Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1349–1352

A highly regio- and chemoselective addition of carbon nucleophiles to pyrimidinones. A new route to C4 elaborated Biginelli compounds

Kamaljit Singh,* Divya Arora and Sukhdeep Singh

Organic Synthesis Laboratory, Department of Applied Chemical Sciences and Technology, Guru Nanak Dev University, Amritsar 143 005, India

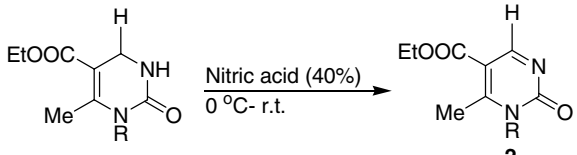
Received 21 November 2006; revised 9 December 2006; accepted 19 December 2006
Available online 23 December 2006

Abstract—Ethyl 6-methyl-pyrimidine-2-one-5-carboxylates react with C-nucleophiles in a diversity oriented synthetic sequence to afford C4 substituted congeners of medicinally potent Biginelli dihydropyrimidinones, in a highly regioselective manner.

The medicinal potential of ethyl 4-substituted-6-methyl-3,4-dihydropyrimidine-2-one-5-carboxylates (Biginelli DHPMs) continues to attract increasing interest from the synthetic chemistry community.[1] This is due, in no small part, to the crucial roles played by DHPMs in biological processes and therapeutic applications.[2] Extensive investigations of structure–activity relationships have described opposite activities (agonistic or antagonistic) for enantiomers as a function of the substituent and its absolute stereochemistry at the 4-position of the DHPM.[3] Molecular modifications at C4 of the DHPM core thus hold potential for significant improvement of the understanding of their structure–activity relationship and their efficacy as drug candidates. Recently, using chiral catalysts, enantiomerically pure DHPMs have been obtained.[4] In general, DHPMs are readily available through the Biginelli three-component synthesis, or related methods, the aldehyde component of which delivers the C4 substituent.[5] However, these methods suffer from the disadvantage of inaccessibility of functionalized aldehydes and thus lack experimental and conceptual simplicity to append tailored substituents at C4. Apart from the traditional Biginelli three-component condensation and its variants,[6] no other general methodology has been reported for the elaboration of C4 of DHPMs, a key feature responsible, in part, for the biological activity of this system.

The synthetic route starts with readily available (80–85% yield)[7] ethyl 6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **1a** and **1b**, which were transformed to the corresponding 6-methyl-pyrimidine-2-one-5-carboxylates **2** (**2a**: 80%, **2b**: 75% yield) via a Kappe type dehydrogenation (40% HNO_3, 0 °C to rt, 30 min)[8] of the precursor 3,4-dihydropyrimidinone (Scheme 1).

The reaction of **2a** and **2b** with various nucleophiles such as stabilized carbanions of carbon acids, Grignard reagents, aryllithiums and heterocyclic anions proceeded smoothly and exclusively at the C4 position. The approach is amenable to append a variety of substituents, derived from appropriate nucleophiles, at the 4-position of C4 unsubstituted pyrimidine-2-ones **2**, in a synthetically useful manner. Further, in contrast to similar reactions with activated *N*-alkoxycarbonylpyridinium salts,[9] where introduction of carbon nucleophiles is strongly dependent upon the choice of reagents and/or reaction conditions, similar activation as the corresponding *N*-acyl C4 unsubstituted pyrimidone derivatives was not required, to yield the corresponding 3,4-dihydropyrimidine-2-ones **3** and **4**.



1: a R = Me; **b** R = H

2

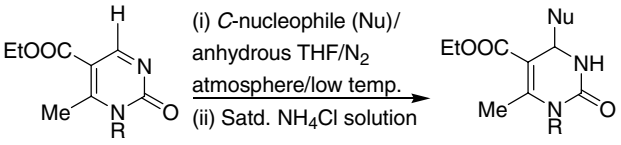
Scheme 1. Synthesis of pyrimidine-2-ones **2**.

Keywords: Lithiation; Biginelli compounds; Carbon nucleophiles; Regioselective addition.

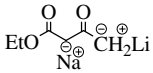
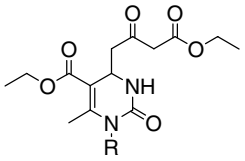
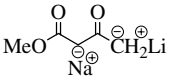
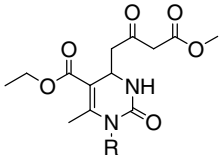
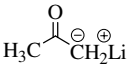
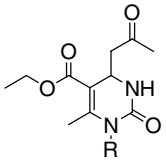
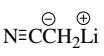
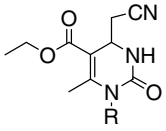
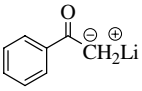
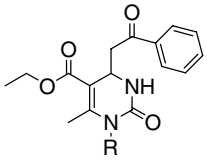
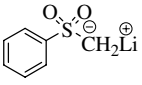
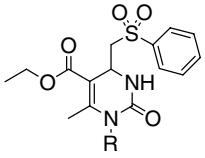
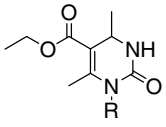
* Corresponding author. Tel.: +91 183 2258853; PABX: +91 183 2258802–09x3508; fax: +91 183 2258819 20; e-mail: kamaljit19in@yahoo.co.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.111

Table 1. Addition of *C*-nucleophiles (Nu) to pyrimidine-2-ones **2**. Synthesis of C4 alkyl substituted Biginelli DHPMs **3**



2: a R = Me; **b** R = H **3**

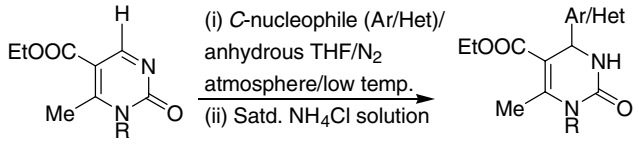
Entry	Nu	Product	3	R	Reaction conditions	Yield[a] (%)	Mp (°C)
1			**3a**[b]	Me	−78 °C/NaH/*n*-BuLi (2.5 equiv)/THF	73	131
			3b	H	−78 °C/NaH/*n*-BuLi (2.0 equiv)/THF	57	135
2			**3c**	H	−78 °C/NaH/*n*-BuLi (2.0 equiv)/THF	35	120
3			**3d**	Me	−78 °C/LDA (2.5 equiv)/THF	75	135
4			**3e**	H	−78 °C/LDA (1.5 equiv)/THF	50	202
5			**3f**	Me	−78 °C/LDA (2.5 equiv)/THF	96	135
6			**3g**	Me	−78 °C/*n*-BuLi (2.5 equiv)/THF	77	168
			3h	H	−78 °C/*n*-BuLi (2.0 equiv)/THF	52	145
7			**3i**	Me	−78 °C/(2.5 equiv)/THF	92	138
			3j	H	−78 °C/(1.0 equiv)/THF	51	180

[a] Isolated purified yield.
[b] Mixture of keto–enol tautomers.

The results of the reactions of aliphatic C-nucleophiles with **2** are listed in Table 1. As illustrated, the reactions exhibited an impressive degree of generality to give the corresponding C4 elaborated DHPMs.[10]

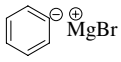
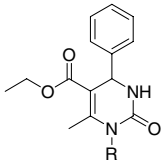
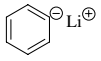
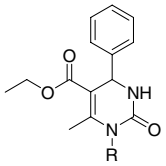
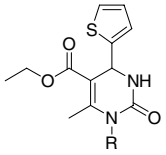
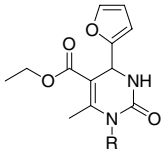
Treatment of **2a** with the intense yellow coloured dianion of ethyl acetoacetate,[11] generated using NaH/*n*-BuLi (2.5 equiv each), in sequence, in anhydrous THF at −78 °C, under a blanket of nitrogen gas, after extractive workup and chromatography furnished product **3a** in 73% yield. A similar reaction of **2b** furnished the corresponding product **3b**. Likewise, reactions of the anions of methyl acetoacetate,[11] acetone,[12] acetonitrile,[12] acetophenone[12] and methyl phenyl sulfone[13] furnished the corresponding C-4 functionalized compounds **3**, which are difficult to synthesize using traditional Biginelli condensation requiring appropriate aliphatic aldehydes. Use of the Grignard reagent (MeMgI) furnished the corresponding DHPMs **3i** and **3j** in 92% and 51% yields, respectively.

Table 2. Addition of *C*-nucleophiles (Nu) to pyrimidine-2-ones **2**. Synthesis of C4 aryl/heterocyclic substituted Biginelli DHPMs **4**



2: a R = Me; **b** R = H

4

Entry	Nu	Product	4	R	Reaction conditions	Yield[a] (%)	Mp (°C)
1			**4a**	H	−78 °C/(2.5 equiv)/THF	45	207
2			**4b**	Me	−78 °C/(2.5 equiv)/THF	78	180
3[b]			**4c** **4d**	Me H	−40 °C/*n*-BuLi (2.5 equiv)/THF	80 40	158 215
4[b]			**4e** **4f**	Me H	−40 °C/*n*-BuLi (2.5 equiv)/THF	81 35	162 199

[a] Isolated purified yield.
[b] Products of ester displacements were also detected (^{1}H NMR) albeit in trace amounts.

The reactions of C-nucleophiles derived from aromatic and heterocyclic substrates are reported in Table 2. The Grignard reagents, phenyl magnesium bromide and phenyllithium, both demonstrated similar patterns of reactivity at C4 and furnished exclusively 4-phenyl DHPM derivatives **4a** and **4b** in fair to good yields. The reaction of phenyllithium was cleaner, in so far as isolation of the product was concerned. Similarly, carbanions derived from thiophene[14] and furan[15] were also reacted with **2a** and **2b** at −40 °C, to give the corresponding DHPMs **4c**–**f**. All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.[16]

In summary, we have demonstrated that C4 unsubstituted pyrimidone derivatives undergo regio- and chemoselective additions at C4, exclusively, with a variety of nucleophiles to furnish C4 elaborated DHPMs in good yields. This methodology permits a variety of nucleophilic functionalities to be introduced at C4 of unsubstituted pyrimidones (Table 1, entries 1–7), to give the corresponding DHPMs, which can serve as valuable templates for further synthetic transformations at C4. Also, the method allows for the preparation of the important class of 4-aryl substituted (Table 2, entries 1 and 2) and 4-heterocyclic (Table 2, entries 3 and 4), substituted DHPMs. Further investigations in procuring enantiomerically pure DHPMs using this methodology are underway.

Acknowledgements

Financial support from CSIR (01(1960)/04/EMR-II) and UGC (31-53/2005/SR), New Delhi, is gratefully acknowledged. D.A. and S.S. thank CSIR and UGC, New Delhi, for Research Fellowships.

References and notes

1. Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1–116.
2. (a) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052; (b) 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*, 3254–3263.
3. Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J. Z.; Hedberg, A.; Malley, M.;

McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119–129.
4. (a) Huang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387; (b) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802–14803.
5. (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963; (b) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630–645.
6. (a) Singh, K.; Singh, S.; Mahajan, A. *J. Org. Chem.* **2005**, *70*, 6114–6117; (b) Singh, K.; Singh, S. *Tetrahedron Lett.* **2006**, *47*, 8143–8146.
7. Singh, K.; Singh, J.; Deb, P. K.; Singh, H. *Tetrahedron* **1999**, *55*, 12873–12880.
8. Puchala, A.; Belaj, F.; Bergman, J.; Kappe, C. O. *J. Heterocycl. Chem.* **2001**, *38*, 1345–1352.
9. Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315–4319.
10. Contrary to our findings, C4 unsubstituted dihydropyrimidinones lacking a C5 ester substituent have shown variation in reactivity depending upon the reagent used. Whereas only MeLi could be added at C-4, RMgX invariably reacted at C-6, see: Kashima, C.; Katoh, A.; Yokota, Y.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 489–492.
11. Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.
12. To a solution of diisopropylamine (0.58 mL, 0.42 g, 4.42 mmol) in THF (2 mL), *n*-BuLi (1.85 mL, 2.2 M) was added dropwise at −78 °C, under a nitrogen atmosphere. The solution was allowed to warm to 0 °C and stirred for an additional 10 min. The solution was cooled to −78 °C and pre-cooled THF (25 mL at −78 °C) was added with stirring. The appropriate carbon acid, for example, acetone, acetonitrile, acetophenone (4.42 mmol), was then introduced via a glass syringe. The solution was stirred for an additional 10 min at the same temperature before use.
13. Generated using *n*-BuLi (−78 °C).
14. Jones, E.; Moodie, I. M. *Org. Synth. Coll. Vol.* **1988**, *6*, 979–980.
15. Perri, S. T.; Rice, P.; Moore, H. W. *Org. Synth. Coll. Vol.* **1993**, *8*, 179–181.
16. *Selected data. Ethyl 1,6-dimethyl-2-oxo-4-(ethyl-3-oxobutyrate-4-yl)-3,4-dihydropyrimidine-5-carboxylate* (**3a**): Creamy solid; R_f: 0.5 (50% ethyl acetate/hexane); yield: 73%; mp 131 °C (dichloromethane); IR (KBr): ν_{max} 1750, 1709, 1649 cm^{-1}; ^1H (300 MHz, $CDCl_3$, 25 °C): δ 1.26 (m, 6H), 2.29 (s, 3H), 2.42–2.71 (m, 2H), 2.90 (s, 3H), 3.45 (s, 1.75H), 4.18 (m, 4H), 4.65 (m, 0.22H), 4.78 (m, 0.78H), 7.96 (br, 0.22H, NH, exchanged with D_2O), 8.02 (br, 0.78H, NH, exchanged with D_2O), 12.04 (s, 0.25 H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 14.0, 14.3, 18.4, 34.0, 39.3, 47.5, 49.8, 54.1, 56.5, 60.1, 61.5, 91.7, 100.0, 148.1, 153.1, 165.2, 166.8, 172.2, 174.1 and 200.2. Anal required for $C_{15}H_{22}N_2O_6$: C, 55.21; H, 6.74; N, 8.58; found: C, 55.60; H, 6.96; N, 8.16; MS: *m*/*z* 349 (M+23).
Ethyl 1,6-dimethyl-2-oxo-4-(2-oxopropyl)-3,4-dihydropyrimidine-5-carboxylate (**3d**): White solid; R_f: 0.5 (60% ethyl acetate/hexane); yield: 75%; mp 135 °C (dichloromethane); IR (KBr): ν_{max} (KBr): 1650, 1710, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 1.27 (t, 3H, *J* 7.2 Hz), 2.17 (s, 3H), 2.28 (s, 3H), 2.72 (ABX system, 2H, *J* 16.2 Hz, *J* 6.9 Hz, *J* 3.9 Hz), 2.97 (s, 3H), 4.17 (q, 2H, *J* 7.2 Hz), 4.75 (dd, 1H, *J* 6.6 Hz, *J* 4.2 Hz), 7.50 (br, 1H, NH, exchanged with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 14.2, 18.3, 30.7, 34.0, 48.2, 54.3, 60.1, 100.3, 147.9, 153.3, 165.3 and 206.0. Anal required for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02; found: C, 56.40; H, 6.96; N, 10.86; MS: 277 (M+23).