



Pergamon

Tetrahedron 55 (1999) 12873–12880

TETRAHEDRON

## An Expedient Protocol of The Biginelli Dihydropyrimidine Synthesis Using Carbonyl Equivalents

Kamaljit Singh\*, Jasbir Singh<sup>†</sup>, Prasant K. Deb and Harjit Singh<sup>†</sup>,

Department of Applied Chemical Sciences & Technology, <sup>†</sup>Department of Chemistry, Guru Nanak Dev University, Amritsar – 143 005, India.

Received 21 June 1999; revised 4 August 1999; accepted 26 August 1999

**Abstract:** A one - pot condensation of perhydro-1,3 heterocycles - aldehyde equivalents with ethyl acetoacetate and ureas provides a convenient synthesis of the title compounds with a variety of substituents at C-4. Yields are equivalent or significantly higher than the conventional methods. © 1999 Elsevier Science Ltd. All rights reserved.

### INTRODUCTION

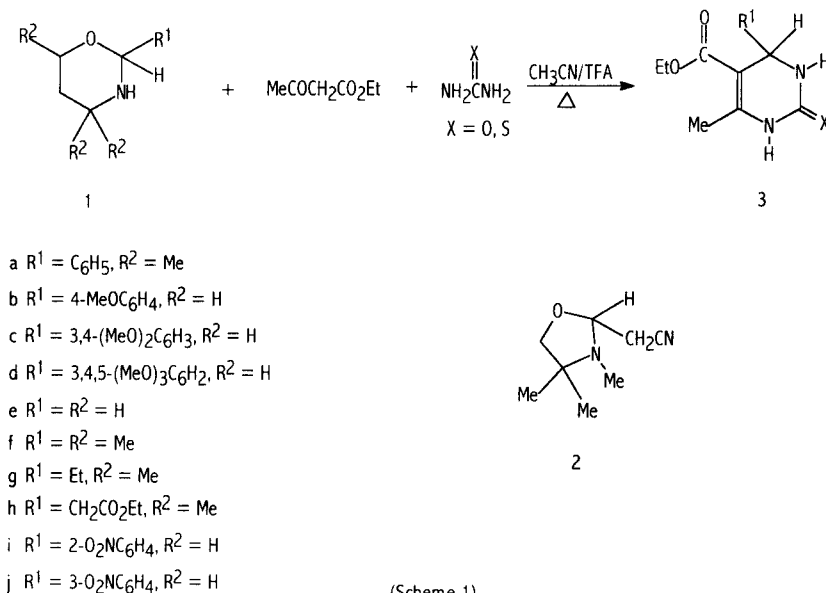
The interest in synthesis of dihydropyrimidines - Biginelli compounds stems from their close structural relationship<sup>1</sup> to clinically important 1,4-dihydropyridine calcium channel modulators of the type nifedipine *etc.* and also because of interesting biological properties of several marine alkaloids<sup>2-4</sup> based upon dihydropyrimidine *viz.* crambine, batzelladine (potent HIV gp-120-CD4 inhibitor) and pitilomycin A. Derivatisation of the dihydropyrimidines especially<sup>5</sup> at C-4 has led to the recognition of several lead compounds that show a very similar pharmacological profile<sup>6-8</sup> to 1,4-dihydropyridine based drugs. Biginelli synthesis involving carbonyl compounds, urea and alkyl acetoacetates and its several modifications<sup>9</sup> give moderate yields especially in case of substituted aromatic as well as aliphatic aldehydes. Thus development of unconventional methodologies and reagents avoiding the direct use of carbonyl compounds for efficient lead structure identification and for pharmacophore variation<sup>10</sup> has always attracted attention. Owing to their ease of synthesis from various reagents and in functionalization of C-2,<sup>11</sup> oxazinanes and oxazolidines have been used in efficacious syntheses of important molecules typified by streptindole<sup>12a</sup> - a genotoxic metabolite, nifedipine<sup>12b</sup> - a coronary vasodilator,  $\alpha$ -tetralones<sup>12c</sup> and alkaloid skeletons<sup>12d</sup> *etc.* by using one - pot acid catalyzed transfer of appropriately substituted C-2 on the desired nucleophilic substrate. Here we report a simple but effective protocol of synthesis of Biginelli dihydropyrimidines preserving the original one-pot strategy of the Biginelli reaction from some oxazinanes and oxazolidines, urea or thiourea and ethyl acetoacetate. We have found that dihydropyrimidines carrying a variety of substituents at C-4 are formed in a

<sup>†</sup>Present address: Ranbaxy Research Labs, A-2, Phase-1, Okhla Industrial Area, New Delhi- 110020, India.

synthetically useful manner. Also we present direct evidence that supports the mechanism of Kappe<sup>13</sup> *et al.* for the Biginelli reaction.

### RESULTS AND DISCUSSION

Reaction of oxazinane **1a** with an equimolar mixture of ethyl acetoacetate and urea or thiourea in anhydrous acetonitrile:trifluoroacetic acid (10:0.1) under reflux furnished ethyl 6-methyl-2-oxo/thione-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **3a/3b** in 94% and 95% isolated yields, respectively. The products crystallized out of the reaction mixtures upon cooling, without the need of any chromatographic separation. Likewise, reactions of oxazinanes **1b-1j** or oxazolidine **2** with ethyl acetoacetate and urea or thiourea under acid catalyzed conditions furnished corresponding **3c-3o**, in excellent yields (Table).



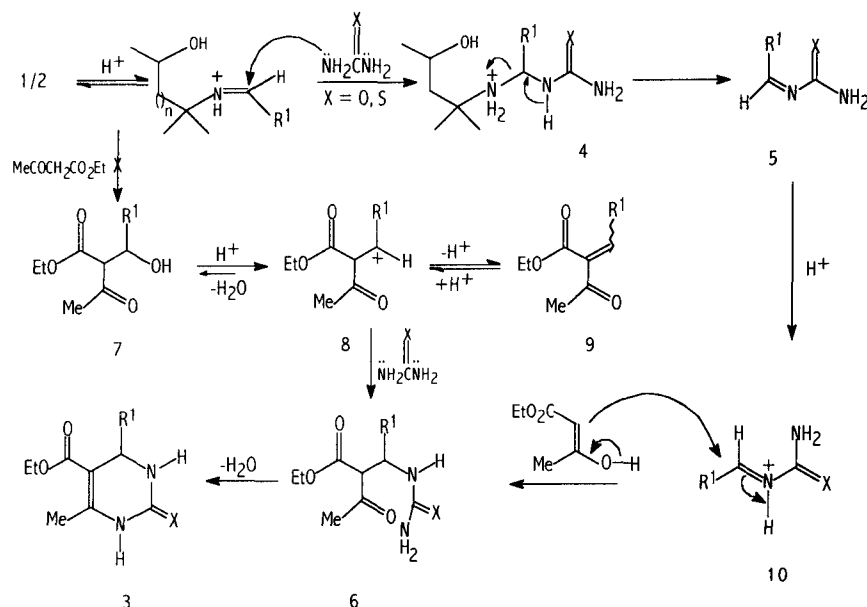
The merit of this method is indicated in the high isolated yields without the need of any chromatographic purification and also in avoiding the direct use of vulnerable aldehydes in the crucial transformation. The transferable C-2 unit in **1** or **2** can be incorporated by making use of reagents other than aldehydes, for which even the corresponding carbonyls are either inaccessible or difficult to handle under the typical Biginelli reaction<sup>14</sup> conditions (ethanolic HCl/ reflux). Thus this protocol is quite flexible to a variety of substitutional variations at C-4 of the target compounds.

In comparison with the solution phase Biginelli reaction where, in order to drive the reaction to completion, an excess of one or more reaction component(s), *i.e.* aldehyde, ethyl acetoacetate or urea is to be employed,<sup>18</sup> and laborious work up includes recrystallization and/or chromatography, only equimolar reactants are employed in the present methodology and the reaction proceeds in a shorter time. The recently developed high yielding solid phase strategy<sup>9a</sup> is quite attractive but involves a multistep process invoking linking and de-

linking of the resin support from the constituting components. However, it provides a throughput of very large number of compounds on a small scale.

**Table : Reaction of 1/2 with urea or thiourea and ethyl acetoacetate.**

Entry	1/2	Dihydropyrimidine R <sup>1</sup>	X	Reaction time (h)	Yield (%)	Reported yield (%)
1	1a	3a C <sub>6</sub> H <sub>5</sub>	O	4	94	94, <sup>15</sup> 78 <sup>16</sup>
2	1a	3b C <sub>6</sub> H <sub>5</sub>	S	4	95	--
3	1b	3c 4-MeOC <sub>6</sub> H <sub>4</sub>	O	5	92	--
4	1b	3d 4-MeOC <sub>6</sub> H <sub>4</sub>	S	4	87	--
5	1c	3e 3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	O	6	82	75, <sup>15</sup> 47 <sup>16</sup>
6	1d	3f 3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	O	5	84	--
7	1e	3g H	O	1	90	--
8	1e	3h H	S	1.5	93	--
9	1f	3i Me	O	6	94	53, <sup>15</sup> 26, <sup>16</sup> 20, <sup>17</sup>
10	1f	3j Me	S	8	84	--
11	1g	3k Et	O	8	86	--
12	1h	3l CH <sub>2</sub> CO <sub>2</sub> Et	O	12	78	--
13	1i	3m 2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	O	4	88	84, <sup>15</sup> 50, <sup>17</sup>
14	1j	3n 3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	O	5	90	87, <sup>15</sup> 51, <sup>17</sup>
15	2	3o CH <sub>2</sub> CN	O	12	68	--



(Scheme 2)

In all the reactions described herein, the overall transfer of the C-2 unit of 1/2 between the nucleophilic carbon of the ethyl acetoacetate and nitrogens of urea/thiourea can be visualized as proceeding through initial acid catalyzed ring opening of 1/2 and its reaction with urea/thiourea to form intermediate 4 (Scheme 2). Subsequently, 4 undergoes β-elimination to generate an alkyldineimine intermediate 5 existing as its

protonated form **10** which then reacts with the enol tautomer of ethyl acetoacetate, a  $\pi$ -nucleophile, to furnish **3** through cyclodehydration of the ureide **6**.

The “carbenium ion mechanism” proposed by Sweet<sup>19</sup> *et al.* suggesting an acid catalyzed aldol condensation of benzaldehyde and ethyl acetoacetate as the first and rate-limiting step to generate **7** and its dehydration to the carbenium ion **8** which is then intercepted by urea to form ureides **6** resulting in the cyclization to **3**, is ruled out on the basis of our earlier finding,<sup>12c</sup> that oxazinanes or even aldehydes do not react with ethyl acetoacetate under acid catalyzed reaction conditions to form<sup>20</sup> **8** or its deprotonated  $\alpha,\beta$ -unsaturated enone **9**, which should be the expected by-product in the reaction. The mechanism proposed by Kappe<sup>21</sup> also involves formation of dehydrated *N*-acyliminium species **10** proceeding through initial reaction of benzaldehyde with urea to generate *N*-(1-hydroxybenzyl)-urea which is in equilibrium with **10**. Our finding that urea and **1a** react in anhydrous acetonitrile : trifluoroacetic acid (10:0.1) to form **5**, which then reacts independently with ethyl acetoacetate to furnish **3a**, unambiguously corroborates this mechanism (Scheme 2).

Thus, we have put forward a simple modification of the Biginelli dihydropyrimidine synthesis through the use of readily available perhydro-1,3-heterocycles. Apart from its simplicity, one important feature of this novel protocol is the ability to tolerate much desired substitutional variations, especially at C-4.

**Acknowledgements:** The authors thank CSIR, New Delhi for the project 01(1441)/97-EMR-II and the G.N.D. University for a research fellowship to PKD.

## EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on Pye UNICAM SP 3-300 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were run on Bruker AC 200 instrument using TMS as the internal standard. Mass (70eV) spectra and elemental analyses were performed on Shimadzu QP 2000A spectrometer and Perkin Elmer 2400 CHN elemental analyser, respectively. TLC was performed on microplates coated with silica gel-G and the spots were developed in iodine chamber. Where necessary column chromatography was performed on silica gel (60-120 mesh). CH<sub>3</sub>CN was dried over P<sub>2</sub>O<sub>5</sub>. Oxazinanes **1**<sup>11,12b,d</sup> and 2-cyanomethyl-3,4,4-trimethyloxazolidine **2**<sup>22</sup> were synthesized by reported methods.

### *Reactions of 1,3-oxazinanes/1,3-oxazolidines with ethyl acetoacetate and ureas.*

A solution of **1** (0.01 mol) or **2** (0.01 mol) and ethyl acetoacetate (0.01 mol) and urea or thiourea (0.01 mol) in anhydrous acetonitrile (30-40 ml) containing trifluoroacetic acid (0.5 ml) was refluxed till the reaction was completed (TLC). The reaction mixture was basified with cold aqueous sodium carbonate and extracted with chloroform (3 x 50 ml). The extract was washed with cold water (2 x 50ml) and dried (anhydrous sodium sulfate). Solvent was removed and the residue was crystallized to get **3**.

The following compounds were prepared.

**Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3a:** m.p. 207°C, (lit.<sup>16</sup>204-205°C); IR (KBr)  $\nu$  3300, 1730, 1700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>+{CD<sub>3</sub>}<sub>2</sub>SO)  $\delta$  1.27 (t, *J* = 7.0 Hz, 3H, CH<sub>3</sub>),

2.28 (s, 3H, CH<sub>3</sub>), 4.00 (q,  $J = 7.0$  Hz, 2H, CH<sub>2</sub>), 5.18 (s, 1H, CH), 7.28 (m, 5H, ArH), 7.71 (br s, NH), 9.17 (br s, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub> + {CD<sub>3</sub>}<sub>2</sub>SO)  $\delta$  12.2, 16.0, 52.2, 57.3, 97.6, 124.5, 125.5, 126.4, 143.3, 150.4, 163.5.

**Ethyl 6-methyl-2-thione-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3b:** m.p. 203°C (lit.<sup>9c</sup>205-206°C); IR (KBr)  $\nu$  3300, 1680, 1200 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>+{CD<sub>3</sub>}<sub>2</sub>SO)  $\delta$  1.12 (t,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>), 2.31 (s, 3H, CH<sub>3</sub>), 4.01(q,  $J = 7.0$  Hz, 2H, CH<sub>2</sub>), 5.21 (s, 1H, CH), 7.29 (m, 5H, ArH), 9.61 (br s, 1H, NH), 10.27 (br s, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub> + {CD<sub>3</sub>}<sub>2</sub>SO)  $\delta$  12.2, 15.5, 52.5, 57.8, 99.2, 124.7, 125.8, 126.6, 143.1, 163.4, 172.6; MS  $m/z$  276 (M<sup>+</sup>).

**Ethyl 6-methyl-2-oxo-4-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3c:** m.p. 198°C (lit.<sup>9c</sup>203-204°C); IR (KBr)  $\nu$  3220, 1725, 1705 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.18 (t,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 3.79 (s, 3H, CH<sub>3</sub>), 4.08 (q,  $J = 7.0$  Hz, 2H, CH<sub>2</sub>), 5.35 (d,  $J = 2.0$  Hz, 1H, CH), 5.48 (br s, 1H, NH) 6.83 (d,  $J = 4.0$  Hz, 2H, ArH), 7.23 (d,  $J = 4.0$  Hz, 2H, ArH), 7.44 (br s, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.1, 18.5, 55.0, 55.2, 59.9, 101.5, 114.0, 127.8, 136.2, 146.2, 153.2, 165.7; MS  $m/z$  209 (M<sup>+</sup>).

**Ethyl 6-methyl-2-thione-4-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3d:** m.p. 140°C (lit.<sup>9c</sup>134-135°C); IR (KBr)  $\nu$  3220, 1680 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.31 (t,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 3.79 (s, 3H, CH<sub>3</sub>), 4.09 (q,  $J = 7.0$  Hz, 2H, CH<sub>2</sub>), 5.34 (d,  $J = 2.0$  Hz, 1H, CH), 6.62-7.25 (m, 4H, ArH), 7.30 (br s, 1H, NH), 7.92 (br s, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.0, 17.9, 55.1, 55.3, 60.2, 103.0, 114.0, 127.9, 134.7, 142.7, 159.4, 165.3, 173.7; MS  $m/z$  306 (M<sup>+</sup>).

**Ethyl 6-methyl-2-oxo-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3e:** m.p. 192-194 °C (lit.<sup>16</sup> 178°C); IR (KBr)  $\nu$  3300, 1735, 1705 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.18 (t,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 3.85 (s, 6H, 2 x OCH<sub>3</sub>), 4.07 (q,  $J = 7.1$  Hz, 2H, CH<sub>2</sub>), 5.35 (s, 1H, CH), 5.68 (s, 1H, NH), 6.77-6.84 (m, 3H, Ar-H), 7.88 (s, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.1, 18.4, 55.1, 55.8, 59.9, 101.3, 109.9, 111.1, 118.5, 136.4, 146.1, 148.6, 148.9, 153.8, 165.6; MS  $m/z$  320 (M<sup>+</sup>).

**Ethyl 6-methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3f:** m.p. 217-219 °C; IR (KBr)  $\nu$  3300, 1735, 1705 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.20 (t,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 3.82 (s, 9H, 3 x OCH<sub>3</sub>), 4.10 (q,  $J = 7.1$  Hz, 2H, CH<sub>2</sub>), 5.36 (s, 1H, CH), 5.68 (s, 1H, NH), 6.54 (s, 2H, ArH), 7.89 (s, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.1, 18.4, 55.6, 56.0, 59.9, 60.6, 101.1, 103.5, 139.3, 146.2, 153.2, 153.7, 165.6; MS  $m/z$ : 350 (M<sup>+</sup>); (Anal. Calcd. For C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>; C 58.28, H 6.28, N 8.00; Found C 58.23, H 6.24, N 7.98).

**Ethyl 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3g:** m.p. 256°C (lit.<sup>16</sup> 253.8-256°C); IR (KBr)  $\nu$  3300, 1730, 1705 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>+{CD<sub>3</sub>}<sub>2</sub>SO)  $\delta$  1.25 (t,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>), 2.22 (s, 3H, CH<sub>3</sub>), 4.02 (s, 2H, CH<sub>2</sub>), 4.11 (q,  $J = 7.0$  Hz, 2H, CH<sub>2</sub>), 6.67 (br s, 1H, NH), 8.53 (br s, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>+{CD<sub>3</sub>}<sub>2</sub>SO)  $\delta$  13.2, 16.7, 39.8, 58.3, 94.2, 147.2, 152.6, 164.7.

**Ethyl 6-methyl-2-thione-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3h:** m.p. 236°C; IR (KBr)  $\nu$  3180,

1715  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3+\{\text{CD}_3\}_2\text{SO}$ )  $\delta$  1.25 (t,  $J = 7$  Hz, 3H,  $\text{CH}_3$ ), 2.23 (s, 3H,  $\text{CH}_3$ ), 3.98 (s, 2H,  $\text{CH}_2$ ), 4.11 (q,  $J = 7$  Hz, 2H,  $\text{CH}_2$ ), 6.68 (br s, 1H, NH), 9.58 (br s, 1H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3+\{\text{CD}_3\}_2\text{SO}$ )  $\delta$  13.2, 16.1, 40.2, 58.6, 94.8, 144.2, 164.3, 175.2; (Anal. Calcd. For  $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ ; C 48.00, H 6.00, N 14.00; Found C 48.32, H 5.82, N 13.87).

**Ethyl 4,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3i:** m.p. 181°C (lit.<sup>16</sup>181-184°C); IR (KBr)  $\nu$  3300, 1707, 1650  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3+\{\text{CD}_3\}_2\text{SO}$ )  $\delta$  1.14 (d,  $J = 6.0$  Hz, 3H,  $\text{CH}_3$ ), 1.23 (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ), 2.17 (s, 3H,  $\text{CH}_3$ ), 3.53 (m, 1H, CH), 4.14 (q,  $J = 7.0$  Hz, 2H,  $\text{CH}_2$ ), 7.14 (br s, 1H, NH), 8.90 (br s, 1H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3+\{\text{CD}_3\}_2\text{SO}$ )  $\delta$  12.5, 16.0, 21.6, 44.7, 57.3, 99.0, 145.7, 151.3, 163.6.

**Ethyl 4,6-dimethyl-2-thione-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3j:** m.p. 191°C; IR (KBr)  $\nu$  3300, 1710, 1659  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3+\{\text{CD}_3\}_2\text{SO}$ )  $\delta$  1.15 (d,  $J = 6.0$  Hz, 3H,  $\text{CH}_3$ ), 1.24 (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ), 2.22 (s, 3H,  $\text{CH}_3$ ), 4.05-4.24 (m, 3H, CH and  $\text{OCH}_2$ ), 9.04 (br s, 1H, NH), 9.90 (br s, 1H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3+\{\text{CD}_3\}_2\text{SO}$ )  $\delta$  12.7, 15.8, 21.2, 45.4, 57.9, 100.8, 143.1, 163.7, 173.3; (Anal. Calcd. For  $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ ; C 50.47, H 6.54, N 13.08; Found C 50.42, H 6.63, N 12.68).

**Ethyl 4-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3k:** m.p. 212-214°C; IR (KBr)  $\nu$  3330, 1730, 1705  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.93 (t,  $J = 7.3$  Hz, 3H,  $\text{CH}_3$ ), 1.28 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ), 1.52-1.61 (m, 2H,  $\text{CH}_2$ ), 2.28 (s, 3H,  $\text{CH}_3$ ), 4.14-4.26 (m, 3H,  $\text{CH}_2$  and CH), 5.81 (s, 1H, NH), 8.22 (s, 1H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.6, 14.3, 18.4, 29.9, 52.7, 59.8, 101.1, 146.8, 154.8, 165.8; MS  $m/z$  212 ( $\text{M}^+$ ); (Anal. Calcd. For  $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_3$ ; C 56.60, H 7.54, N 13.20; Found C 56.40, H 7.52, N 13.18).

**Ethyl 4-methoxycarbonyl methyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3l:** m.p. 132°C; IR (KBr)  $\nu$  3220, 1720, 1705, 1640  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.24-1.32 (two triplets, 6H,  $2\times\text{CH}_3$ ), 2.29 (s, 3H,  $\text{CH}_3$ ), 2.59 (m, 2H,  $\text{CH}_2$ ), 4.11-4.24 (two quartets, 4H,  $2\times\text{CH}_2$ ), 4.81 (m, 1H, CH), 8.48 (br s, exchanges with  $\text{D}_2\text{O}$ , 1H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.2, 14.4, 18.6, 40.7, 48.4, 60.1, 60.8, 99.2, 148.2, 153.8, 165.3, 171.4; (Anal. Calcd. For  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_5$ ; C 53.33, H 6.67, N 10.37; Found C 53.33, H 6.67, N 10.37).

**Ethyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3m<sup>17</sup>:** m.p. 239°C; IR (KBr)  $\nu$  3110, 1690, 1640, 1520, 1340  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.96 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ), 2.47 (s, 3H,  $\text{CH}_3$ ), 3.93 (q,  $J = 7.1$  Hz, 2H,  $\text{CH}_2$ ), 5.82 (s, 1H, CH), 6.00 (s, 1H, NH), 7.41-7.66 (m, 3H, ArH), 7.89 (d,  $J = 8.11$  Hz, 1H, ArH), 8.03 (s, 1H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.7, 18.1, 50.8, 59.9, 96.7, 124.3, 128.8, 128.9, 134.0, 137.4, 148.3, 149.1, 152.8, 164.7.

**Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3n:** m.p. 230-32°C (lit.<sup>16</sup> 226-227°C); IR (KBr)  $\nu$  3110, 1700, 1630, 1520, 1350  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.19 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ), 2.39 (s, 3H,  $\text{CH}_3$ ), 4.08 (q,  $J = 7.0$  Hz, 2H,  $\text{CH}_2$ ), 5.54 (s, 1H, CH), 7.01 (s, 1H, NH), 7.51-7.67 (m, 3H, ArH), 8.13 (s, 1H, ArH), 8.17 (s, 1H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9, 18.1, 54.1, 59.5, 98.9, 121.4, 122.0, 129.2, 132.7, 146.7, 147.8, 148.8, 152.4, 165.2.

**Ethyl 6-methyl-4-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3o:** m.p. 202-204°C; IR (KBr)  $\nu$  3330, 2220, 1730, 1710  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3 + \{\text{CD}_3\}_2\text{SO}$ )  $\delta$  1.28 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ), 2.30 (s, 3H,  $\text{CH}_3$ ), 2.59-2.66 (m, 2H,  $\text{CH}_2$ ), 4.15 (q,  $J = 7.1$  Hz, 2H,  $\text{CH}_2$ ), 4.52-4.56 (m, 1H, CH), 7.39 (s, 1H, NH), 9.10 (s, 1H, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3 + \{\text{CD}_3\}_2\text{SO}$ )  $\delta$  12.4, 16.3, 24.3, 46.4, 57.6, 94.1, 116.0, 148.7, 150.0, 163.1; MS  $m/z$  223 ( $\text{M}^+$ ); (Anal. Calcd. For  $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_3$ ; C 53.81, H 5.82, N 18.83 ; Found C 53.79, H 5.80, N 18.62 ).

#### REFERENCES AND NOTES

1. Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.*, 1991, 341, 806.
2. 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.; Potts, B. C. *J. Org. Chem.* 1995, 60, 1182.
3. Sinder, B. B.; Shi, Z. *J. Org. Chem.*, 1993, 58, 3828 and references cited therein.
4. Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.*, 1995, 117, 2675 and references cited therein.
5. Kappe, C. O.; Fabian, M. F. *Tetrahedron*, 1997, 53(8), 2803.
6. Hurst, E. W.; Hull, R. *J. Med. Pharm. Chem.*, 1961, 3, 215.
7. 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.*, 1981, 46, 3433.
8. Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, 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.
9. (a) Wipf, P.; Cunningham, A. *Tetrahedron Lett.*, 1995, 36(43)7819. (b) Zavyalov, S. I.; Kulikova, L. B. *Khim.-Farm. Zh.* 1992, 26, 116. (c) Gupta, R.; Gupta, A. K.; Paul, S.; Kachroo, P. L. *Ind. J. Chem.*, 1995, 34B, 151. (d) Hu, E. H.; Sidler, D. R.; Dolling, U. H.; Patane, M. A. *PCT Int Appl. WO 97 21,687; Chem. Abstr.* 1997, 127, 121750v.
10. Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P.; Gordon, E. M.; *J. Med. Chem.*, 1994, 37, 1233.
11. (a) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.*, 1973, 38, 36 (b) Singh, K.; Singh, J.; Singh, H. *Tetrahedron*, 1989, 45, 3567 and references cited therein.
12. (a) Singh, H.; Singh, K. *Tetrahedron*, 1988, 44, 5897 (b) Singh, H.; Singh, K. *Tetrahedron*, 1989, 45, 3967 (c) Singh, K.; Singh, J.; Singh, H. *Tetrahedron*, 1996, 52, 14273 (d) Singh, K.; Deb, P. K. *Heterocycles*, 1999, 51, 7, 1509.
13. Kappe, C. O.; Peters, E. M.; Peters, K. *J. Org. Chem.*, 1997, 62, 3109.

14. Biginelli, P.; *Gazz. Chim. Ital.*, 1893, 23, 360.
15. Kappe, C. O.; Falsone, S. F. *Synlett*, 1998, 718.
16. Folkers, K.; Harwood, H. J.; Johnson, T. B. *J. Am. Chem. Soc.*, 1932, 54, 3751.
17. Ehsan, A.; Karimullah. *Pakistan J. Sci. Ind. Res.* 1967, 10, 83. *Chem. Abstr.* 1968, 68, 78231z.
18. Kappe, C. O. *Tetrahedron*, 1993, 49, 6937 and references cited therein.
19. Sweet, F.; Fissekis, J. D. *J. Am. Chem. Soc.*, 1973, 95, 8741.
20. Potts, K. T.; Chen, S. J.; Kane, J.; Marshall, J. L. *J. Org. Chem.*, 1974, 39, 3627.
21. Kappe, C. O. *J. Org. Chem.*, 1997, 62, 7201.
22. Singh, K; Singh, J; Singh, H. *Tetrahedron*, 1998, 54, 3567.