Microwave assisted synthesis of some novel thiadiazolothienopyrimidines

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3-Amino-2-mercapto-3,5,6,7,8,9-hexahydro-4*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-one (**4**) was prepared, and from this a series of 2-(arylaminomethyl)-7,8,9,10-tetrahydro-6*H*,11*H*-cyclohepta[4,5]thieno[2,3-*d*][1,3,4]thiadiazolo [3,2-*a*]pyrimidin-11-ones (**6a–d**) were synthesised through the corresponding 2-chloromethyl compound (**5**) with aromatic amines under microwave irradiation.

Keywords: fused pyrimidines, 1,3,4-thiadiazoles, thiophenes; microwave heating

Pyrimidine derivatives are very important in biochemistry and biotransformations.[1] The ring system is present in cytosine, adenine, guanine and thiamine, constituents of DNA and RNA, and in vitamins such as B_2 and B_6. Heterocondensed quinazolines such as thiadiazoloquinazolines and its thidiazolothienopyrimidine isosteres, analogues of the purines, exhibit various medicinal properties such as antihypertensive,[2] antibacterial,[3] antiallergic,[4] anticonvulsant,[5] analgesic[6] and $5HT_{1A}$-antagonistic[7] activities. Thiadiazolopyrimidines have been reported to possess antibacterial,[8] fungicidal and herbicidal[9] activities. These observations prompted us to attempt the synthesis of thiadiazolothienopyrimidines.

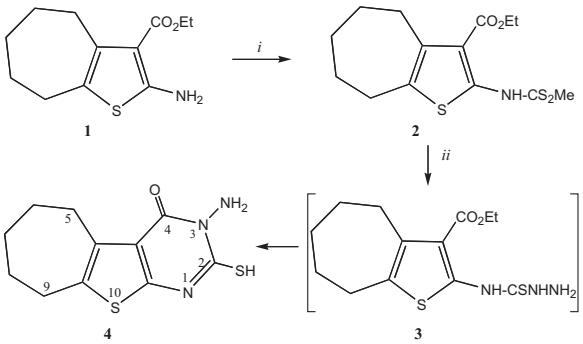
Microwave-assisted organic synthesis has had a significant impact on synthetic organic chemistry since 1986, with the introduction of controlled, precise microwave reactors,[10] and has gained popularity due to enhanced selectivity, improved reaction rates, ease of manipulation and eco-friendliness of the reactions. Here we report a microwave-assisted route for the preparation of 2-(arylaminomethyl)-7,8,9,10-tetrahydro-6*H*,11*H*-cyclohepta[4,5]thieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-11-ones (**6a–d**).

Results and discussion

Only few reports are available in the literature on the synthesis of condensed 3-amino-2-mercaptothieno[2,3-*d*]pyrimidin-4(5*H*)-ones. Modica *et al.*[7] reported the synthesis of 2,3,5,6,7,8-hexahydro-3-amino-2-thioxobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(1*H*)-one from the reaction of the corresponding ethyl 2-isothiocyanatobenzothiophene-3-carboxylate with hydrazine hydrate. However, this route was not attractive as it involves the use of the highly toxic thiophosgene, making it less environment friendly, and it proceeds in low yield.[7] Here a novel, simple route for the preparation of compound **4** is described. (Scheme 1)

Although *ortho*-aminothiophenecarboxylic esters have been prepared by various methods,[12,13] Gewald's synthesis is the most popular route.[14] However, we found that the required starting material, ethyl 2-amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carboxylate (**1**), could not be prepared by the direct Gewald method, and so it was made by a modification of that route. Cycloheptanone, ethyl cyanoacetate, ammonium acetate and benzene were heated to reflux for 8 h in a Dean-Stark apparatus with constant removal of water. The solution was washed with 10% aqueous sodium carbonate solution and dried, and the benzene was removed. The residue was stirred with sulfur in ethanol for one hour, with slow addition of diethylamine. The reaction mixture was then cooled in a refrigerator for 12 h to provide the target compound (**1**), evidently identical (m.p., IR) with material previously[12] reported.

The dithiocarbamate derivative, methyl *N*-(3-ethoxycarbonyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thien-2-yl) dithiocarbamate (**2**) was obtained by reacting the thiophene **1** with carbon disulfide, sodium hydroxide and then dimethyl sulfate in DMSO. The disappearance of two peaks between 3200 and 3400 cm^{-1} and the appearance of a single peak in the same range indicated the conversion of primary amine to secondary amide. The ^1H NMR spectrum showed SCH_3 protons as a singlet at δ 2.65. This material was converted into the fused pyrimidine **4** by heating in isopropanol with hydrazine hydrate in a microwave oven at 960 W for 300 s. The appearance of two peaks of the primary amino group at 3250 and 3353 cm^{-1} in the IR and the shift of the C=O peak from 1690 to 1670 cm^{-1} consistent with formation of the cyclised product. The NMR spectrum showed the primary amino protons at δ 4.7 as a broad singlet which, together with the loss of the OEt and SMe signals, further confirmed the formation of **4**. The mass spectrum showed the molecular ion as the base peak.



Reagents: i, (a) CS_2/NaOH, *(b)* Me_2SO_4/DMSO; *ii,* $N_2H_4.H_2O$, MW

Scheme 1

2-(Arylaminomethyl)-7,8,9,10-tetrahydro-6*H*,11*H*-cyclohepta[4,5]thieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-11-ones (**6a–d**) were prepared by following the route depicted in Scheme 2. The 2-chloromethyl compound **5** was prepared by two methods. In the first, equimolar quantities of compound **4** and chloroacetic acid were fused in a microwave oven in presence of a catalytic amount of conc. sulfuric acid to give the target compound in moderate yields. In the second method, equimolar quantities of **4** and chloroacetyl chloride were heated for 180 s in a microwave oven to provide compound **5**, identical (m.p., TLC, IR) with the former sample. The disappearance of the IR peaks at 3250 and 3353 cm^{-1}, and appearance of C–Cl peak at 780 cm^{-1} indicated the formation of the product. The disappearance of amino signal at δ 4.7 and appearance of CH_2Cl signal at δ 4.92 as a singlet in the ^1H NMR gave further confirmation of structure **5**.

The chloromethyl compound **5** was taken in dioxan with various arylamines in the presence of an equimolar quantity of triethylamine and irradiated in a microwave oven to give 2-(arylaminomethyl)-7,8,9,10-tetrahydro-6*H*,11*H*-cyclohepta-[4,5]thieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-11-ones

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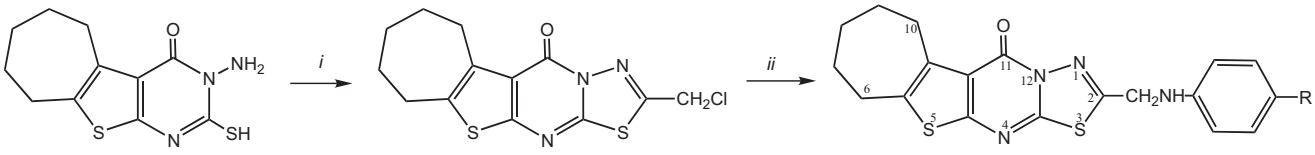

4 **5** **6a-d**

Reagents: *i*, $ClCH_2CO_2H$ or $ClCH_2COCl$; MW; *ii*, $RC_6H_4NH_2$,/Et_3N, MW R = (**a**) H, (**b**) OMe, (**c**) CH_3, (**d**) NO_2

Scheme 2

(**6a–d**) in fair to good yields. These compounds showed the disappearance of the C-Cl peak at 780 cm^{-1} in IR and shift of the signal from δ 4.92 (CH_2Cl) to *ca* 5.5 (CH_2NHAr) in the NMR. The mass spectra of the products showed the molecular ion peaks at their respective molecular weights, and the fragmentation patterns were in accordance with the assigned structures. The physical and spectral data of all the newly synthesised compounds are presented in the Experimental section.

Experimental

Analytical TLC was performed on silica gel F_{254} plates (Merck) with visualisation by UV or iodine vapor. Melting points were determined in open capillaries on a Gallenkamp melting point apparatus (Sanyo Gallenkamp, Loughborough, UK). The IR spectra (KBr discs) were run on a Perkin-Elmer Spectrophotometer model 577. ^1H NMR ($CDCl_3$) spectra were recorded using a Bruker WM-400 spectrometer with TMS as internal standard (Bruker, Flawil, Switzerland). Mass spectra were recorded on JEOL D-300 (EI/CI) spectrometer (JEOL, Tokyo, Japan). Elemental analyses were performed on a Carlo Erba 1108 elemental analyser (Milan, Italy). All the chemicals used were of analytical grade (Merck). Microwave irradiations were carried out in an unaltered domestic microwave oven (LG-Intello Chef-MOD-MS-257PL, 960 W).

Ethyl 2-amino-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carboxylate (**1**): A mixture of cycloheptanone (4.48 g, 0.04 mole), ethyl cyanoacetate (4.52 g, 0.04 mole) and ammonium acetate (2.0 g, 0.023 mole) with glacial acetic acid (2.0 ml) was taken in benzene (80 ml) and heated to reflux for 8 h in a Dean-Stark apparatus, removing benzene–water mixture and replacing it with fresh benzene. After 8 h, heating was stopped and 10% sodium bicarbonate solution was added to mixture in separating funnel and upper layer was collected and dried over anhydrous sodium sulfate. The solvent was distilled off until 7–8 ml solution was left and this was added to a heated solution of sulfur (1.28 g, 0.04 g-atom) in ethanol (40 ml). It was stirred for 60 min with constant slow addition of diethylamine (2.92 g, 0.04 mole). The stirring was continued until the sulfur dissolved. The solution was cooled in refrigerator over night. The precipitate obtained was filtered and dried, and the crystalline product was recrystallised from ethanol as a pale yellow crystalline material (7.33 g, 78%), m.p. 85°C (lit.[12] m.p. 84–85ºC).

Methyl N-(3-ethoxycarbonyl-5,6,7,8-tetrahydro-4H-cyclohepta[b]thien-2-yl)dithiocarbamate (**2**): To a vigorously stirred solution of the amino-ester **1** (4.78 g, 0.02 mole) in DMSO (10.0 ml) at room temperature, carbon disulfide (1.6 ml, 0.026 mole) and aqueous sodium hydroxide (1.2 ml, 20 mole) were added dropwise. After 30 min stirring the containing flask was surrounded by an ice bath and dimethyl sulfate (1.2 ml, 0.025 mole) was added dropwise to the solution. Stirring was continued for 3 h. The reaction mixture was poured into ice-water mixture. The precipitate so obtained was filtered, dried and recrystallised from ethanol as a pale yellow amorphous powder (5.35 g, 81%), m.p. 80°C. IR: 1685, 3231 cm^{-1}. ^1H NMR: δ 1.39–1.42 (t, 2H, CH_2, J = 4.1 Hz), 1.60–1.69 (m, 4H, CH_2), 1.81–1.84 (t, 2H, CH_2, J = 3.9 Hz), 2.68 (s, 3H, SCH_3), 2.71–2.73 (t, 3H, $OCH_2C\underline{H}_3$, J = 3.8 Hz), 3.04–3.06 (t, 2H, CH_2, J = 4.0 Hz), 4.36–4.41 (q, 2H, $OC\underline{H}_2CH_3$, J = 3.8 Hz), 12.9 (s, 1H, NH, D_2O exchangeable). MS: *m/z* 329 (M^+). Anal. Calcd for $C_{14}H_{19}NO_2S_3$: C, 51.06; H, 5.77; N, 4.25. Found: C, 51.25; H, 6.10; N, 4.45%.

3-Amino-2-mercapto-3,5,6,7,8,9-hexahydro-4H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4-one (**4**): Compound **2** (0.329 g, 0.001 mole) in isopropanol (1.0 ml) was heated at 960 W in a domestic microwave oven with hydrazine hydrate (99%) (0.5 g, 0.001 mole), until the evolution, of methyl mercaptan ceased (300 s). After cooling, the solid obtained was filtered, dried and recrystallised from ethanol as white needles (0.165 g, 61%), m.p. 242°C. IR: 1680, 3353 cm^{-1}. ^1H NMR: δ 1.65–1.72 (m, 4H, CH_2), 1.84–1.87 (p, 2H, CH_2, J = 3.55 Hz), 2.74–2.76 (t, 2H, CH_2, J = 3.65 Hz), 3.21–3.24 (t, 2H, CH_2, J = 3.65 Hz). MS: *m/z* 267 (M^+). Anal. Calcd for $C_{11}H_{13}N_3OS_2$: C, 49.41; H, 4.90; N, 15.72. Found: C, 49.65; H, 5.10; N, 15.89%.

2-Chloromethyl-7,8,9,10-tetrahydro-6H,11H-cyclohepta[4,5]thieno[2,3-d] [1,3,4]thiadiazolo[3,2-a]pyrimidin-11-one (**5**): *Method A*. Fusion of compound **4** (0.267 g, 0.001 mole) and chloroacetic acid (0.095 g, 0.001 mole) was carried out in the presence of a catalytic amount of sulfuric acid by irradiating the mixture for 300 s at 960 W in a domestic microwave oven. The reaction mixture was cooled and ice-water was added to extract the unreacted chloroacetic acid. The solid obtained was filtered off, dried, and recrystallised from benzene as white crystals (0.265 g, 82%).

Method B: Fusion of compound **4** (0.267 g, 0.001 mole) and chloroacetyl chloride (0.113 g, 0.001 mole) was carried out by irradiating the mixture for 180 s at 960 W in a domestic microwave oven. The reaction mixture was cooled and ice water was added to neutralise the unreacted chloroacetyl chloride. The solid obtained was filtered off, washed with water to remove the traces of acid, dried, and recrystallised from benzene as white crystals, m.p. 226°C. IR: 784, 1677, 2976 cm^{-1}. ^1H NMR: δ 1.62–1.66 (m, 4H, CH_2), 1.87 (p, 2H, CH_2, J = 8.0 Hz), 2.78–2.80 (t, 2H, CH_2, J = 8.0 Hz), 3.28–3.30 (t, 2H, CH_2, J = 8.0 Hz), 4.92 (s, 2H, CH_2Cl). MS: *m/z* 325 (M^+). Anal. Calcd for $C_{13}H_{12}ClN_3OS_2$: C, 47.92; H, 3.71; N, 12.90. Found: C, 48.28; H, 3.85; N, 13.15%.

2-(Arylaminomethyl)-7,8,9,10-tetrahydro-6H,11H-cyclohepta[4,5]thieno[2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidin-11-ones (**6a–d**): A mixture of compound **5** (0.325 g, 1 mmol), triethylamine (0.101 ml, 1 mmol) and the aromatic amine (1 mmol) in dioxan (1.0 ml) was taken in a test tube and irradiated for 180 s at 960 W in a domestic microwave oven by switch off/on method. (The irradiation was carried out for 30 s, switched off and again switched on after adding dioxan to maintain the losses due to evaporation). The reaction mixture was cooled to room temperature, poured into ice-cold water, and the excess of amine was neutralised by dilute hydrochloric acid (10%). The precipitate obtained was filtered, dried and recrystallised from ethanol.

2-(Phenylaminomethyl)-7,8,9,10-tetrahydro-6H,11H-cyclohepta[4,5]thieno[2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidin-11-one (**6a**): Light brown crystals, (0.275 g, 72%), m.p. 250°C. IR: 1673, 2917, 3297 cm^{-1}. ^1H NMR: δ 1.69–1.71 (m, 6H, CH_2), 2.77–2.80 (t, 2H, CH_2, J = 4.43 Hz), 3.33–3.36 (t, 2H, CH_2, J = 4.1 Hz), 5.68 (s, 2H, $C\underline{H}_2NH$), 6.66–6.70 (t, 1H, CH, J = 8.0 Hz), 6.77–6.79 (d, 2H, CH, J = 8.0 Hz), 7.11–7.15 (t, 2H, CH, J = 7.8 Hz), 7.61 (s, 1H, NH). MS: *m/z* 382 (M^+). Anal. Calcd for $C_{19}H_{18}N_4OS_2$: C, 59.68; H, 4.71; N, 14.65. Found: C, 59.85; H, 4.96; N, 14.89%.

2-[(4-Methoxyphenyl)aminomethyl]-7,8,9,10-tetrahydro-6H,11H-cyclohepta[4,5]thieno[2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidin-11-one (**6b**): Pale yellow crystals (0.272 g, 66%), m.p. 216°C. IR: 2848, 3004 cm^{-1}. ^1H NMR: δ 1.66–1.70 (m, 6H, CH_2), 2.77–2.80(t, 2H, CH_2, J = 4.8 Hz), 3.32–3.34 (t, 2H, CH_2 (6), J = 5.0 Hz), 3.68 (s, 3H, OCH_3), 5.48 (s, 2H, $C\underline{H}_2NH$), 5.94–5.95 (d, 2H, CH, J = 5 Hz), 6.72–6.73 (d, 2H, CH, J = 5 Hz), 7.81 (s, 1H, N$\underline{H}$). MS: m/z 412 (M^+). Anal. Calcd for $C_{20}H_{20}N_4O_2S_2$: C, 58.25; H, 4.85; N, 13.59. Found: C, 58.35; H, 5.05; N, 13.75%.

2-(4-Tolylaminomethyl)-7,8,9,10-tetrahydro-6H,11H-cyclohepta[4,5]thieno[2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidin-11-one (**6c**): Brownish crystals (0.277 g, 70%), m.p. 276°C. IR: 2918, 3364 cm^{-1}. ^1H NMR: δ 1.66–1.70 (m, 6H, CH_2), 2.25 (s, 3H, CH_3), 2.79–2.82 (t, 2H, CH_2, J = 4.85 Hz), 3.30–3.33 (t, 2H, CH_2, J = 4.9 Hz), 5.55 (s, 2H, $C\underline{H}_2NH$), 6.65–7.15 (m, 4H, ArH), 7.52 (s, 1H, NH). CI-MS: *m/z* 397 (M^+ + 1). Anal. Calcd for $C_{20}H_{20}N_4OS_2$: C, 60.60; H, 5.05; N, 14.14. Found: C, 60.85; H, 5.25; N, 14.35%.

2-[(4-Nitrophenyl)aminomethyl]-7,8,9,10-tetrahydro-6H,11H-cyclohepta[4,5]thieno[2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidin-11-one (**6d**): Brownish crystals (0.295 g, 69%), m.p. 127°C. IR: 1550, 2916,

3364 cm^{-1}. ^1H NMR: δ 1.66–1.70 (m, 6H, CH_2), 2.82–2.85 (t, 2H, CH_2, J = 5.2 Hz), 3.33–3.35 (t, 2H, CH_2, J = 5.2 Hz), 5.54 (s, 2H, $C\underline{H}_2NH$), 7.67 (s, 1H, NH), 8.01–8.03 (d, 2H, ArH, J = 7.2 Hz), 8.81–8.83 (d, 2H, ArH, J = 7.2 Hz). MS: m/z 427 (M^+). Anal. Calcd for $C_{19}H_{17}N_5O_3S_2$: C, 53.39; H, 3.98; N, 16.39. Found: C, 53.55; H, 4.19; N, 16.5%.

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