Synthesis of 5-Acyl-3,4-dihydropyrimidine-2-thiones via Solvent-Free, Solution-Phase and Solid-Phase Biginelli Procedures

Horacio Comas,[a] David-Alexandre Buisson,[a] Romain Najman,[a] Frank Kozielski,[b,1] Bernard Rousseau,[a] Roman Lopez*[a,2]

[a] CEA, LifeScience Division, iBiTec-S, Service de Chimie Bioorganique et de Marquage, Bat. 547, 91191 Gif sur Yvette, France

[b] Laboratoire des Moteurs Moleculaires, Institut de Biologie Structurale (CEA-CNRS-UJF), 41 Rue Jules Horowitz, 38027, Grenoble Cedex 01, France

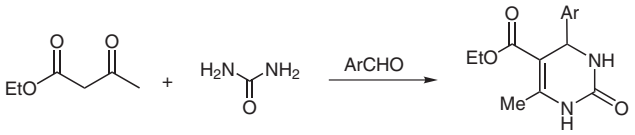
Fax +33(1)58103848; E-mail: roman.lopez@ymail.com

Received 20 January 2009

Abstract: Compounds belonging to the 5-acyl-3,4-dihydropyrimidine-2-thione family were obtained using a solvent-free Biginelli condensation with or without the use of a catalyst. An unprecedented solid-phase procedure involving a polymer-supported aldehyde allowed the preparation of a series of 5-aroyl derivatives starting with crude diketones obtained from their corresponding aryl esters.

Key words: multicomponent reaction, heterocycles, solid-phase synthesis, β-diketones, monastrol

The 3,4-dihydropyrimidine-2-one core is a well known pharmacophore found in many biologically active compounds including natural products.[3] The discovery in 1999 of 4-(3-hydroxyphenyl)-3,4-dihydropyrimidine-2(1*H*)-thione, best known as monastrol (**1**; Figure 1), which arrests cells in mitosis, reinforced the interest in this class of compounds. Monastrol is a weak inhibitor of the mitotic kinesin Eg5 (kinesin-5 family), responsible for the formation of the bipolar spindle.[4] Monastrol inhibits the ATPase activity of Eg5 by binding to its motor domain.[5] Due to their specific functions during the cell cycle, these proteins represent attractive, novel targets for the development of new anti-cancer agents.[6] We were therefore interested in the synthesis of further analogues of monastrol as potential Eg5 inhibitors.[7]



Scheme 1 The original Biginelli multicomponent reaction[8a]

The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by the Biginelli reaction[8a] has been particularly successful starting from an aromatic aldehyde, urea and ethyl acetoacetate in acidic ethanol (Scheme 1). Several groups have developed improved protocols to overcome the prolonged reaction time and low yields of this reaction whilst still allowing the synthesis of more complex target molecules.[8] Modern methodologies like microwave irradiation,[8h,i] the use of ionic liquids,[8j–l] novel catalysts[8m–r] and solvent-free protocols,[8s–v] have recently been reported to be successful. In contrast, the synthesis of 3,4-dihydropyrimidin-2(1*H*)-thiones by the Biginelli reaction, i.e. replacing urea by thiourea, has rarely been exemplified in those studies and there have been only a few reports describing *exclusively* their synthesis.[9] Furthermore, we observed that 5-acyl derivatives were usually ignored[10] and the N-1 substituted derivatives were frequently neglected.

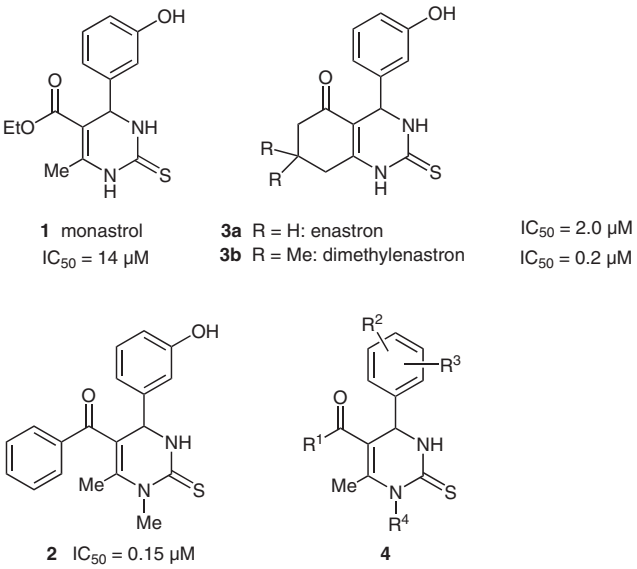


Figure 1 Biologically important dihydropyrimidine-2-thiones as inhibitors of human kinesin Eg5

During our studies on 3,4-dihydropyrimidine-2-thiones as Eg5 inhibitors, we noticed that the presence of an acyl group at the 5-position improved the potency of the analogues, as did the addition of an aryl moiety at the 4-position. This observation allowed us to identify compounds up to 100-fold more potent than racemic monastrol,[7,11] such as compound **2** (Figure 1). This outcome was in agreement with observations made by Surrey and Giannis using enastron **3a** and dimethylenastron **3b** (Figure 1).[12] In addition, we noticed that the alkyl moiety at N-1 in compound **2** showed an interesting role that deserved to be explored (Figure 1). Based on our SAR studies, we decided to focus on the synthesis of 5-acyl-3,4-dihydropyrimidine-2-thiones **4** with an aryl moiety on position 4 (Figure 1).

SYNLETT 2009, No. 11, pp 1737–1740
Advanced online publication: 12.06.2009
DOI: 10.1055/s-0029-1217373; Art ID: D02609ST

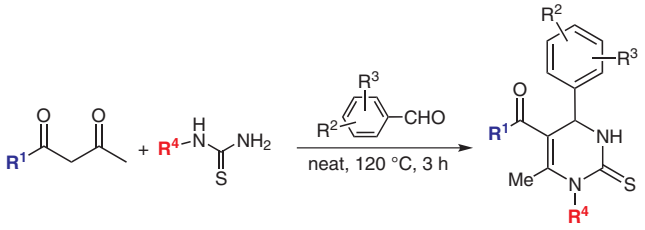
We report herein a convenient methodology for the synthesis of 5-acyl-3,4-dihydropyrimidine-2-thiones using either a one-pot, solvent-free protocol or an unprecedented solvent-free, solid-phase approach. Both methods are suitable for parallel modes.

Table 1 One-Pot, Solvent-Free Condensation of Thioureas, β-Diketones and Aromatic Aldehydes Leading to Dihydropyrimidine Thiones[a]

Entry	R^1	R^2	R^3	R^4	Cat.[b]	Yield (%)[c]
1	Me	2-OH	3-NO_2	H	–	93
2	Me	2-OMe	5-Br	H	–	81
3	Me	2-Cl	5-Cl	H	–	62
4	Me	2-OMe	5-OMe	H	–	92
5	Me	3-OMe	5-OMe	H	–	59
6	Me	3-OH	H	Allyl	+	27[d]
7	Me	3-OH	H	H	–	67[d]
8	Me	3-OH	H	Me	+	33[d]
9	Me	4-OH	H	H	–	73
10	Me	4-OH	H	Me	+	39[d]
11	Me	4-NMe_2	H	H	–	21[d]
12	Me	H	H	H	–	78
13	Me	H	H	Me	+	45[d]
14	Ph	2-OH	3-NO_2	H	–	66
15	Ph	2-OMe	5-Br	H	–	50
16	Ph	2-Cl	5-Cl	H	–	31
17	Ph	2-Cl	5-Cl	Me	–	34
18	Ph	2-OMe	5-OMe	H	–	65[d]
19	Ph	3-OMe	5-OMe	H	–	34
20	Ph	3-OH	H	Allyl	+	25[d]
21	Ph	3-OH	H	H	+	37[d]
22	Ph	3-OH	H	Me	+	35[d]
23	Ph	3-OAc	H	Me	+	43
23	Ph	4-OH	H	H	–	54
24	Ph	4-OH	H	Me	+	28[d]
25	Ph	H	H	H	–	63
26	Ph	H	H	Me	+	31[d]

[a] All experiments were performed on 1 mmol scale.
[b] $Yb(OTf)_3$ (0.05 equiv) was used as catalyst.
[c] Isolated yield after direct precipitation.
[d] Purification by preparative HPLC-MS (>99% purity).

Looking for a convenient method to perform parallel synthesis without special equipment, the reactions were carried out in simple screw-capped vials placed in a metal rack, which ensured a uniform heat-transfer. The aldehyde, diketone and thiourea (1:1:1.5) mixtures were heated for three hours without stirring (Scheme 2) and the desired products were obtained in high purities based on LC/MS analysis (Table 1).



Scheme 2 Biginelli condensation leading to the 5-acyl-3,4-dihydropyrimidine-2-thione scaffold

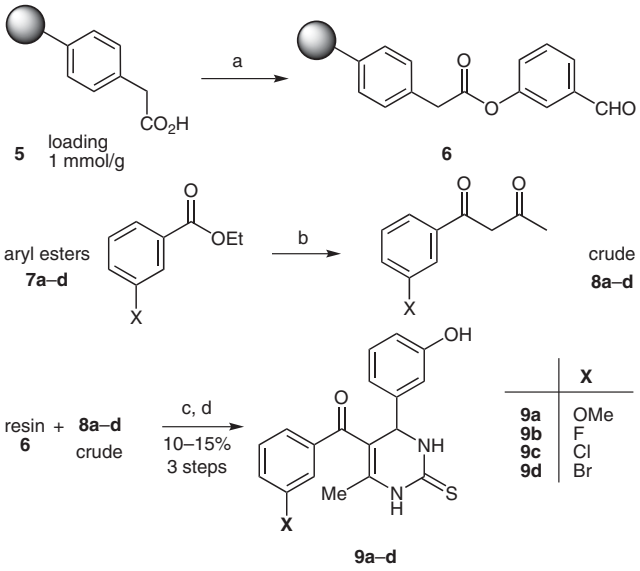
The lowest yields were obtained in the case of mono-substituted benzaldehydes bearing an electron-donating group (OH, OMe, NMe_2) and/or when substituted thioureas were used. The use of ytterbium triflate (0.05 equiv) as catalyst slightly improved some reactions, affording compounds in moderate yields.

This procedure allowed the isolation of the unsubstituted N-derivatives (R^4 = H) in excellent purity (>99% by HPLC) through a very simple work-up carried out in parallel mode. The work-up consisted of crushing the resulting solid in the presence of diethyl ether, followed by filtration and washings with hot water to remove the excess of thiourea. The yields ranged between 21 and 93%, with the poorest corresponding to the 5-aroyl derivatives (e.g. entries 1 *vs* 14 and 2 *vs* 15).

In agreement with previous reports, the combination of N-substituted thioureas and β-diketones proved to be challenging. The formation of side-products did not allow the isolation of the product by precipitation as described above, and reverse-phase chromatography was necessary to reach the high standards of purity (>99%) required for the biological assays.

The preliminary SAR analysis on Eg5[7] prompted us to focus on the synthesis of aroyl analogs (R^1 = aryl) bearing a 3-hydroxyl group as R^3. With this purpose in mind, we envisaged a 'catch and release' strategy on solid-phase taking advantage of the OH function (Scheme 3). To achieve this, 3-hydroxybenzaldehyde was therefore attached to carboxylic acid resin **5** using a standard DCC/DMAP esterification protocol, leading to resin **6**.

Non-commercially available β-diketones were prepared by treatment of the corresponding arylesters with acetone in the presence of sodium hydride.[13] Unfortunately, the Biginelli condensation on resin **6** under classical conditions[14] failed to give the desired products **9**. However, compounds **9a–d** could be obtained via the solvent-free condensation between the supported aldehyde **6**, thio-



Scheme 3 Solid-phase, solvent-free protocol using the supported aldehyde. *Reagents and conditions*: (a) DCC, DMAP, 3-OH-benzaldehyde, CH_2Cl_2, r.t., 48 h; (b) NaH, acetone, Et_2O, 3–5 d; (c) thiourea, $Yb(OTf)_3$ (0.05 equiv), 110 °C, 4 h; (d) K_2CO_3, MeOH, r.t. then HPLC/MS purification.

urea and a large excess of diketone **8a–d** in the presence of catalytic amounts of $Yb(OTf)_3$ at 110 °C. After removal of all excess reagents by simple washings, cleavage was performed using K_2CO_3/MeOH to afford pure compounds after HPLC-MS purification. Although the overall yields (10–15% for 3 steps) were low, this non-optimized, solid-phase protocol allowed the preparation of compounds **9a–d** (X = OMe, Cl, Br, I) in excellent purities. Since very few β-diketones are commercially available, this protocol paves the way for major diversification on the aroyl part of those adducts.

In conclusion, we have synthesized a series of 5-acyl-3,4-dihydropyrimidine-2-thiones using a solvent-free, solution-phase procedure even in the least favorable cases: β-diketones and substituted thioureas. In the case of 3-hydroxyl-substituted benzaldehyde, we showed that the attachment of this aldehyde to a resin enabled the preparation of the Biginelli adduct starting directly from the aryl ester precursors of the corresponding β-diketones. Due to the ready availability of such esters compared to the β-diketones, this methodology opens the way to the facile synthesis of analogues with increased diversity at the aroyl position, which are difficult to achieve via standard procedures. Details of the biological evaluation of this promising series will be reported in due course.

Solvent-Free Biginelli Condensations (Table 1); Typical Procedure

In a screw-capped vial, a mixture of the aldehyde (1 mmol, 1 equiv), the β-diketone (1 mmol, 1 equiv) and thiourea or *N*-alkylthiourea (1.5 mmol, 1.5 equiv) was heated at 110 °C without stirring for 3 h. In some cases (see Table 1), $Yb(OTf)_3$ (0.05 equiv) was used as catalyst. The reaction mixture was allowed to cool to room temperature and was washed with Et_2O (4 mL). The resulting solid was filtered, washed first with Et_2O (2 × 1 mL), then hot water (2 × 1 mL) and dried under vacuum over P_2O_5. When Et_2O was added and the product did not precipitate, the crude product was dissolved in DMSO and purified by HPLC-MS affording pure compounds.

1-[4-(4-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (entry 9)

^{1}H NMR (DMSO-d_6): δ = 10.19 (s, 1 H), 9.65 (s, 1 H), 9.43 (s, 1 H, Ar-OH), 7.02 (d, *J* = 7.8 Hz, 2 H), 6.71 (d, *J* = 7.8 Hz, 2 H), 5.17 (d, *J* = 3.7 Hz, 1 H), 2.32 (s, 3 H), 2.09 (s, 3 H). MS (ES+): *m*/*z* = 263.3 $(M + H)^+$.

[4-(2,6-Dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]phenylmethanone (entry 16)

^{1}H NMR (DMSO-d_6): δ = 10.24 (s, 1 H), 9.42 (s, 1 H), 7.60–7.20 (m, 8 H), 6.39 (s, 1 H), 1.57 (s, 3 H). MS (ES+): *m*/*z* = 378.3 $(M + H)^+$.

[4-(2,6-Dichlorophenyl)-1,6-dimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]phenylmethanone (entry 17)

^{1}H NMR (DMSO-d_6): δ = 9.43 (d, *J* = 2.5 Hz, 1 H), 7.80–7.20 (m, 8 H), 6.33 (s, 1 H), 3.63 (s, 3 H), 1.83 (s, 3 H). MS (ES+): *m*/*z* = 392.3 $(M + H)^+$.

Acknowledgment

We thank the 'Conseil Regional Ile de France' and l'Association pour la Recherche sur le Cancer (ARC, contract number 5197) for financial support.

References and Notes

(1) Present address: The Beatson Institute for Cancer Research, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1BD, UK
(2) Present address: Hybrigenics, 3-5 Impasse Reille, 75014 Paris, France
(3) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.
(4) (a) Blangy, A.; Lane, H. A.; d'Herin, P.; Harper, M.; Kress, M.; Nigg, E. A. *Cell* **1995**, *83*, 1159. (b) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971.
(5) (a) Maliga, Z.; Kapoor, T. M.; Mitchison, T. J. *Chem. Biol.* **2002**, *9*, 989. (b) DeBonis, S.; Simorre, J. P.; Crevel, I.; Lebeau, L.; Skoufias, D. A.; Blangy, A.; Ebel, C.; Gans, P.; Cross, R.; Hackney, D. D.; Wade, R. H.; Kozielski, F. *Biochemistry* **2003**, *42*, 338.
(6) (a) Jackson, J. R.; Patrick, D. R.; Dar, M. M.; Huang, P. S. *Nat. Rev. Cancer* **2007**, *7*, 107. (b) Duhl, D.; Renhowe, P. *Curr. Opin. Drug Discovery Dev.* **2005**, 431. (c) Wood, K. W.; Cornwell, W. D.; Jackson, J. R. *Curr. Opin. Pharmacol.* **2001**, *1*, 370.
(7) (a) Lopez, R.; Rousseau, B.; Kozielski, F.; Skoufias, D.; DeBonis, S. FR patent 2883284, **2005**. (b) Lopez, R.; Rousseau, B.; Kozielski, F.; Skoufias, D.; DeBonis, S. WO patent 2006097617, **2006**.
(8) (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360. (b) For a review, see: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937; and references cited therein. (c) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (d) For the mechanism, see: Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201. (e) Enantioselective version: Huang, Y.; Fengyue, Y.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386. Two-step procedures: (f) Atwal, K. S.; O'Reilly, B. C. *Heterocycles* **1987**, *26*, 1185. (g) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. F. *Heterocycles* **1987**, *26*, 1189. Microwaves: (h) Misra,

A. K.; Agnihotri, G.; Madhusudan, S. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2004**, *43*, 2018. (i) Dallinger, D.; Kappe, C. O. *Nat. Protoc.* **2007**, *2*, 317. Ionic liquids: (j) Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 5917. (k) Legeay, J. C.; Vanden Eynde, J. J.; Bazureau, J. P. *Tetrahedron* **2005**, *61*, 12386. (l) Legeay, J. C.; Vanden Eynde, J. J.; Toupet, L.; Bazureau, J. P. *ARKIVOC* **2007**, *(iii)*, 13. Novel catalysts: (m) Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454. (n) Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075. (o) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270. (p) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett* **2001**, 863. (q) Varala, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, 67. (r) Gupta, R.; Gupta, M.; Paul, S.; Gupta, R. *Can. J. Chem.* **2007**, *85*, 197. Solvent free: (s) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864. (t) Brindaban, C. R.; Alakananda, H.; Suvendu, S. D. *Org. Process Res. Dev.* **2002**, *6*, 817. (u) Rodríguez-Domínguez, J. C.; Bernardi, D.; Kirsch, G. *Tetrahedron Lett.* **2007**, *48*, 5777. (v) Shirini, F.; Marjani, K.; Nahzomi, H. T. *ARKIVOC* **2007**, *(i)*, 51.

(9) (a) Wang, L.; Qian, C.; Tian, H.; Ma, Y. *Synth. Commun.* **2003**, *33*, 1459. (b) Pathak, P.; Kaur, R.; Kaur, B. *ARKIVOC* **2006**, *(xvi)*, 160.

(10) An elegant two-step procedure using a Liebeskind–Srog coupling to obtain 5-aroyl-3,4-dihydropyrimidines-2-ones was recently described, see: (a) Prokopcova, H.; Pisani, L.; Kappe, C. O. *Synlett* **2007**, 43. (b) Pisani, L.; Prokopcova, H.; Kremsner, J. M.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 415.

(11) Garcia-Saez, I.; DeBonis, S.; Lopez, R.; Trucco, F.; Rousseau, B.; Thuéry, P.; Kozielski, F. *J. Biol. Chem.* **2007**, *282*, 9740; In this publication, compound **2** was named 'Mon-97'.

(12) Gartner, M.; Sunder-Plassmann, N.; Seiler, J.; Utz, M.; Vernos, I.; Surrey, T.; Giannis, A. *ChemBioChem* **2005**, *6*, 1173.

(13) (a) Swamer, F. W.; Hauser, C. R. *J. Am. Chem. Soc.* **1950**, *72*, 1352. (b) Chaney, A.; Astle, M. J. *J. Org. Chem.* **1951**, *16*, 57.

(14) For solid-phase protocols with a supported ester or thiourea, see: Dallinger, D.; Stadler, A.; Kappe, C. O. *Pure Appl. Chem.* **2004**, *76*, 1017.