

# Microwave assisted synthesis of annelated benzosuberone as new penta-heterocyclic ring systems

Thoraya A. Farghaly and Sayed M. Riyadh\*

Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

E-mail: [riyadh1993@hotmail.com](mailto:riyadh1993@hotmail.com)

---

## Abstract

Derivatives of novel penta-heterocyclic ring systems, namely, 5,6,7,11-tetrahydro-15H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-15-ones (**9a-g**) and 6,7-dihydrobenzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d][1,3]thiazolo[3,2-a]pyrimidin-15(5H)-ones (**11a-d**) were easily prepared *via* reactions of 3-thioxo-2,3,4,7,8,9-hexahydro-1H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d]pyrimidin-1-one (**3**) with hydrazonoyl halides and active methylene compounds, respectively. The foregoing reactions were carried out with conventional heating as well as pressurized microwave irradiation and a comparative study was employed.

**Keywords:** Penta-heterocyclic ring systems, hydrazonoyl halides, microwave irradiation, benzosuberone

---

## Introduction

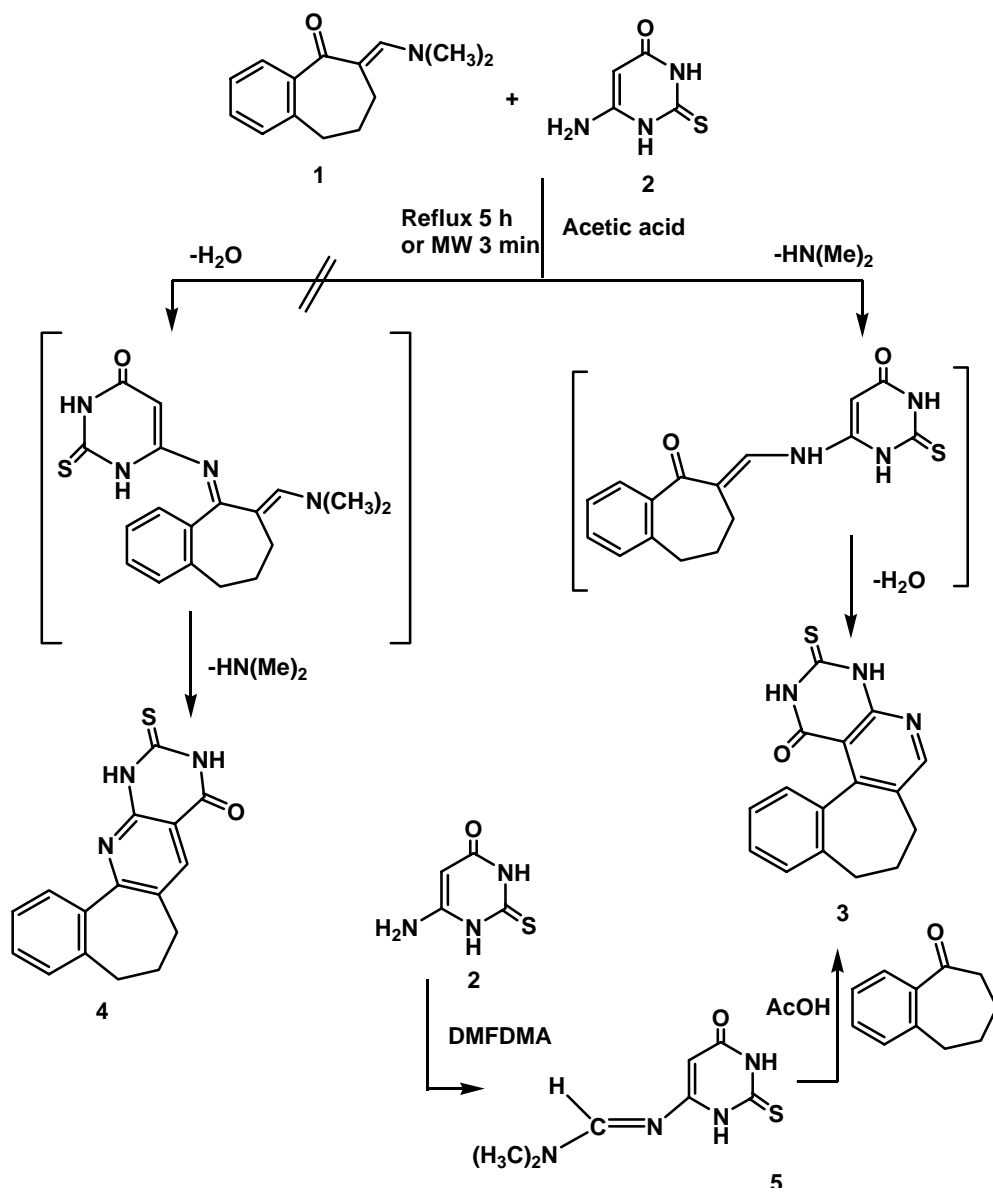
Benzocycloheptapyridines are active in inhibiting cholesterol biosynthesis and modulating blood serum lipids.<sup>1</sup> The inhibition of the farnesyl protein transferase, a novel approach to antitumour therapy, is based on compounds such as piperazinyl substituted cycloheptapyridines.<sup>2</sup> Various derivatives of 1,2,4-triazolopyrimidine have high affinity for binding with A<sub>1</sub> adenosine receptors,<sup>3</sup> and the others can be used as calcium-channel-blocking vasodilators, antihypertensive, cardiovascular, anxiolytic activities and photographic materials.<sup>4-7</sup> Thiazolo[3,2-a]pyrimidine derivatives have been ascertained as a new type of acetyl cholinesterase inhibitor for the treatment of Alzheimer disease.<sup>8</sup> In this context, we have prepared novel pentacyclic ring systems incorporated benzo- cycloheptapyridines and both of 1,2,4-triazolopyrimidines and thiazolopyrimidines. Despite recent interest in microwave as

energy source which enhances the reaction rates and improves the regioselectivity,<sup>9-12</sup> the use of microwave in reactions of hydrazoneyl halides has received limited study.<sup>13</sup>

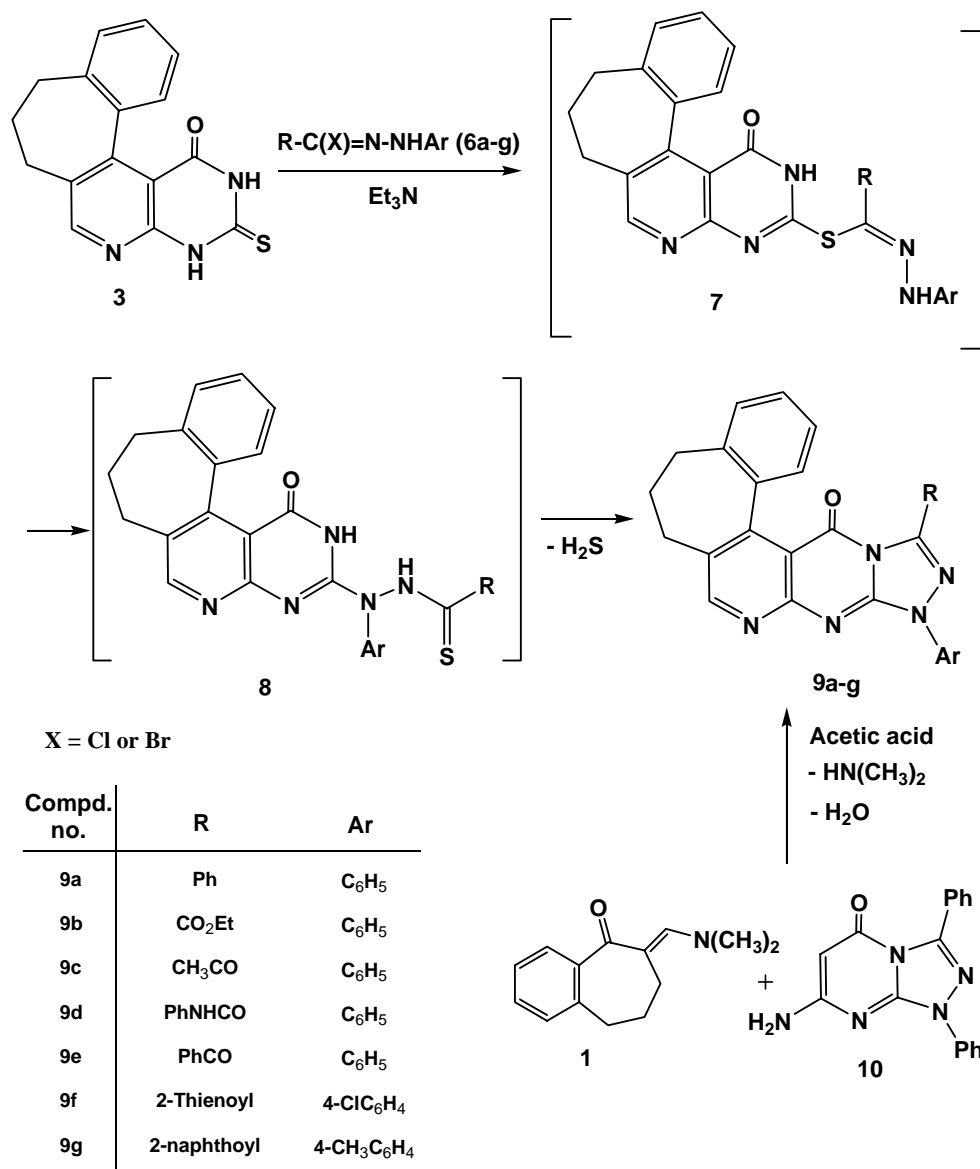
## Results and Discussion

Various attention has been paid to the reactions of enaminones with amino heterocycles.<sup>14,15</sup> To explore the utility of this, we investigated the reaction between 6-[(dimethylamino)methylene]-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**1**) and 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (**2**) in glacial acetic acid [under reflux for 5 hours or pressurized microwave irradiation for 5 min.]. This reaction produced tetra-heterocyclic ring system, namely, 3-thioxo-2,3,4,7,8,9-hexahydro-1H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d]pyrimidin-1-one (**3**) or its isomeric structure (**4**) (Scheme 1). Mass, IR spectra and elemental analysis data of the isolated product were consistent with each of the isomeric structures **3** and **4** (Scheme 1), while, <sup>1</sup>H NMR spectra revealed singlet signal at  $\delta$  8.23 ppm assigned for pyridine-2H proton not pyridine-4H proton<sup>16</sup> which is consistent with the isomeric structure **3**. Furthermore, alternative synthesis of compound **3** was achieved *via* condensation of 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (**2**) with dimethylformamide dimethylacetal (DMF-DMA) to give compound **5**,<sup>17</sup> and treatment of the product **5** with benzosuberone to yield authentic product **3** (Scheme 1). In addition, literature reports explained that, the reaction of heterocyclic amine with enaminone proceeded firstly *via* nucleophilic attack of the amino group of the heterocyclic amine to the double bond of the enaminone with concurrent elimination of the dimethylamine rather than condensation of water molecule.<sup>18-20</sup> On the basis of these findings, structure **4** was discarded and the isolated product from the studied reaction was assigned structure **3** (Scheme 1). It is worthily mentioned that compound **3** had been prepared by Remp *et al*<sup>21</sup> *via* a different method.

Despite of numerous reports on the reactions of heterocyclic thiones with hydrazoneyl halides by conventional thermal heating,<sup>22</sup> the utility of microwave in such reactions has received only limited study. Thus, heating of hydrazoneyl halides **6a-g** with 3-thioxo-2,3,4,7,8,9-hexahydro-1H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d]pyrimidin-1-one (**3**) in dioxane in the presence of triethylamine for 6-10 minutes in a pressurized microwave oven, or 20-24 hours by conventional thermal heating, afforded, in each case, one isolable product that was identified on the basis of its spectra (Ms, IR, <sup>1</sup>H NMR) and its elemental analysis data (see experimental). For example, whereas the IR spectrum of **9a** shows only one CO band at  $\nu$  1699 cm<sup>-1</sup>, the IR spectra of **9b-g** showed, in each case, two CO bands in the regions 1749 -1700 and 1702 - 1672 cm<sup>-1</sup>. Their <sup>1</sup>H NMR spectra showed, in each case, one characteristic singlet signal at  $\delta$  8.18–8.49 ppm assignable to the pyridine CH. The above results indicated that the products are novel penta-heterocyclic ring systems, namely, 5,6,7,11-tetrahydro-15H-benzo[6',7']cyclohepta-[1',2':4,5]pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-15-ones **9a-g** as shown in Scheme 2.



Scheme 1



## Scheme 2

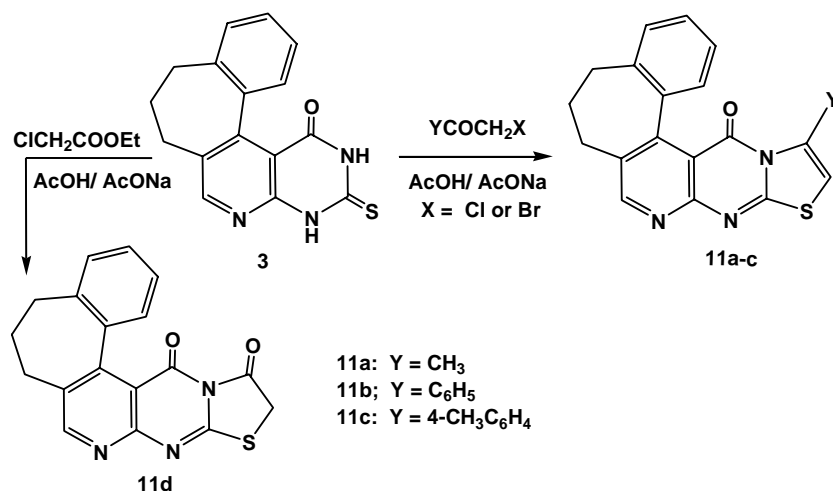
As depicted in Scheme 2, the reaction proceeded through *S*-alkylation<sup>23</sup> to give *S*-alkylated products **7** followed by Smiles rearrangement,<sup>24</sup> affording intermediates **8** which eliminated hydrogen sulfide gas to give the desired products **9a-g**. The assignment for the structure of the products and reaction mechanism can be manifested by alternate synthesis. Thus, treatment of 6-[(dimethylamino)methylene]-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (**1**) with 7-amino-1,3-diphenyl[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**10**)<sup>25</sup> in acetic acid led to formation of product that proved to be identical in all respects (mp, mixed mp and IR) with compound **9a** (Scheme 2). A comparative study of the yields of the products under pressurized microwave irradiation (method A) and conventional heating (method B) (Table 1) showed that the use of

microwave irradiation substantially reduced the reaction times from hours scale to minutes scale and appreciably increased the yields.

**Table 1.** Formation of **9a-g** using pressurized microwave and conventional heating procedures

Compd. no.	Microwave Irradiation		Conventional Heating	
	Time (min)	Yield (%)	Time (h)	Yield (%)
<b>9a</b>	10	93	20	76
<b>9b</b>	7	90	21	74
<b>9c</b>	6	85	24	70
<b>9d</b>	6	90	22	72
<b>9e</b>	8	83	20	74
<b>9f</b>	8	88	20	72
<b>9g</b>	10	82	24	70

$\alpha$ -Haloketones and  $\alpha$ -haloesters have demonstrated synthetic application for construction of heterocyclic azoles *via* their reactions with *bis*-nucleophiles.<sup>8</sup> In continuation of these studies, we examined the reactions of 3-thioxo-2,3,4,7,8,9-hexahydro-1*H*-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*]pyrimidin-1-one (**3**) with  $\alpha$ -haloketones and  $\alpha$ -haloester in acetic acid in the presence of sodium acetate under various conditions (conventional heating and pressurized microwave irradiation). In both cases, the corresponding novel penta-heterocyclic 6,7-dihydrobenzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*][1,3]thiazolo[3,2-*a*] pyrimidin-15(5*H*)-ones **11a-d** were isolated as shown in Scheme 3 (Table 2). The structure of the isolated products was established on the basis of IR, <sup>1</sup>H NMR, mass spectra and elemental analyses (see Experimental Section).



**Scheme 3****Table 2.** Formation of **11a-d** using pressurized microwave and conventional heating procedures

Compd. no.	Microwave Irradiation		Conventional Heating	
	Time (min)	Yield (%)	Time (h)	Yield (%)
<b>11a</b>	8	90	4	72
<b>11b</b>	7	88	3	70
<b>11c</b>	8	91	4	73
<b>11d</b>	8	90	4	68

**Conclusions**

We described in this context a synthetic route for new penta-heterocyclic ring systems from hydrazonoyl halides and tetra-heterocyclic thione in one-pot reactions. The microwave-assisted process, in contrast to conventional heating, gave the desired products in higher yields with shorter reaction times. In pressurized microwave, the solvent can be heated up to temperatures from 2 to 4 times their respective boiling points which enhanced the reaction rates.

**Experimental Section**

**General Procedures.** All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz for  $^1\text{H}$ -NMR and 75 MHz for  $^{13}\text{C}$  NMR) and the chemical shifts were related to that of the solvent DMSO- $d_6$ . The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. Microwave experiments were carried out using CEM Discover Labmate microwave apparatus (300 W with Chem. Driver Software). Hydrazonoyl halides **6a-g** were prepared following literature methods.<sup>26-31</sup>

**General procedures for the synthesis of 3-thioxo-2,3,4,7,8,9-hexahydro-1H-benzo [6',7']cyclohepta[1',2':4,5]pyrido[2,3-d]pyrimidin-1-one (3)**

**Method A.** A mixture of enaminone (**1**)<sup>32</sup> (2.15 g, 10 mmol) and 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**2**) (1.43 g, 10 mmol) in glacial acetic acid (30 mL) was heated under reflux for 5 h. or under pressurized microwave irradiation for 5 min. After cooling, the reaction mixture was poured into ice/HCl mixture and the solid product was collected and recrystallized from DMSO as pale yellow crystals [78% thermal, 92% Microwave], mp 278 °C [Lit. mp 275 °C]<sup>21</sup>; IR (KBr)  $\nu$  = 3360, 3102 (2NH), 1688 (C=O)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  = 2.14-2.52 (m, 6H, 3CH<sub>2</sub>), 7.34-7.65 (m, 4H, Ar-H), 8.23 (s, 1H, pyridine-H), 12.53 (s, 1H, NH), 13.10 (s, 1H, NH) ppm; MS, *m/z* (%) 297 (M<sup>+</sup>+2, 7), 296 (M<sup>+</sup>+1, 23), 295 (M<sup>+</sup>, 100), 294 (18), 252 (11), 207 (9), 153 (8), 103 (9), 77 (7), 76 (8). *Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>OS (295.08): C, 65.06; H, 4.44; N, 14.23; S, 10.86. Found: C, 65.11; H, 4.64; N, 14.42; S, 10.72%.

**Method B.** A mixture of 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**2**)<sup>33</sup> (1.47 g, 10 mmol) and dimethylformamide dimethylacetal (DMF-DMA) (5 mL) was refluxed for 3 hours. Methanol was added to the reaction mixture and the solid product was collected by filtration to give *N,N*-dimethyl-*N'*-(6-oxo-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)imido-formamide (**5**).<sup>17</sup> Refluxing of **5** (1.98 g, 10 mmol) with benzosuberone (1.6 g, 10 mmol) in acetic acid (30 mL) for 5 hours yield the authentic product **3**, identical in all respects (mp, mixed mp, IR) to that prepared by method A.

**General Procedure for the reaction of hydrazoneyl halides with 3-thioxo-2,3, 4,7,8,9-hexahydro-1*H*-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*]pyrimidin-1-one (**3**). Pressurized microwave method (method A)**

To a solution of **3** and the appropriate hydrazoneyl halides **6a-g** (1 mmol of each) in dioxane (20 mL) was added triethylamine (0.14 mL, 1 mmol) at room temperature. The reaction mixture was irradiated in a pressurized microwave (17.2 Bar, 140 °C) for 6-10 min. at a power of 300 W. After cooling to room temperature, the solution was extracted with chloroform (3X10 ml). The organic extracts were dried over anhydrous magnesium sulfate, and then evaporated under reduced pressure. The solid residue was recrystallized from the appropriate solvent to give products **9a-g**.

**Thermal method (method B).** To a solution of **3** and the appropriate hydrazoneyl halides **6a-g** (1 mmol of each) in dioxane (20 mL) was added triethylamine (0.14 mL, 1 mmol). The reaction mixture was refluxed till all of the starting materials had disappeared (20-24 h, monitored by TLC). The solvent was evaporated and the residue was triturated with methanol. The solid formed was collected and recrystallized from the appropriate solvent to give products identical to those produced by microwave method.

**11,13-Diphenyl-5,6,7,11-tetrahydro-15*H*-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*]**

**[1,2,4]triazolo[4,3-*a*]pyrimidin-15-one (**9a**).** Pale yellow crystals (Ethyl acetate/petroleum ether), mp 296 °C; IR (KBr)  $\nu$  = 1699 (C=O)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  = 2.17-2.59 (m, 6H, 3CH<sub>2</sub>), 7.36-8.35 (m, 14H, Ar-H), 8.42 (s, 1H, pyridine-H) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  = 28.66, 31.59, 31.98, 109.91, 121.34, 125.96, 126.88, 129.01, 129.11, 129.34, 129.59, 130.51,

132.62, 134.92, 136.05, 136.61, 137.21, 138.67, 139.24, 139.44, 143.62, 153.41, 155.36, 159.84, 163.21; MS,  $m/z$  (%) 455 ( $M^+$ , 100), 394 (61), 285 (33), 194 (28), 167 (50), 105 (17), 91 (61), 89 (56), 77 (60). *Anal.* Calcd. for  $C_{29}H_{21}N_5O$  (455.17): C, 76.47; H, 4.65; N, 15.37. Found: C, 76.31; H, 4.54; N, 15.42%.

**Ethyl 15-oxo-11-phenyl-6,7,11,15-tetrahydro-5H-benzo[6',7']cyclohepta[1',2':4,5] pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-13-carboxylate (9b).** Pale yellow crystals (EtOH), mp 212 °C; IR (KBr)  $\nu$  = 1749, 1713 (2C=O)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  = 1.53 (t,  $J$  = 7Hz, 3H,  $CH_3$ ), 1.55-2.67 (m, 6H, 3 $CH_2$ ), 4.63 (q,  $J$  = 7Hz, 2H,  $CH_2$ ), 7.27-7.94 (m, 9H, Ar-H), 8.25 (s, 1H, pyridine-H) ppm;  $^{13}C$  NMR (DMSO- $d_6$ )  $\delta$  = 17.05, 28.82, 30.22, 31.99, 66.31, 110.40, 112.11, 120.68, 126.51, 128.67, 128.83, 129.32, 129.89, 131.68, 135.90, 138.11, 139.43, 150.26, 159.67, 163.47, 166.05, 175.55, 179.80, 180.00; MS,  $m/z$  (%) 451 ( $M^+$ , 44), 378 (50), 295 (56), 207 (26), 205 (20), 191 (17), 127 (22), 118 (30), 115 (28), 105 (13), 103 (30), 91 (46), 77 (100). *Anal.* Calcd. for  $C_{26}H_{21}N_5O_3$  (451.16): C, 69.17; H, 4.69; N, 15.51. Found: C, 69.31; H, 4.54; N, 15.41%.

**13-Acetyl-11-phenyl-5,6,7,11-tetrahydro-15H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-15-one (9c).** Yellow crystals (EtOH), mp 230 °C; IR (KBr)  $\nu$  = 1726, 1702 (2C=O)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  = 1.92-2.63 (m, 6H, 3 $CH_2$ ), 2.78 (s, 3H,  $COCH_3$ ), 7.35-8.27 (m, 9H, Ar-H), 8.49 (s, 1H, pyridine-H) ppm; MS,  $m/z$  (%) 422 ( $M^+$ +1, 30), 421 ( $M^+$ , 100), 378 (17), 207 (19), 192 (15), 77 (80). *Anal.* Calcd. for  $C_{25}H_{19}N_5O_2$  (421.15): C, 71.25; H, 4.54; N, 16.62. Found: C, 71.51; H, 4.34; N, 16.42%.

**15-Oxo-*N*,11-diphenyl-6,7,11,15-tetrahydro-5H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-13-carboxamide (9d).** Yellow crystals (Dioxan/MeOH), mp 306 °C; IR (KBr)  $\nu$  = 3201 (NH), 1711, 1672 (2C=O)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  = 2.19-2.60 (m, 6H, 3 $CH_2$ ), 7.22-8.17 (m, 14H, Ar-H), 8.49 (s, 1H, pyridine-H), 11.15 (s, 1H, NH) ppm;  $^{13}C$  NMR (DMSO- $d_6$ )  $\delta$  = 28.76, 31.68, 32.39, 110.31, 120.97, 126.07, 127.62, 128.48, 128.58, 128.90, 129.58, 130.61, 131.62, 133.42, 135.65, 136.64, 137.43, 138.20, 139.13, 139.74, 145.62, 153.45, 156.14, 159.70, 166.44, 179.51; MS,  $m/z$  (%) 498 ( $M^+$ , 100), 484 (32), 392 (27), 378 (25), 192 (34), 153 (28), 152(30), 128 (22), 120 (19), 119 (43), 117 (20), 104 (34), 91 (95), 77 (66). *Anal.* Calcd. for  $C_{30}H_{22}N_6O_2$  (498.18): C, 72.28; H, 4.45; N, 16.86. Found: C, 72.50; H, 4.64; N, 16.65%.

**13-Benzoyl-11-phenyl-5,6,7,11-tetrahydro-15H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-15-one (9e).** Yellow crystals (MeOH), mp 270 °C; IR (KBr)  $\nu$  = 1702, 1688 (2C=O)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  = 2.18-2.58 (m, 6H, 3 $CH_2$ ), 7.36-8.31 (m, 14H, Ar-H), 8.41 (s, 1H, pyridine-H) ppm;  $^{13}C$  NMR (DMSO- $d_6$ )  $\delta$  = 28.83, 30.28, 31.70, 109.06, 120.40, 126.03, 127.05, 128.61, 128.97, 129.04, 129.29, 129.87, 129.97, 130.14, 131.68, 134.88, 135.24, 136.64, 138.81, 139.17, 139.43, 146.30, 155.95, 157.69, 165.78, 181.93; MS,  $m/z$  (%) 484 ( $M^+$ +1, 13), 483 ( $M^+$ , 40), 378 (20), 220 (10), 105 (93), 77 (100). *Anal.* Calcd. for  $C_{30}H_{21}N_5O_2$  (483.17): C, 74.52; H, 4.38; N, 14.48. Found: C, 74.31; H, 4.51; N, 14.40%.



**11-(4-Chlorophenyl)-13-(2-thienylcarbonyl)-5,6,7,11-tetrahydro-15H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-15-one (9f).** Pale orange crystals (EtOH), mp 294 °C; IR (KBr)  $\nu$  = 1716, 1694 (2C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.19-2.59 (m, 6H, 3CH<sub>2</sub>), 7.23-7.53 (m, 7H, Ar-H), 7.72 (d,  $J$  = 8 Hz, 2H, Ar-H), 8.19 (d,  $J$  = 8 Hz, 2H, Ar-H), 8.44 (s, 1H, pyridine-H) ppm; MS,  $m/z$  (%) 525 ( $M^+$ +2, 7), 524 ( $M^+$ +1, 8), 523 ( $M^+$ , 15), 428 (50), 111 (100). *Anal.* Calcd. for C<sub>28</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>2</sub>S (523.09): C, 64.18; H, 3.46; N, 13.37; S, 6.12. Found: C, 64.32; H, 3.53; N, 13.40; S, 5.99%.

**11-(4-Methylphenyl)-13-(1-naphthoyl)-5,6,7,11-tetrahydro-15H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-15-one (9g).** Pale orange crystals (EtOH), mp 262 °C; IR (KBr)  $\nu$  = 1700, 1680 (2C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.25-2.72 (m, 6H, 3CH<sub>2</sub>), 2.64 (s, 3H, Ar-CH<sub>3</sub>), 7.31 (d,  $J$  = 7 Hz, 2H, Ar-H), 7.42-7.99 (m, 11H, Ar-H), 8.00 (d,  $J$  = 7 Hz, 2H, Ar-H), 8.18 (s, 1H, pyridine-H) ppm; MS,  $m/z$  (%) 547 ( $M^+$ , 100), 392 (50), 180 (10), 158 (3), 128 (14), 106 (24), 91 (16), 77 (37). *Anal.* Calcd. for C<sub>35</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub> (547.20): C, 76.77; H, 4.60; N, 12.79. Found: C, 76.62; H, 4.53; N, 12.60%.

**Alternative synthesis of 11,13-diphenyl-5,6,7,11-tetrahydro-15H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-15-one (9a).** A mixture of 7-amino-1,3-diphenyl[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (**10**)<sup>25</sup> (0.303 g, 1 mmol) and enaminone (**1**) (0.215 g, 1 mmol) in acetic acid was refluxed for 6 hours. After cooling, the mixture was poured into ice and the solid product was filtered off and recrystallized from (ethyl acetate/ petroleum ether) mixture to give compound **9a**.

**General procedure for the reaction of  $\alpha$ -haloketones or  $\alpha$ -haloester with 3-thioxo-2,3,4,7,8,9-hexahydro-1H-benzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-d]pyrimidin-1-one (3) Pressurized microwave method (method A)**

To a solution of **3** (0.295 g, 1 mmol) in acetic acid (20 mL) in the presence of sodium acetate (0.082 g, 1 mmol) was added the appropriate  $\alpha$ -haloketones or  $\alpha$ -haloester (1 mmol of each) at room temperature. The reaction mixture was irradiated in a pressurized microwave (15.2 Bar, 120 °C) for 7-8 min. at a power of 300 W. After cooling to room temperature, the solution was extracted with chloroform (3X10 mL). The organic extracts were dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The solid residue was recrystallized from ethanol to give products **11a-d**.

**Thermal method (method B).** To a solution of **3** (0.295 g, 1 mmol) in acetic acid (20 mL) in the presence of sodium acetate (0.082 g, 1 mmol) was added the appropriate  $\alpha$ -haloketones or  $\alpha$ -haloester (1 mmol of each) at room temperature. The reaction mixture was refluxed till all of the starting materials had disappeared (3-4 h, monitored by TLC). The solvent was evaporated and the residue was triturated with methanol. The solid formed was collected and recrystallized from ethanol to give products identical to those obtained by microwave method.

**13-Methyl-6,7-dihydrobenzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*][1,3]thiazolo [3,2-*a*]pyrimidin-15(5*H*)-one (11a).** Pale yellow crystals, mp 302 °C; IR (KBr)  $\nu$  = 1682 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.52 (s, 3H, CH<sub>3</sub>), 2.54-2.67 (m, 6H, 3CH<sub>2</sub>), 7.27-7.84 (m, 4H, Ar-H), 7.91 (s, 1H, thiazole-H), 8.22 (s, 1H, pyridine-H) ppm; MS,  $m/z$  (%) 333 (M<sup>+</sup>, 100), 318 (50), 292 (60), 215 (30), 143 (25), 118 (10), 76 (20). *Anal.* Calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>OS (333.09): C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.31; H, 4.44; N, 12.41; S, 9.52%.

**13-Phenyl-6,7-dihydrobenzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*][1,3]thiazolo [3,2-*a*]pyrimidin-15(5*H*)-one (11b).** Orange crystals, mp 196 °C; IR (KBr)  $\nu$  = 1685 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.48-2.69 (m, 6H, 3CH<sub>2</sub>), 7.29-7.85 (m, 9H, Ar-H), 7.78 (s, 1H, thiazole-H), 8.24 (s, 1H, pyridine-H) ppm; MS,  $m/z$  (%) 395 (M<sup>+</sup>, 100), 292 (40), 143 (30), 118 (25), 102 (25), 91 (10), 77 (60). *Anal.* Calcd. for C<sub>24</sub>H<sub>17</sub>N<sub>3</sub>OS (395.11): C, 72.89; H, 4.33; N, 10.63; S, 8.11. Found: C, 72.81; H, 4.37; N, 10.45; S, 8.19%.

**13-(4-Methylphenyl)-6,7-dihydrobenzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*] [1,3]thiazolo [3,2-*a*]pyrimidin-15(5*H*)-one (11c).** Orange crystals, mp 186 °C; IR (KBr)  $\nu$  = 1680 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.42 (s, 3H, Ar-CH<sub>3</sub>), 2.44-2.67 (m, 6H, 3CH<sub>2</sub>), 7.27-7.30 and 7.42-7.75 (m, 4H, Ar-H), 7.36 (d,  $J$  = 7 Hz, 2H, Ar-H), 7.81 (d,  $J$  = 7 Hz, 2H, Ar-H), 7.98 (s, 1H, thiazole-H), 8.21 (s, 1H, pyridine-H) ppm; MS,  $m/z$  (%) 409 (M<sup>+</sup>, 60), 291 (100), 143 (25), 118 (15), 91 (60), 77 (40). *Anal.* Calcd. for C<sub>25</sub>H<sub>19</sub>N<sub>3</sub>OS (409.12): C, 73.32; H, 4.68; N, 10.26; S, 7.83. Found: C, 73.21; H, 4.47; N, 10.40; S, 7.59%.

**6,7-Dihydrobenzo[6',7']cyclohepta[1',2':4,5]pyrido[2,3-*d*][1,3]thiazolo[3,2-*a*] pyrimidine-13,15(5*H*,12*H*)-dione (11d).** Pale yellow crystals, mp 290 °C; IR (KBr)  $\nu$  = 1699, 1680 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.44-2.67 (m, 6H, 3CH<sub>2</sub>), 4.38 (s, 2H, thiazole-CH<sub>2</sub>), 7.27-7.64 (m, 4H, Ar-H), 8.27 (s, 1H, pyridine-H) ppm;  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 28.62, 30.46, 32.19, 44.56, 119.26, 127.35, 128.21, 128.93, 129.14, 136.45, 138.26, 139.41, 150.10, 151.61, 155.42, 159.76, 162.60, 169.20; MS,  $m/z$  (%) 335 (M<sup>+</sup>, 40), 293 (100), 217 (20), 143 (30), 118 (25), 76 (30). *Anal.* Calcd. for C<sub>18</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S (335.07): C, 64.46; H, 3.91; N, 12.53; S, 9.56. Found: C, 64.21; H, 4.07; N, 12.43; S, 9.69%.

## References

1. Robl, J. A.; Bang-Chi, C.; Chong-Qing, S. US Patent US 2000 2 061 901; *Chem. Abstr.* **2001**, *136*, 401651.
2. Ganguly, A. K.; Doll, A. K.; Girijavallabhan, V. M. *Curr. Med. Chem.* **2001**, *8*, 1419.
3. Irene Giorgi, I.; Bianucci, A. M.; Biagi, G.; Livi, O.; Scartoni, V.; Leonardi, M.; Pietra, D.; Coi, A.; Massarelli, I.; Fatena, F. A.; Fiamingo, F. L.; Anastasi, P.; Giannini, G. *Eur. J. Med. Chem.* **2007**, *42*, 1.
4. Awal, K. Ger. Pat. 3 839 711, **1989**; *Chem. Abstr.* **1990**, *112*, 55902.

5. Barthelmy, G.; Hallot, A.; Vallat, J. N. Fr. Pat. 2 549 834, **1985**; *Chem. Abstr.* **1985**, 103, 71335u.
6. Bru-Magniez, N.; Guengor, T.; Teulon, J. M. US Pat. 5 387 747, **1995**; *Chem. Abstr.* **1995**, 123, 228204p.
7. Nakamura, H.; Hosor, Y.; Fukacoa, J. Jpn. Kokai 0 313 934, **1991**; *Chem. Abstr.*, **1991**, 115, 60769k.
8. Zhi, H.; Chen, L.; Zhang, L.; Liu, S.; Wan, D. C. C.; Lin, H.; Hu, C. *Arkivoc* **2008**, (xiii), 266.
9. Andrade, C. K. Z.; Barreto, A. S.; Silva, W. A. *Arkivoc* **2008**, (xii), 226.
10. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, 57, 9225.
11. Bortolini, O.; D'Agostino, M.; De Nino, A.; Maiuolo, L.; Nardi, M.; Sindona, G. *Tetrahedron* **2008**, 64, 8078.
12. El Ashry, E. H.; Kassem, A. A. *Arkivoc* **2006**, (ix), 1.
13. Riyadh, S. M.; Al-Matar, H. M. *Org. Prep. Proced. Int.* **2007**, 39, 385.
14. Hassaneen, H. M.; Abdallah, T. A.; Abdelhadi, H. A.; Hassaneen, H. M. E.; Pagni, R. M. *Heteroatom Chem.* **2003**, 14, 491.
15. Hassaneen, H. M. E. *Arkivoc* **2007**, (i), 154.
16. Quiroga, J.; Rengifo, A.; Insuasty, B.; Abomí, R.; Nogueras, M.; Sa'nchez, A. *Tetrahedron Lett.* **2002**, 43, 9061.
17. Hassaneen, H. M.; Abdallah, T. A. *Molecules* **2003**, 8, 333.
18. Riyadh, S. M.; Abdelhamid, I. A.; Al-Matar, H. M.; Helmy, N. M.; Elnagdi, M. H. *Heterocycles* **2008**, 75, 1849.
19. Dawood, K. M. *J. Heterocycl. Chem.* **2005**, 42, 221.
20. Al-Saleh, B.; El-Asasery, M. A.; Abdel-Aziz, R. S.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2005**, 42, 563.
21. Remp, W.; Junek, H. *Monatsh. Chem.* **1973**, 104, 1101.
22. Shawali, A. S.; Farghaly, T. A. *Arkivoc* **2008**, (i), 18.
23. Geis, A. A.; Kamal-Eldeen, A. M.; Abdelhafez, A. A.; Gaber, A. M. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, 56, 87.
24. Elliott, A. J.; Callaghan, P. D.; Gibson, M. S.; Nemeth, S. T. *Can. J. Chem.* **1975**, 53, 1484.
25. Mosselhi, M. A. N. *Monatsh. Chem.* **2002**, 133, 1297.
26. Shawali, A. S.; Osman, A. *Tetrahedron* **1971**, 27, 2517.
27. Shawali, A. S.; Eweiss, N. F.; Hassaneen, H. M.; Algharib, M. S. *Bull. Chem. Soc. Jpn.* **1973**, 48, 365.
28. Shawali, A. S.; Abdelhamid, A. O. *Bull. Chem. Soc. Jpn.* **1976**, 49, 321.
29. Parkanyi, C.; Shawali, A. S. *J. Heterocycl. Chem.* **1980**, 17, 897.
30. Eweiss, N. F.; Osman, A. *J. Heterocycl. Chem.* **1980**, 17, 1713.
31. Wolkoff, P. *Can. J. Chem.* **1975**, 53, 1333.
32. Farghaly, T. A.; Abdel-Hafez, N. A.; Ragab, E. A.; Awad, H. H. Submitted for publication.

33. Hubsch, W.; Pfeleiderer, W. *Helv. Chem. Acta* **1988**, *71*, 1379.