Tetrahedron 67 (2011) 1294–1297

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A rapid and convenient synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-ones and thiones

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ARTICLE INFO

Article history:
Received 25 August 2010
Received in revised form 29 October 2010
Accepted 23 November 2010
Available online 27 November 2010

Keywords:
Cyclocondensation
Chemoselectivity
Multicomponent reaction
Biginelli reaction
Microwave reaction

ABSTRACT

A rapid and convenient synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-ones and thiones was developed. The reaction involves a one-pot reaction between oxalacetic acid, thiourea/urea, and aldehyde under microwave irradiation and provides the products in good yields and much shorter reaction times.

1. Introduction

3,4-Dihydropyrimidine-2-ones/thiones are useful targets in chemical synthesis as they have been associated with a diverse range of therapeutic and medicinal properties.[1] The dihydropyrimidinone scaffold is also found in various marine alkaloids, which have been shown to possess antiviral, antitumor, antibacterial, and anti-inflammatory activities.[2] In particular, the batzelladine alkaloids are known to be potent HIV gp-120-CD4 inhibitors.[3] Our group has earlier explored the sodium channel blockade activities of pyrimidi-2-ones and pyrimidi-2-thiones and identified two compounds, **1** and **2** (Fig. 1a), which possess neuronal sodium channel blockade activities.[4] In continuing our interest in the investigation of pyrimidi-2-ones and pyrimidi-2-thiones for their sodium channel blockade activities, the synthesis of these compounds carrying different substituents from **1** and **2** was explored.

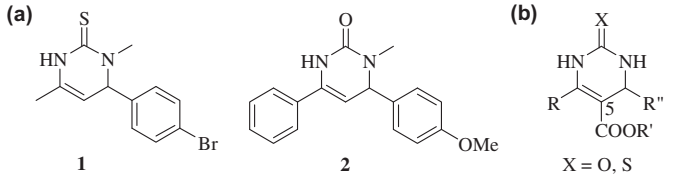
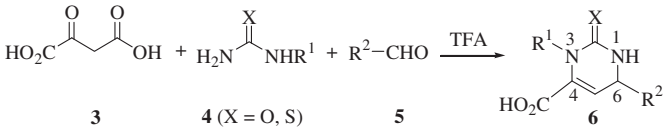


Fig. 1. (a) Pyrimidi-2-thione **1** and pyrimidi-2-one **2** with sodium channel blockage ability; (b) Typical Biginelli product.

Typically, dihydropyrimidinones obtained via Biginelli reaction[5] would house an ester at the C5 position (Fig. 1b). However Bussolari and McDonnell had demonstrated that replacing alkyl acetoacetate with oxalacetic acid **3** as a substrate for the Biginelli reaction led to the formation of 5-unsubstituted 3,4-dihydropyrimidin-2-ones due to in-situ decarboxylation after cyclization.[6] These compounds are of interest to us as they bear resemblance to compounds **1** and **2**. However, the major drawback of this reaction is the long reaction time (12 h). For library preparation, it would be desirable if the reaction could be (i) conducted expeditiously with good yield and (ii) applied to a variety of reagents. To achieve this, we explored the use of microwave irradiation and also expanded the diversity by applying thiourea and substituted urea/thiourea to the reaction (Scheme 1).



Scheme 1.

2. Results and discussion

According to Bussolari and co-worker, 5-unsubstituted 3,4-dihydropyrimidin-2-ones could be effectively synthesized from oxalacetic acid, urea, and aldehyde when trifluoroacetic acid was used as a catalyst and dichloroethane as the solvent. In our initial synthesis of 6-phenyl-2-thioxo-1,2,3,6-tetrahydro-pyrimidine-4-

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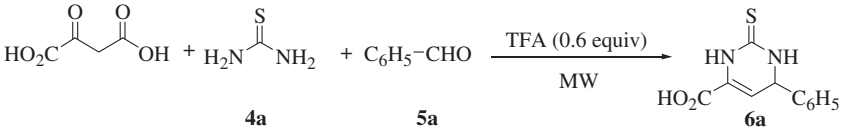
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.075

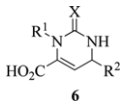
carboxylic acid **6a**, we adopted Bussolari's procedure but replaced urea with thiourea and obtained the product in 64%. This result was encouraging as it demonstrated the first synthesis of 2-thioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid. To optimize the reaction, we explored microwave irradiation under different reaction conditions (Table 1) and found that **6a** was obtained in good yields when the reaction was performed in solvents like dichloromethane, THF or dichloroethane (entries ii, viii and x, Table 1). To demonstrate the versatility of these reaction conditions for the synthesis of **6**, we carried out the reaction with different aldehydes. However further experimentation showed that when dichloromethane and dichloroethane were used in the synthesis of certain analogs, in particular **6b** and **6c**, the desired product was not obtained and instead a black tar-like substance was found coated to the sides of the microwave vessel. Hence the reaction condition shown in entry viii of Table 1 was used as the general procedure for our synthesis and a diverse set of **6** was prepared in good yields with both electron-withdrawing and electron-donating aldehydes (Table 2). For reactions with substituted thiourea/urea, the reaction was observed to proceed chemoselectively to provide only the N3-substituted 3,4-dihydropyrimidin-2-ones/thiones (as determined by the X-ray structure of **6w**[7] and the 1D NoE of **6p** and **6r**).

Table 1
Optimization of the synthesis of **6a**



Entry	Equivalents of **3**	Equivalents of **4a**	Equivalents of **5a**	Solvent	Time (min)	Temp (°C)	Yield (%)
i	1	1.5	1.2	EtOH	10	120	60
ii	1	1.3	1.2	CH_2Cl_2	10	90	79
iii	1	1.3	1.2	CH_2Cl_2	15	90	74
iv	1	1.3	1.2	Toluene	10	90	0
v	1	1.3	1.2	THF	10	90	61
vi	1	1.3	1.2	THF	15	90	69
vii	1	1.3	1.2	THF	15	95	76
viii	1.2	1.2	1	THF	15	95	82
ix	1	1.3	1.2	$ClCH_2CH_2Cl$	10	90	78
x	1.2	1.2	1	$ClCH_2CH_2Cl$	10	90	84

Table 2
Library of compound **6**



6

Compound	X	R^1	R^2	Yield (%)[a]
6a	S	H	C_6H_5	82 (64[b])
6b	S	H	4-FC_6H_4	83
6c	S	H	2,4-$(CH_3O)_2C_6H_3$	83
6d	S	H	2-furyl	93
6e	S	H	2-thienyl	76
6f	S	H	2-naphthyl	82
6g	O	H	C_6H_5	94 (88[c])
6h	O	H	4-FC_6H_4	73
6i	O	H	2,4-$(CH_3O)_2C_6H_3$	91
6j	O	H	2-furyl	83
6k	O	H	2-thienyl	71 (72[c])
6l	O	H	2-naphthyl	89
6m	S	CH_3	C_6H_5	89
6n	S	CH_3	4-FC_6H_4	84
6o	S	allyl	C_6H_5	78
6p	S	allyl	3-ClC_6H_4	75
6q	S	allyl	2-naphthyl	79
6r	O	CH_3	C_6H_5	84
6s	O	CH_3	4-FC_6H_4	83
6t	O	CH_3	2,4-$(CH_3O)_2C_6H_3$	76
6u	O	allyl	C_6H_5	83
6v	O	allyl	3,5-$Br_2C_6H_3$	77
6w	O	allyl	2-naphthyl	81

[a] Isolated yield.
[b] Using the conventional heating method as reported by Bussolari et al. (Ref. 6)
[c] Yield reported in Ref. 6.

3. Conclusion

In summary, we have demonstrated an expeditious and high yielding synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-thiones and 5-unsubstituted 3,4-dihydropyrimidin-2-ones. We have shown that under microwave irradiation, the reaction time was shortened from 12 h to 15 min. These results further demonstrate the value of microwave-assisted synthesis in increasing yield, shortening reaction time and streamlining high throughput synthesis.

4. Experimental section

4.1. General

All chemical reagents were obtained from Aldrich, Merck, Lancaster or Fluka and used without further purification. Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F_{254}) and visualized with UV light or stained with ninhydrin. ^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker AMX 500 Fourier Transform spectrometer. Chemical shifts were reported in δ (ppm), relative to the internal standard of TMS. The signals observed were described as: s, d, t, q, m. The number of protons (n) for a given resonance was indicated as nH. Mass spectrometry was performed on a Finnigan MAT 95/XL-T spectrometer under electron impact (EI) or electrospray ionization (ESI) technique. Microwave reactions were performed on a Biotage Initiator™ microwave synthesizer.

4.2. General procedure for the synthesis of 6a–6l

To a mixture of oxalacetic acid (2.6 mmol), aldehyde (2.0 mmol), and urea/thiourea (2.6 mmol) in THF (3 mL) was added TFA (0.10 mL). The mixture was heated at 95 °C for 15 min using microwave irradiation in a sealed tube. Thereafter, the mixture was cooled and the solvent was removed under reduced pressure. The residue obtained was washed with Et_2O and dried under vacuum to afford the final product.

4.2.1. 6-Phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6a***. Yellow solid, mp 234–235 °C; IR (KBr): 3259, 3100, 3001, 1711,1674, 1561; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, NH, 1H), 8.47 (s, NH, 1H), 7.43–7.27 (m, ArH, 5H), 6.05 (d, C*CH*CH, J=4.8 Hz, 1H), 5.18 (dd, CH*CH*Ph, J=2.4, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.4, 162.3, 142.6, 128.8, 127.9, 126.3, 125.8, 110.8, 54.6; HRMS (ESI) [M−H]$^-$: calcd for $C_{11}H_9N_2O_2S$, 233.0379; found 233.0383.

4.2.2. 6-(4-Fluorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6b***. Pale yellow solid, mp 211–212 °C; IR (KBr): 3269, 3100, 3004, 1716, 1676, 1614, 1567; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.22 (s, NH, 1H), 8.50 (s, NH, 1H), 7.33–7.30 (m, ArH, 2H), 7.26–7.22 (m, ArH, 2H), 6.04 (dd, C*CH*CH, J=1.3, 3.2 Hz, 1H), 5.20 (dd, CH*CH*Ph, J=2.5, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.3, 163.3, 162.3, 160.1, 138.9, 138.8, 128.5, 128.4, 126.0, 115.8, 115.5, 110.6, 53.9; HRMS (EI): calcd for $C_{11}H_9FN_2O_2S$, 252.0369; found 252.0363.

4.2.3. 6-(2,4-Dimethoxyphenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6c***. Yellow solid, mp 209–210 °C; IR (KBr): 3237, 3103, 3002, 1709, 1672, 1615, 1564, 1506; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, NH, 1H), 8.38 (s, NH, 1H), 7.01 (d, ArH, J=8.2 Hz, 1H), 6.60–6.58 (m, ArH, 2H), 5.95–5.94 (m, C*CH*CH, 1H), 5.29 (dd, CH*CH*Ph, J=2.5, 4.4 Hz, 1H), 3.82 (s, O*CH*$_3$, 3H), 3.76 (s, O*CH*$_3$, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.9, 162.4, 160.4, 156.3, 127.5, 125.6, 122.5, 110.2, 105.1, 98.6, 55.7, 55.3, 49.6; HRMS (ESI) [M+H]$^+$: calcd for $C_{13}H_{15}N_2O_4S$, 295.0747; found 295.0753.

4.2.4. 6-(Furan-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6d***. Dark brown solid, mp 184–186 °C; IR (KBr): 3254, 3102, 3003, 1712, 1675, 1616, 1566; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (s, NH, 1H), 8.56 (s, NH, 1H), 7.67 (s, ArH, 1H), 6.46 (dd, ArH, J=1.9, 3.2 Hz, 1H), 6.30 (d, ArH, J=3.2 Hz, 1H), 5.97–5.96 (m, C*CH*CH, 1H), 5.26 (dd, CH*CH*Ph, J=2.6, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.5, 162.2, 153.4, 143.2, 127.3, 110.7, 107.6, 107.2, 48.2; HRMS (EI): calcd for $C_9H_8N_2O_3S$, 224.0256; found 224.0250.

4.2.5. 6-(Thiophen-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6e***. Yellow solid, mp 215–216 °C; IR (KBr): 3256, 3100, 2997, 1714, 1676, 1562; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (s, NH, 1H), 8.61 (s, NH, 1H), 7.51 (dd, ArH, J=1.9, 3.8 Hz, 1H), 7.03–7.01 (m, ArH, 2H) 6.08–6.07 (m, C*CH*CH, 1H), 5.46 (dd, CH*CH*Ph, J=2.6, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.0, 162.2, 146.2, 127.1, 126.3, 126.2, 125.0, 110.0, 49.8; HRMS (ESI) [M−H]$^-$: calcd for $C_9H_7N_2O_2S_2$, 238.9943; found 238.9944.

4.2.6. 6-(Naphthalen-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6f***. Yellow solid, mp 248–251 °C; IR (KBr): 3248, 3101, 3001, 1711, 1674, 1558; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (s, NH, 1H), 8.56 (s, NH, 1H), 7.97–7.90 (m, ArH, 3H), 7.76 (s, ArH, 1H), 7.53–7.47 (m, ArH, 3H), 6.14 (d, C*CH*CH, J=4.5 Hz, 1H), 5.39 (dd, CH*CH*Ph, J=2.5, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.5, 162.3, 140.0, 132.8, 132.6, 128.8, 127.9, 127.6, 126.6, 126.3, 126.0, 124.9, 124.6, 110.6, 54.9; HRMS (EI): calcd for $C_{15}H_{12}N_2O_2S$, 284.0619; found 284.0612.

4.2.7. 6-(4-Fluorophenyl)-2-oxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid ***6h***. Off-white solid, mp 225–226 °C; IR (KBr): 3400, 3212, 3098, 1712, 1673, 1509; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (s, NH, 1H), 7.35–7.32 (m, ArH, 2H), 7.22–7.19 (m, ArH, 2H), 5.78–5.77 (m, C*CH*CH, 1H), 5.18 (dd, CH*CH*Ph, J=1.9, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.9, 162.5, 160.6, 152.3, 140.0, 140.0, 128.2, 128.2, 127.8, 115.5, 115.4, 108.7, 54.0; HRMS (EI): calcd for $C_{11}H_9FN_2O_3$, 236.0597; found 236.0594.

4.2.8. 6-(2,4-Dimethoxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6i***. Yellow solid, mp 204–205 °C; IR (KBr): 3441, 3294, 2932, 1714, 1674, 1615, 1506; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63 (s, NH, 1H), 7.10 (d, ArH, J=8.2 Hz, 1H), 7.02 (s, NH, 1H), 6.58–6.55 (m, ArH, 2H), 5.75 (d, C*CH*CH, J=4.4 Hz, 1H), 5.31 (dd, CH*CH*Ph, J=1.9, 4.4 Hz, 1H), 3.81 (s, O*CH*$_3$, 3H), 3.76–3.75 (d, O*CH*$_3$, J=5.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.0, 160.0, 156.3, 152.9, 127.5, 127.0, 123.4, 108.2, 104.9, 98.5, 55.6, 55.3, 49.2; HRMS (EI): calcd for $C_{13}H_{14}N_2O_5$, 278.0903; found 279.0913.

4.2.9. 6-(Furan-2-yl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6j***. Dark brown solid, mp 176–178 °C; IR (KBr): 3254, 1722, 1672, 1468; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, NH, 1H), 7.62, (s, ArH, 1H), 7.34 (s, NH, 1H), 6.42–6.41 (m, ArH, 1H), 6.25 (d, ArH, J=3.2 Hz, 1H), 5.75 (dd, C*CH*CH, J=1.9, 3.2 Hz, 1H), 5.21 (dd, CH*CH*Ph, J=2.5, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.8, 154.7, 152.3, 142.8, 129.3, 110.5, 106.1, 105.5, 48.5; HRMS (EI): calcd for $C_9H_8N_2O_4$, 208.0484; found 208.0479.

4.2.10. 6-(Naphthalen-2-yl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6l***. Yellow solid, mp 224–226 °C; IR (KBr): 3308, 3236, 1716, 1668, 1464; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91–7.90 (m, ArH, 3H), 7.80 (s, NH, 1H), 7.77 (s, ArH, 1H), 7.53–7.49 (m, ArH, 3H), 7.43 (s, NH, 1H), 5.87 (d, C*CH*CH, J=4.4 Hz, 1H), 5.35 (dd, CH*CH*Ph, J=1.9, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.0, 152.5, 141.1, 132.9, 132.5, 128.6, 128.0, 127.8, 127.6, 126.4, 126.1, 124.7, 124.3, 108.6, 55.0; HRMS (EI): calcd for $C_{15}H_{12}N_2O_3$, 268.0848; found 268.0838.

4.3. General procedure for the synthesis of 6m–6w

To a mixture of oxalacetic acid (2.6 mmol), aldehyde (2.0 mmol) and *N*-substituted urea/thiourea (2.6 mmol) in THF (3 mL) was added TFA (0.10 mL). The mixture was heated at 95 °C for 15 min using microwave irradiation in a sealed tube. Thereafter, the mixture was cooled and the solvent was removed under reduced pressure. 0.5 M NaOH (20 mL) was then added to the residue and the resulting solution was extracted with EtOAc (3×15 mL). Subsequently, the aqueous phase was acidified using concd HCl and extracted with 10% ^{i}PrOH in CH_2Cl_2 (3×15 mL). The combined organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was washed with Et_2O and dried under vacuum to afford the final product.

4.3.1. 3-Methyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6m***. Yellow solid, mp 88–90 °C; IR (KBr): 3249, 2361, 1724, 1621, 1496; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, NH, 1H), 7.41–7.26 (m, ArH, 5H), 6.22 (d, C*CH*CH, J=5.7 Hz, 1H), 5.00 (dd, CH*CH*Ph, J=3.2, 6.3 Hz, 1H), 3.39 (s, N*CH*$_3$, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.3, 163.5, 141.9, 131.9, 128.8, 127.8, 126.0, 115.5, 52.6, 38.1; HRMS (EI): calcd for $C_{12}H_{12}N_2O_2S$, 248.0619; found 248.0622.

4.3.2. 6-(4-Fluorophenyl)-3-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6n***. Yellow solid, mp 86–88 °C; IR (KBr): 3411, 2361, 1723, 1650, 1605, 1510; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, NH, 1H), 7.32–7.39 (m, ArH, 2H), 7.24–7.21 (m, ArH, 2H), 6.21 (d, C*CH*CH, J=5.1 Hz, 1H), 5.02 (dd, CH*CH*Ph, J=3.2, 5.7 Hz, 1H), 3.39 (s, N*CH*$_3$, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.2, 163.5, 162.7, 160.7, 138.1, 138.1, 132.1, 128.2, 128.2, 115.7, 115.5, 115.2, 51.9, 38.1; HRMS (EI): calcd for $C_{12}H_{11}FN_2O_2S$, 266.0525; found 266.0518.

4.3.3. 3-Allyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6o***. Yellow solid, mp 144–146 °C; IR (KBr): 3172, 1693,

1652, 1528; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, NH, 1H), 6.97–6.94 (m, ArH, 2H), 6.88–6.62 (m, ArH, 3H), 5.78 (dd, C*CH*CH, J=1.3, 5.7 Hz, 1H), 5.26–5.18 (m, CH_2*CH*CH_2, 1H), 5.07–5.03 (m, CH*CH*Ph, 1H), 4.62–4.60 (m, *CH*$_2$CHCH_2, 2H), 4.54–4.50 (m, CH_2CH*CH*$_2$, 1H), 4.19 (dd, CH_2CH*CH*$_2$, J=7.0, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.9, 163.5, 141.8, 133.8, 130.5, 128.7, 127.8, 126.0, 117.3, 116.5, 52.6, 49.6; HRMS (EI): calcd for $C_{14}H_{14}N_2O_2S$, 274.0776; found 274.0770.

4.3.4. 3-Allyl-6-(3-chlorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6p***. Yellow solid, mp 136–138 °C; IR (KBr): 3178, 3027, 2361, 1710, 1690, 1653, 1536; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.5 (br, CO_2H, 1H), 9.35 (s, NH, 1H), 7.46–7.24 (m, ArH, 4H), 6.26 (d, C*CH*CH, J=5.1 Hz, 1H), 5.66 (dd, CH_2*CH*CH_2, J=5.0, 10.7 Hz, 1H), 5.49 (d, CH*CH*Ph, J=15.8 Hz, 1H), 5.08–5.06 (m, *CH*$_2$CHCH_2, 2H), 4.96 (d, CH_2CH*CH*$_2$, J=17.0 Hz, 1H), 4.64 (dd, CH_2CH*CH*$_2$, J=5.7, 15.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.1, 163.5, 144.2, 133.7, 133.4, 131.1, 130.8, 127.7, 126.0, 124.6, 117.4, 115.8, 52.0, 49.6; HRMS (EI): calcd for $C_{14}H_{13}ClN_2O_2S$, 308.0386; found 308.0372.

4.3.5. 3-Allyl-6-(naphthalen-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6q***. Yellow solid, mp 169–171 °C; IR (KBr): 3189, 1693, 1651, 1525, 1450; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, NH, 1H), 7.98–7.87 (m, ArH, 3H), 7.74 (s, ArH, 1H), 7.54–7.47 (m, ArH, 3H), 6.33 (d, C*CH*CH, J=5.1 Hz, 1H), 5.76–5.68 (m, CH_2*CH*CH_2, 1H), 5.52 (dd, CH_2CH*CH*$_2$, J=4.5, 15.8 Hz, 1H), 5.25–5.24 (m, CH*CH*Ph, 1H), 5.08–5.00 (m, *CH*$_2$CHCH_2 2H), 4.71 (dd, CH_2CH*CH*$_2$, J=6.3, 15.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.0, 163.6, 139.2, 133.8, 132.7, 132.4, 130.8, 128.7, 127.7, 127.6, 126.6, 126.3, 124.6, 124.3, 117.5, 116.4, 52.9, 49.7; HRMS (EI): calcd for $C_{18}H_{16}N_2O_2S$, 324.0932; found 324.0918.

4.3.6. 3-Methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6r***. White solid, mp 166–168 °C; IR (KBr): 3282, 2367, 1705, 1667, 1628; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 (s, NH, 1H), 7.41–7.28 (m, ArH, 5H), 5.89–5.88 (m, C*CH*CH, 1H), 5.05–5.04 (m, CH*CH*Ph, 1H), 3.07 (s, N*CH*$_3$, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 154.2, 143.2, 132.5, 128.7, 127.5, 126.0, 112.3, 53.2, 31.5; HRMS (EI): calcd for $C_{12}H_{12}N_2O_3$, 232.0848; found 232.0841.

4.3.7. 6-(4-Fluorophenyl)-3-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6s***. Off-white solid, mp 170–171 °C; IR (KBr): 3281, 2360, 1710, 1694, 1659, 1605, 1509; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44 (s, NH, 1H), 7.35–7.32 (m, ArH, 2H), 7.23–7.19 (m, ArH, 2H), 5.88 (d, C*CH*CH, J=4.5 Hz, 1H), 5.07 (d, CH*CH*Ph, J=3.2 Hz, 1H), 3.07 (s, N*CH*$_3$, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 162.5, 160.6, 154.2, 139.5, 139.4, 132.7, 128.2, 128.1, 115.6, 115.4, 112.0, 52.5, 31.5; HRMS (EI): calcd for $C_{12}H_{11}FN_2O_3$, 250.0754; found 250.0746.

4.3.8. 6-(2,4-Dimethoxyphenyl)-3-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6t***. Yellow solid, mp 169–170 °C; IR (KBr): 3282, 1709, 1666, 1612, 1504; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.10 (s, NH, 1H), 7.06 (d, ArH, J=8.2 Hz, 1H), 6.58–6.55 (m, ArH, 2H), 5.84 (d, C*CH*CH, J=4.4 Hz, 1H), 5.16 (d, CH*CH*Ph, J=3.2 Hz, 1H), 3.80 (s, O*CH*$_3$, 3H), 3.76 (s, O*CH*$_3$, 3H), 3.05 (s, NH, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.0, 160.1, 156.6, 154.9, 132.5, 126.9, 122.9, 111.9, 104.8, 98.6, 55.6, 55.3, 48.2, 31.6; HRMS (EI): calcd for $C_{14}H_{16}N_2O_5$, 292.1059; found 292.1071.

4.3.9. 3-Allyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6u***. Yellow solid, mp 181–183 °C; IR (KBr): 3283, 1699, 1658, 1610, 1458; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.2 (s, CO_2H, 1H), 7.52 (s, NH, 1H), 7.41–7.38 (m, ArH, 2H), 7.31–7.28 (m, ArH, 3H), 5.91 (d, C*CH*CH, J=4.4 Hz, 1H), 5.77–5.69 (m, CH_2*CH*CH_2, 1H), 5.10 (d, CH*CH*Ph, J=5.0 Hz, 1H), 5.06–4.98 (m, *CH*$_2$CHPh, 2H), 4.58 (dd, CH_2CH*CH*$_2$, J=3.8, 16.4 Hz, 1H), 4.33 (dd, CH_2CH*CH*$_2$, J=6.3, 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 153.7, 143.1, 135.2, 131.4, 128.7, 127.6, 126.0, 116.3, 113.2, 53.3, 43.8; HRMS (EI): calcd for $C_{14}H_{14}N_2O_3$, 258.1004; found 258.0996.

4.3.10. 3-Allyl-6-(3,5-dibromophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6v***. Yellow solid, mp 185–187 °C; IR (KBr): 3260, 3074, 1703, 1661, 1628, 1582; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.3 (s, CO_2H, 1H), 7.77 (s, NH, 1H), 7.62 (s, ArH, 1H), 7.50 (s, ArH, 2H), 5.96–5.95 (m, C*CH*CH, 1H), 5.73–5.67 (m, CH_2*CH*CH_2, 1H), 5.14–5.13 (m, CH*CH*Ph, 1H), 5.07–4.96 (m, *CH*$_2$CHCH$_2$, 2H), 4.56 (dd, CH_2CH*CH*$_2$, J=2.5, 16.4 Hz, 1H), 4.31 (dd, CH_2CH*CH*$_2$, J=5.7, 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.7, 153.5, 147.5, 134.9, 132.5, 132.3, 128.1, 122.8, 116.4, 111.8, 52.1, 43.8; HRMS (EI): calcd for $C_{14}H_{12}Br_2N_2O_3$, 413.9215; found 413.9201.

4.3.11. 3-Allyl-6-(naphthalen-2-yl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ***6w***. Yellow solid, mp 180–181 °C; IR (KBr): 3287, 3054, 1703, 1666, 1623, 1509; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96–7.89 (m, ArH, 3H), 7.78 (s, ArH, 1H), 7.65 (s, NH, 1H), 7.53–7.50 (m, ArH, 3H), 6.00 (dd, C*CH*CH, J=1.3, 5.1 Hz, 1H), 5.82–5.74 (m, CH_2*CH*CH_2 1H), 5.30 (dd, CH*CH*Ph, J=1.9, 5.0 Hz, 1H), 5.08–5.03 (m, *CH*$_2$CHCH$_2$, 2H), 4.64–4.60 (m, CH_2CH*CH*$_2$, 1H), 4.39 (dd, CH_2CH*CH*$_2$, J=5.7, 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 153.7, 140.5, 135.2, 132.9, 132.5, 131.6, 128.6, 127.8, 127.6, 126.5, 126.1, 124.5, 124.3, 116.3, 113.0, 53.5, 43.9; HRMS (EI): calcd for $C_{18}H_{16}N_2O_3$, 308.1161; found 308.1154.

Acknowledgements

The authors thank the A*Star for the funding provided (BMRC grant: R-143-000-348-305).

Supplementary data

Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2010.11.075.

References and notes

1. (a) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043; (b) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119; (c) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629; (d) Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satoh, F.; Morita, M.; Noguchi, T. *J. Med. Chem.* **1989**, *32*, 2399; (e) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254; (f) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *342*, 806; (g) Sidler, D. R.; Larsen, R. D.; Chartrain, M.; Ikemoto, N.; Roberge, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. *PCT Int. Appl.* **1999**, WO 9907695; (h) Nagarathnam, D.; Wong, W. C.; Miao, S. W.; Patane, M. A.; Gluchowski, C. *PCT Int. Appl.* **1997**, WO 9717969; (i) Mishra, R.; Mishra, B.; Moorthy, N. S. H. N. *Trends Appl. Sci. Res.* **2008**, *3*, 203; (j) Kruse, L. I.; Ross, S. T. *Eur. Pat. Appl.* **1989**, EP 323147.
2. Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828.
3. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Debrosse, C.; Mai, S.; Trunch, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Ports, B. C. M. *J. Org. Chem.* **1995**, *6*, 1182.
4. Kong, K.-H.; Chen, Y.; Ma, X.; Chui, W. K.; Lam, Y. *J. Comb. Chem.* **2004**, *6*, 928.
5. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
6. Bussolari, J. C.; McDonnell, P. A. *J. Org. Chem.* **2000**, *65*, 6777.
7. X-ray crystal data has been deposited in the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 783709.