* 376 (M + 1), 307, 289; *Anal.* Calcd for $C_{16}H_{17}N_5O_4S$: C, 51.19; H, 4.56; N, 18.66; S, 8.54%. Found: C, 51.24; H, 4.47; N, 18.71; S, 8.50%.

5-(2-Methoxyphenyl)-5,7,8,9-tetrahydro-4*H*-thiopyrano[2,3-*e*][1,2,3]triazolo[1,5 - *a*]pyrimidine - 3 - carboxamide - 6,6 - dioxide (4c). Colorless crystals, mp 291–292°C; ^{1}H NMR (DMSO-d_6): δ 2.23 (m, 2H, CH_2), 2.66 (m, 1H, CH_2), 2.90 (m, 1H, CH_2), 3.23 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 6.89 (s, 1H, 9-H), 6.93 (m, 1H, Ar), 7.01 (dd, 1H, Ar), 7.25 (dd, 1H, Ar), 7.30 (m, 1H, Ar), 7.38 (bs, 1H, NH_2), 7.72 (bs, 1H, NH_2), 9.84 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 23.4, 31.3, 35.9, 55.4, 61.6, 110.8, 117.6, 125.8, 128.1, 133.3, 134.5, 135.6, 141.1, 146.4, 162.3, 167.7 ppm; MS (EI): *m/z* 376 (M + 1), 307, 289; *Anal.* Calcd for $C_{16}H_{17}N_5O_4S$: C, 51.19; H, 4.56; N, 18.66; S, 8.54%. Found: C, 51.21; H, 4.41; N, 18.60; S, 8.61%.

5-(4-Bromophenyl)-5,7,8,9-tetrahydro- 4*H*-thiopyrano[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine-3-carboxamide-6,6- dioxide (4d). Colorless crystals, mp 307°C (with decomposition); ^{1}H

NMR (DMSO-d_6): δ 2.25 (m, 2H, CH_2), 2.63 (m, 1H, CH_2), 2.91 (m, 1H, CH_2), 3.31 (m, 2H, CH_2), 6.62 (s, 1H, 9-H), 6.93 (d, 2H, Ar), 7.27 (d, 2H, Ar), 7.43 (bs, 1H, NH_2), 7.80 (bs, 1H, NH_2), 9.99 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 19.2, 27.4, 52.1, 53.9, 107.0, 113.8, 122.9, 128.5, 132.2, 134.9, 141.1, 160.5, 162.5 ppm; MS (EI): *m/z* 424 (M + 1), 338, 307, 289; *Anal*. Calcd for $C_{15}H_{14}BrN_5O_3S$: C, 42.46; H, 3.33; N, 16.51; S, 7.56%. Found: C, 42.50; H, 3.27; N, 16.59; S, 7.50%.

5-(4-Methylphenyl)-5,7,8,9-tetrahydro - 4*H* - thiopyrano[2,3 - *e*] [1,2,3]triazolo[1,5- *a*]pyrimidine - 3 - carboxamide - 6,6 - dioxide (4e). Colorless crystals, mp 289–290°C; ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.26 (m, 2H, CH_2), 2.61 (m, 1H, CH_2), 2.91 (m, 1H, CH_2), 3.28 (m, 2H, CH_2), 6.65 (s, 1H, 9-H), 7.12 (d, 2H, Ar), 7.20 (d, 2H, Ar), 7.42 (bs, 1H, NH_2), 7.80 (bs, 1H, NH_2), 9.95 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 18.9, 21.3, 26.8, 51.0, 55.6, 107.3, 124.1, 127.8, 129.8, 136.0, 137.6, 138.8, 142.1, 163.0 ppm; MS (EI): *m/z* 360 (M + 1), 314, 289, 212; *Anal*. Calcd for $C_{16}H_{17}N_5O_3S$: C, 53.47; H, 4.77; N, 19.49; S, 8.92%. Found: C, 53.55; H, 4.68; N, 19.52; S, 8.88%.

Acknowledgments. We are grateful for the financial support from DAAD (scholarship A/09/02523).

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