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# Cascade assembly of *N,N′*-dialkylbarbituric acids and aldehydes: a simple and efficient one-pot approach to the substituted 1,5-dihydro-2*H*,2′*H*-spiro-(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′(1′*H*,3*H*,3′*H*)-pentone framework

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ABSTRACT

Cascade assembly of *N,N′*-dialkylbarbituric acids and aldehydes in the presence of bromine leads to the selective and efficient formation of substituted 1,5-dihydro-2*H*,2′*H*-spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′-(1′*H*,3*H*,3′*H*)-pentones in 70–88% yields via a complex cascade process. Spirobarbiturates containing the furo[2,3-*d*]pyrimidine framework are a class of compounds with interesting pharmacological and physiological activity.

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The discovery of novel synthetic methodologies to facilitate the preparation of compound libraries is a pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry.[1] Molecular complexity and diversity in natural and biologically relevant systems encourage chemists to investigate new methods and reactions.

One powerful approach towards this goal is to combine two or more distinct reactions into a single transformation, thereby producing cascade reactions as a sequential process. Cascade reactions have been utilized to introduce molecular complexity from readily available starting materials by combining two or more reactions into a single transformation.[2] As such, cascade reactions are of increasing importance in modern organic chemistry. This is not only due to the need for more efficient and less labour-intense methods, but also a consequence of the increasing importance of environmental considerations in chemistry.

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetriones are a type of privileged medicinal scaffold also known as barbiturates (derivatives of barbituric acid), are well-known class of drugs that act as central nervous system depressants and by virtue of this they produce a wide spectrum of effects, from mild sedation to anaesthesia.[3] They are also effective as anxiolytics and as anticonvulsants.[3a,4] Phenobarbital is the most widely used anticonvulsant and the oldest still in use.[5] The current interest in barbiturates arises from their pharmacological potential as analeptics, immunomodulating, anti-AIDS and anticancer agents.[6]

Among 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones, spirobarbiturates are a class of compounds with interesting pharmacological and physiological activity.[7] The spirobarbiturate system incorporates a spiro-connected hexahydropyrimidine-2,4,6-trione heterocyclic ring and may be promising with respect to biological responses.

During the course of our studies on cascade and multicomponent reactions we suggested a new strategy to cyclopropanes by chemical and electrocatalytic construction of substituted cyclopropane rings[8] from CH-acids,[9] activated olefins and CH-acids[10] and carbonyl compounds and CH-acids.[11]

Recently, we reported the first example of the cascade assembly of a spirocyclopropane structure via direct transformation of benzylidenemalononitriles and *N,N′*-dialkylbarbituric acids into substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles[12] (Scheme 1).

Continued investigations in this area resulted in a cascade process, namely direct cascade transformation of aromatic aldehydes **1a–j** and *N,N′*-dialkylbarbituric acids **2a**,**b** into spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)pentones **3a–m** (Scheme 2, Table 1).

Under the conditions of method A (bromine as the active halogen compound, 1.2 equivalents of EtONa as base, and ethanol as solvent) aldehydes **1a–j** and *N,N′*-dialkylbarbituric acids **2a**,**b** were transformed into the corresponding substituted spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)pentones **3a–m** in 75–88% yields

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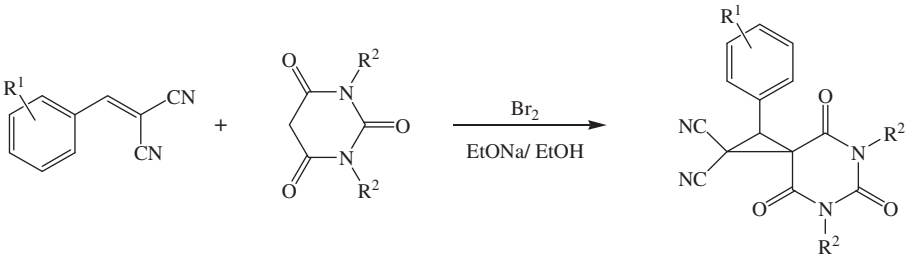
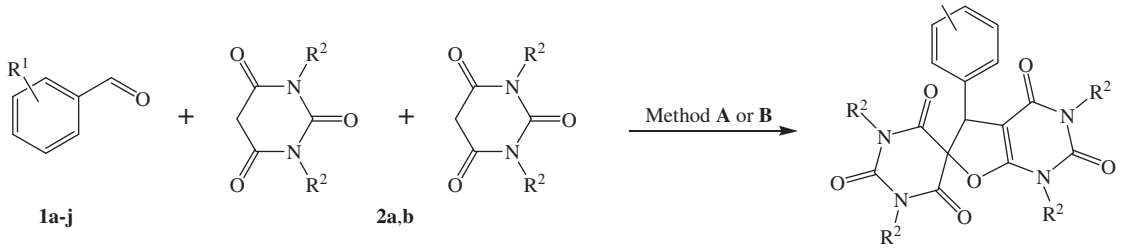


**Scheme 1.**



**1a-j** **2a**,**b** **3a-m**

**a** $R^1$ = H, **b** $R^1$ = 4-Me, **c** $R^1$ = 4-*t*-Bu, **d** $R^1$ = 2-MeO, **e** $R^1$ = 4-MeO, **f** $R^1$ = 2-Cl, **g** $R^1$ = 3-Cl, **h** $R^1$ = 4-Cl, **i** $R^1$ = 3-Br, **j** $R^1$ = 4-$NO_2$

**a** $R^2$ = Me; **b** $R^2$ = Et

Method **A**: 1. EtONa / EtOH; 2. $Br_2$, 3 h, r.t.
Method **B**: 1. EtOH; 2. 0.2 M $Br_2$ in $H_2O$, 1 h, 40 °C

**Scheme 2.**

**Table 1**
Cascade one-pot transformation of aldehydes **1a**–**j** and *N*,*N*′-dialkylbarbituric acids **2a**,**b** into spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)pentones **3a**–**m**[a,14]

| Entry | Aldehyde | Barbituric acid | $R^1$ | $R^2$ | Product, method, yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** | H | Me | **3a**, A (88); B (83) |
| 2 | **1b** | **2a** | 4-Me | Me | **3b**, A (86); B (81) |
| 3 | **1c** | **2a** | 4-*t*-Bu | Me | **3c**, A (85); B (78) |
| 4 | **1d** | **2a** | 2-MeO | Me | **3d**, A (77); B (69) |
| 5 | **1e** | **2a** | 4-MeO | Me | **3e**, A (82); B (70) |
| 6 | **1f** | **2a** | 2-Cl | Me | **3f**, A (85); B (79) |
| 7 | **1g** | **2a** | 3-Cl | Me | **3g**, A (88); B (81) |
| 8 | **1h** | **2a** | 4-Cl | Me | **3h**, A (82); B (73) |
| 9 | **1i** | **2a** | 3-Br | Me | **3i**, A (86); B (80) |
| 10 | **1j** | **2a** | 4-$NO_2$ | Me | **3j**, A (79); B (75) |
| 11 | **1a** | **2b** | H | Et | **3k**, A (75); B (68) |
| 12 | **1b** | **2b** | 4-Me | Et | **3l**, A (82); B (74) |
| 13 | **1j** | **2b** | 4-$NO_2$ | Et | **3m**, A (85); B (79) |

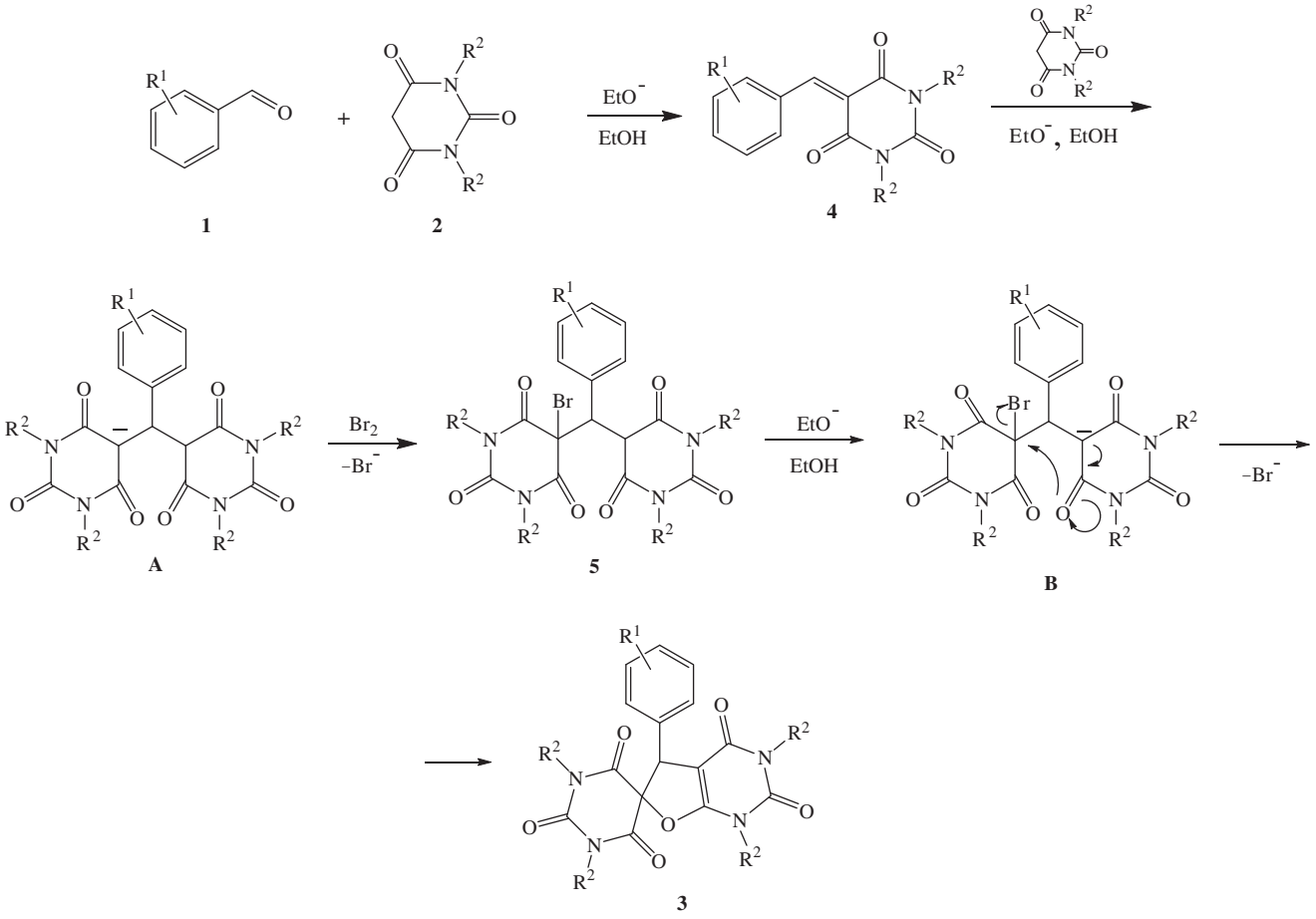
[a] Method A: 10 mmol of aldehyde **1**, 20 mmol of *N*,*N*′-dialkylbarbituric acid **2**, 10 mmol of bromine, 12 mmol of EtONa, 20 mL of EtOH, 3 h. Method B: 10 mmol of aldehyde **1**, 20 mmol of *N*,*N*′-dialkylbarbituric acid **2**, 10 mmol of bromine in 50 mL of $H_2O$, 20 mL of EtOH, 40 °C, 1 h.
[b] Isolated yield (isolation by filtration of the reaction mixture).

(Table 1). Method A was earlier used for the direct transformation of benzylidenemalononitriles and *N*,*N*′-dialkylbarbituric acids into substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles[12] (Scheme 1).

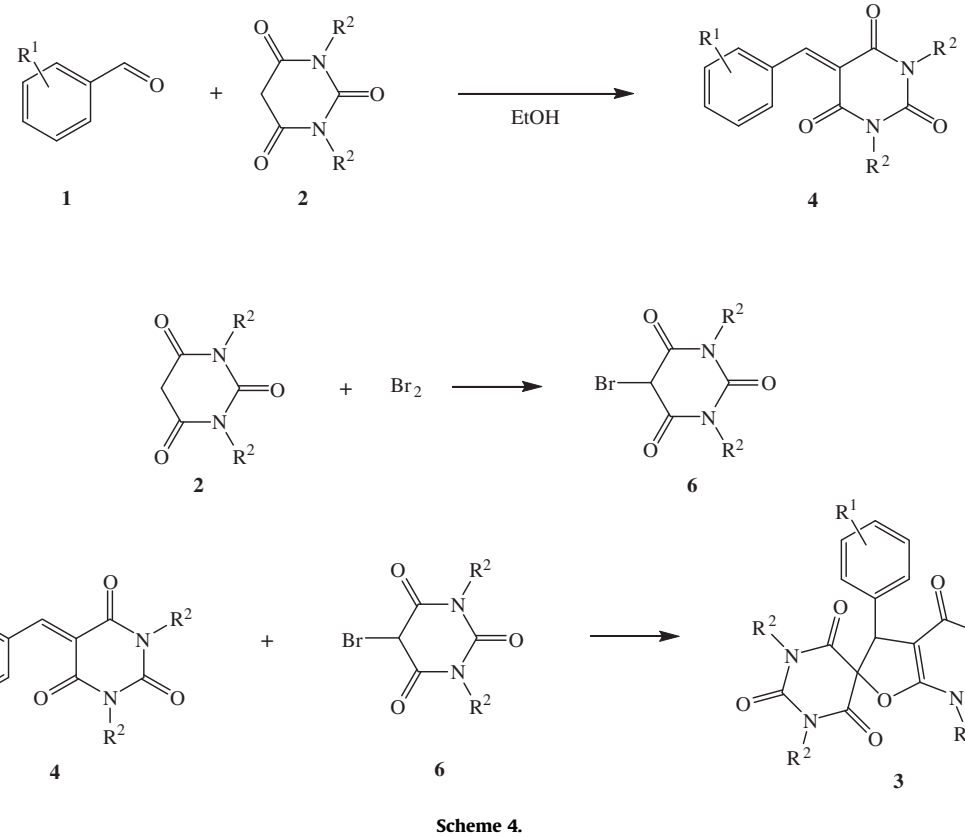
Recently, we developed new conditions avoiding the use of a base for the cascade synthesis of tetracyanocyclopropanes from benzylidenemalononitriles and malononitrile.[13] This process was accomplished by the direct action of bromine as shown in Method B, Scheme 2. Thus, the next step of our research was investigation of spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)pentones **3a**–**m** formation from aldehydes **1a–j** and *N*,*N*′-dialkylbarbituric acids **2a**,**b** by the direct action of bromine using Method B, (Table 1). The yields of spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)pentones **3a–m** using Method B were generally slightly lower, in the range of 68–83%.

Based on the above results and the mechanistic data on the cascade transformation of alkylidenemalononitriles and malononitrile into tetracyano-substituted cyclopropanes,[15] the cascade transformation of benzylidenemalononitriles and *N*,*N*′-dialkylbarbituric acids into substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]-octane-1,1-dicarbonitriles[12] and the direct cascade conversion of carbonyl compounds and malononitrile into substituted tetracyanocyclopropanes,[16] the following mechanism for the transformation of aldehydes **1a–j** and barbituric acids **2a**,**b** into the spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)pentones **3a–m** in the presence of EtONa is proposed (Method A, Scheme 3).

In the first step benzylidenebarbituric acid **4** is formed via Knoevenagel condensation of aldehyde **1** and *N*,*N*′-dialkylbarbituric acid **2** in the presence of EtONa. Next, Michael addition of a second *N*,*N*′-dialkylbarbituric acid **2** to the benzylidenebarbituric acid



**Scheme 3.**



**Scheme 4.**

**4** takes place in the presence of EtONa to give anion **A**. Bromination of anion **A** gives substituted 5-bromo-5-[aryl(2,4,6-trioxohexahydropyrimidin-5-yl)methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **5**. Finally, cyclization of **5** into substituted 1,5-dihydro-2*H*,2′*H*-spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′-(1′*H*,3*H*,3′*H*)-pentone **3** takes place in alcoholic solution (Scheme 3).

Of more interest was spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)pentone **3** formation directly from aldehydes **1** and *N*,*N*′-dialkylbarbituric acids **2** via the direct action of bromine (Method B, Scheme 4). In this case, rapid Knoevenagel condensation of aldehyde **1** with *N*,*N*′-dialkylbarbituric acid **2** takes place in the absence of base, as was reported earlier,[17] along with simultaneous bromination of *N*,*N*′-dialkylbarbituric acid **2** to give bromobarbituric acid **6**. Then, addition of bromobarbituric acid **6** to benzylidenebarbituric acid **4** results in the formation of spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)pentones **3** in a manner similar to that of Method A (Scheme 4).

In summary, a new cascade assembly of barbituric acids and aldehydes leading to the selective and efficient formation of substituted 1,5-dihydro-2*H*,2′*H*-spiro(furo[2,3-*d*]pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′-(1′*H*,3*H*,3′*H*)-pentones in 70–88% yields is reported. The cascade process proceeds smoothly with aromatic aldehydes bearing both electron-donating and electron-withdrawing groups. This novel process offers a facile and convenient method to prepare diversely substituted privileged spirobarbiturates, which are a class of small-molecule ligands with different biomedical properties. The developed cascade procedures require simple and reasonable starting materials. The reaction products are crystallized directly from the reaction mixture. These novel types of cascade processes bring us closer to the notion of 'ideal synthesis'.[18]

## Acknowledgements

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14. *General procedure*. *Method A*: To an EtOH (10 mL) suspension of aromatic aldehyde **1** (10 mmol) and barbituric acid **2** (20 mmol) in a 50 ml beaker, NaOEt (12 mmol) in 10 mL of EtOH was added during 1 min. Next, $Br_2$ (10 mmol) was added during 1 min without external cooling. The mixture was stirred at room temperature for 3 h, the solid phase filtered, washed with $H_2O$ and dried in a desiccator over $P_2O_5$ to give pure product **3**. *Method B*: To an EtOH (20 mL) solution of aromatic aldehyde **1** (10 mmol) and barbituric acid **2** (20 mmol) in a three-necked flask, was added bromine water (50 mL, 10 mmol, 0.2 M) during 5 min. The mixture was stirred at 40 °C for 1 h, the solid phase filtered, washed with $H_2O$ and dried in a desiccator over $P_2O_5$ to give pure product **3**.
*1,1′,3,3′-Tetramethyl-5-phenyl-1,5-dihydro-2H,2′H-spiro(furo[2,3-d]pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′ (1′H,3H,3′H)-pentone* (**3a**): white solid; mp 256–258 °C; IR (KBr): $\nu$ = 1720, 1700, 1688, 1676, 1620, 1520, 1480, 1432, 1396, 1036 $cm^{-1}$; MS (70 eV, EI): *m*/*z* (%): 398 (71) [$M^+$], 370 (10), 340 (7), 311 (44), 283 (16), 243 (100), 197 (36), 186 (20), 142 (57), 102 (52). Elemental Anal. Calcd for $C_{19}H_{18}N_4O_6$ (398.4): C, 57.28; H, 4.55; N, 14.06. Found: C, 57.16; H, 4.61; N, 13.92. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.40 (s, 3H, $CH_3$), 3.12 (s, 3H, $CH_3$), 3.22 (s, 3H, $CH_3$), 3.40 (s, 3H, $CH_3$), 5.11 (s, 1H, CH), 7.11–7.18 (m, 2H, Ph), 7.25–7.35 (m, 3H, Ph); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 28.00, 28.19, 29.29, 29.77, 58.98, 85.30, 90.08, 128.05, 128.73, 129.28, 132.63, 149.41, 151.04, 158.45, 162.51, 162.82, 165.33.
*5-(4-tert-Butylphenyl)-1,1′,3,3′-tetramethyl-1,5-dihydro-2H,2′H-spiro(furo[2,3-d]pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′ (1′H,3H,3′H)-pentone* (**3c**): white solid; mp 228–230 °C; IR (KBr): $\nu$ = 1716, 1700, 1688, 1680, 1652, 1516, 1440, 1288, 1040 $cm^{-1}$; MS (70 eV, EI): *m*/*z* (%): 454 (3) [$M^+$], 397 (1), 351 (6), 299 (7), 285 (2), 237 (5), 168 (4), 128 (8), 115 (20), 58 (100). Elemental Anal. Calcd for $C_{23}H_{26}N_4O_6$ (454.5): C, 60.78; H, 5.77; N, 12.33. Found: C, 60.62; H, 5.93; N, 12.25. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 1.25 (s, 9H, $CH_3$), 2.33 (s, 3H, $CH_3$), 3.12 (s, 3H, $CH_3$), 3.22 (s, 3H, $CH_3$), 3.40 (s, 3H, $CH_3$), 5.06 (s, 1H, CH), 7.05 (d, $^3J$(H,H) = 8.3 Hz, 2H, CH, Ar), 7.29 (d, $^3J$(H,H) = 8.3 Hz, 2H, CH, Ar); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 27.15, 27.69, 28.97, 29.71, 31.00, 34.28, 56.00, 85.22, 90.26, 124.69, 128.31, 131.36, 150.01, 150.82, 151.01, 158.12, 162.28, 163.24, 165.53.
*5-(2-Chlorophenyl)-1,1′,3,3′-tetramethyl-1,5-dihydro-2H,2′H-spiro(furo[2,3-d]pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′ (1′H,3H,3′H)-pentone* (**3f**): white solid; mp 264–266 °C; IR (KBr): $\nu$ = 1712, 1696, 1688, 1676, 1516, 1440, 1384, 1300, 1188, 1036 $cm^{-1}$; MS (70 eV, EI): *m*/*z* (%): 397 (17) [$M^+$−Cl], 340 (5), 283 (59), 226 (11), 176 (30), 136 (45), 113 (24), 75 (26), 66 (39), 58 (100). Elemental Anal. Calcd for $C_{19}H_{17}ClN_4O_6$ (432.8): C, 52.73; H, 3.96; Cl, 8.19; N, 12.94. Found: C, 52.58; H, 4.09; Cl, 8.03; N, 12.83. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.69 (s, 3H, $CH_3$), 3.30 (s, 3H, $CH_3$), 3.38 (s, 3H, $CH_3$), 3.50 (s, 3H, $CH_3$), 5.56 (s, 1H, CH), 7.10–7.18 (m, 1H, CH, Ar), 7.21–7.31 (m, 2H, CH, Ar), 7.33–7.41 (m, 1H, CH, Ar); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 27.68, 27.75, 28.72, 29.73, 52.57, 85.15, 88.93, 127.28, 129.02, 130.41, 131.36, 131.46, 132.92, 150.07, 150.85, 157.95, 162.63, 162.88, 165.48.
*1,1′,3,3′-Tetraethyl-5-(4-methylphenyl)-1,5-dihydro-2H,2′H-spiro(furo[2,3-d]pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′ (1′H,3H,3′H)-pentone* (**3l**): white solid; mp 160–162 °C; IR (KBr): $\nu$ = 1712, 1688, 1676, 1656, 1504, 1440, 1408, 1380, 1312, 1228 $cm^{-1}$; MS (70 eV, EI): *m*/*z* (%): 468 (19) [$M^+$], 353 (23), 298 (23), 285 (99), 211 (62), 170 (60), 142 (77), 115 (98), 70 (84), 44 (100). Elemental Anal. Calcd for $C_{24}H_{28}N_4O_6$ (468.5): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.35; H, 5.95; N, 11.83. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.69 (t, $^3J$(H,H) = 7.3 Hz, 3H, $CH_3$), 1.20 (t, $^3J$(H,H) = 7.1 Hz, 3H, $CH_3$), 1.35 (t, $^3J$(H,H) = 7.1 Hz, 3H, $CH_3$), 1.44 (t, $^3J$(H,H) = 7.1 Hz, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 3.02–3.18 (m, 1H), 3.28–3.44 (m, 1H), 3.88–4.20 (m, 6H), 4.85 (s, 1H, CH), 6.97 (d, $^3J$(H,H) = 8.1 Hz, 2H, CH, Ar), 7.12 (d, $^3J$(H,H) = 8.1 Hz, 2H, CH, Ar); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 12.03, 12.81, 13.01, 13.53, 20.85, 36.39, 37.54, 37.87, 38.73, 58.59, 85.86, 89.49, 128.19, 129.30, 129.63, 139.04, 148.71, 150.16, 158.11, 162.07, 162.55, 165.27.
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