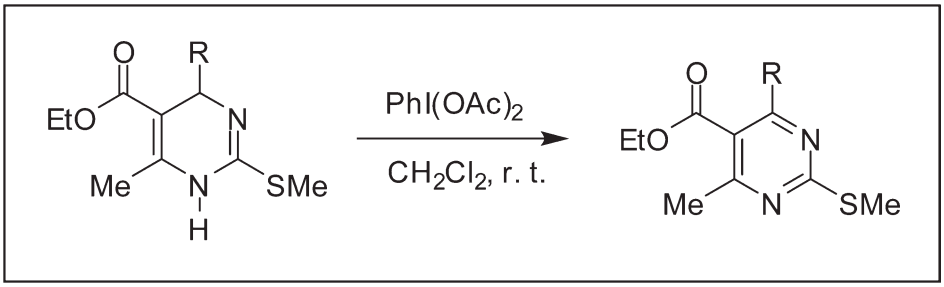
Mild and Efficient Oxidative Aromatization of 4-Substituted-1,4-dihydropyrimidines Using (Diacetoxyiodo)benzene

Nandkishor N. Karade,* Sumit V. Gampawar, Nilesh P. Tale, and Sanjay B. Kedar

Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra 440 033, India
*E-mail: nnkarade@gmail.com

Additional Supporting Information may be found in the online version of this article.
Received June 28, 2009
DOI 10.1002/jhet.389
Published online 3 May 2010 in Wiley InterScience (www.interscience.wiley.com).



4-Alkyl or aryl-1,4-dihydropyrimidines were readily oxidized by (diacetoxyiodo)benzene under mild reaction conditions to the corresponding pyrimidine derivatives in good to excellent yields.

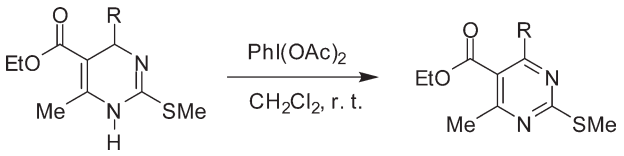
J. Heterocyclic Chem., **47**, 740 (2010).

INTRODUCTION

4-Aryl-3,4-dihydropyrimidin-2(1*H*)-ones (Biginelli compounds, DHPMs) represent an azaheterocyclic system of remarkable pharmacological profile [1]. It was investigated during 1980s and 1990s that DHPMs exhibit a similar pharmacological profile to the Hantzsch's 1,4-dihydropyridine calcium channel modulators of the nifedipine type drugs [2]. In particular, the 2-heterosubstituted 4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters were investigated by Atwal and coworkers as potent mimics of 1,4-dihydropyridine [3]. The metabolism of these drugs involves an oxidative dehydrogenation of 1,4-dihydro ring nucleus to the corresponding aromatic derivatives, which is catalyzed in the liver by cytochrome P-450 [4]. The chemical oxidation of 4-substituted-1,4-dihydropyrimidine also provides an easy access to multi-substituted pyrimidine derivatives, which are further known to exhibit anti-anoxic and anti-lipid peroxidation activities [5]. Recently, the S-alkylation of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thione followed by oxidative aromatization has been demonstrated for the generation of a variety of 2-substituted pyrimidines via displacement of the reactive sulfonyl group with nitrogen, oxygen, sulfur, and carbon nucleophiles [6]. In contrast to Hantzsch 1,4-dihydropyridine [7], the chemical oxidative aromatization of 1,4-dihydropyrimidine is relatively less investigated reaction. All the reported methods for the chemical oxidation of 4-substituted-1,4-dihydropyrimidine utilize mainly transition metal based oxidizing agents such as $Mn(OAc)_3$ [8], MnO_2 [6], $(NH_4)_2Ce(NO_3)_6$ [6], and $CuCl_2/Na_2CO_3$/*tert*-BuOOH [9]. The optimized conditions for the oxidative aromatization of 2-methylthio-1,4-dihydropyrimidine requires four or five equivalents of $Mn(OAc)_3$ or MnO_2 respectively under different reaction conditions. Thus, there is a need for the development of an efficient and general method for the oxidative aromatization of 4-aryl or alkyl-1,4-dihydropyrimidine.

Hypervalent iodine reagents are used extensively in organic synthesis as a mild, safe, and economical alternative to heavy metal reagents [10]. A literature survey showed that phenyliodine(III) bis(trifluoroacetate) [$PhI(OCOCF_3)_2$] can be used for the solid state oxidation of Hantzsch's 1,4-dihydropyridines under microwave irradiation conditions [11]. Similarly, (diacetoxyiodo)benzene has been reported for the oxidative aromatization of 1,3,5-trisubstituted pyrazolines [12] and 2-imidazolines [13]. Recently, we have reported a clean and efficient oxidative dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones to 1,2-dihydropyrimidines using a combination of (diacetoxyiodo)benzene and *tert*-butylhydroperoxide in CH_2Cl_2 [14]. The application of hypervalent iodine reagents for the oxidative aromatization of 1,4-dihydropyrimidines is hitherto unknown in the literature. Herein, we wish to report a simple and highly efficient oxidative dehydrogenation of 4-substituted-1,4-dihydropyrimidine to afford the multi-substituted pyrimidine derivatives by using (diacetoxyiodo)benzene (DIB) as the mild oxidizing agent (Scheme 1).

Scheme 1



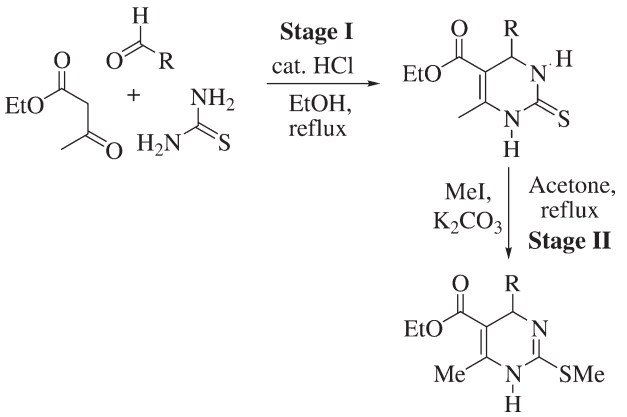
RESULTS AND DISCUSSION

Variously substituted 4-aryl or alkyl-1,4-dihydropyrimidines precursor were prepared via two steps: (a) the Biginelli reaction involving three component condensation of ethyl acetoacetate, aldehyde and thiourea under reflux conditions in ethanol using a catalytic quantity of HCl to afford 3,4-dihydropyrimidin-2(1*H*)-thiones and (b) the S-methylation reaction of the resulting 3,4-dihydropyrimidin-2(1*H*)-thiones using MeI/K_2CO_3/acetone system (Scheme 2). The structures of 4-aryl or alkyl-1,4-dihydropyrimidines were confirmed by IR, ^{1}H NMR, and LCMS spectra.

The oxidative aromatization of **1a** (R = C_6H_5) was selected as a model reaction using different iodine based oxidizing agents such as I_2, I_2/K_2CO_3, KIO_3, $PhI(OAc)_2$, and Dess-Martin periodinane and the results are summarized in Table 1. The oxidative aromatization using molecular iodine in MeOH was previously reported for the oxidative aromatization of Hantzsch's 1,4-dihydropyridine [15]. It is interesting to mention that molecular iodine and I_2/K_2CO_3 (Table 1, entry 1 and 2) did not produce oxidative aromatization of **1a** in satisfactory yields. The oxidation of **1a** to **2a** took place in 63% yield using the pentavalent hypervalent iodine reagent, Dess-Martin periodinane (DMP) but with a relatively long reaction time of 12 h. The trivalent hypervalent iodine reagent, $PhI(OAc)_2$ was found to be the most effective reagent to produce the aromatized product **2a** in 89% yield within 1 h.

With optimal conditions in hand, the reaction of different 4-substituted-1,4-dihydropyrimidines with DIB was examined to explore the scope of the reaction (Table 2). In all the cases, the expected products **2a–l** were obtained in excellent yields. All the reactions were carried out at room temperature using stochiometric use of DIB. 4-Aryl-1,4-dihydropyrimidine containing either an electron-withdrawing group or an electron-donating group all afforded the corresponding products smoothly (Table 2, entries 2a–h). The oxidative aromatization of 4-alkyl-1,4-dihydropyridine is most frequently accompanied by the dealkylation reaction. The side product formation due to the dealkylation reaction was also observed in the DIB mediated oxidative aromatization of 4-alkyl-1,4-dihydropyrimidine (Table 2). Dealkylation was a major pathway in the case of *i*-propyl at 4-position of 1,4-dihydropyrimidine. The aromatized products

Scheme 2. Preparation of 1,4-dihydropyrimidine.

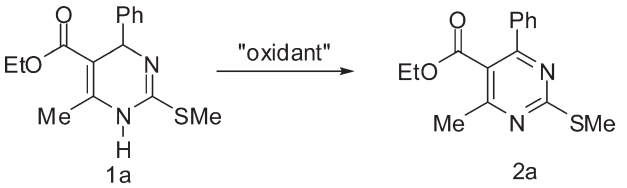


2a–k except **2a** are new compounds in the literature and the structures of these products were confirmed from IR, ^{1}H, and C^{13} NMR spectroscopy and LCMS analysis. The ^{1}H NMR of the precursor 4-aryl-1,4-dihydropyrimidine showed characteristic peak around δ 5.82 due to C-4 proton and a broad peak around δ 6.36 due to N-H proton. These two signals were found to be absent in the ^{1}H NMR spectra of the aromatized product **2**. The methyl group at 6-position of 4-aryl-1,4-dihydropyrimidine appears at δ 2.37 which is shifted downfield to δ 2.55 in the case of aromatized product.

A tentative reaction mechanism is shown in Scheme 3. The oxidative aromatization takes place around the coordination sphere of trivalent iodine, DIB **3**. The ligand exchange reaction between 1,4-dihydropyrimidine **1** and DIB **3** forms a resonance stabilized carbocation **4** which is subsequently deprotonated to form **5**. The concomitant reductive elimination of iodobenzene from **5** leads to form aromatized product **2**.

Table 1

Optimization of the reaction conditions.

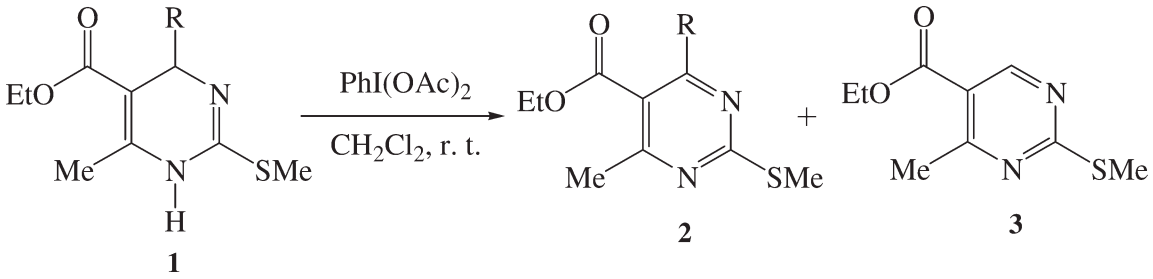


Entry	Oxidizing agent	Solvent	Reaction time and conditions	Yield of **2a** (%)[a]
1	I_2	MeOH	12 h, reflux	09
2	I_2/K_2CO_3	MeOH	12 h, reflux	22
3	KIO_3	MeOH	12 h, reflux	00
4	DMP	CH_2Cl_2	12 h, r.t.	63
5	$PhI(OAc)_2$	MeOH	12 h, r.t.	73
6	$PhI(OAc)_2$	CH_2Cl_2	1 h, r.t.	89

[a] Isolated yields.

Table 2

Oxidative aromatization of 4-substituted-1,4-dihydropyrimidine using (diacetoxyiodo)benzene.



1 **2** **3**

Entry	Substrate, **1** R	Yield (%)[a,b] **2**	**3**
a	C_6H_5	81	–
b	4—$CH_3C_6H_4$	75	–
c	3—$CH_3OC_6H_4$	78	–
d	4—$CH_3OC_6H_4$	79	–
e	3,4—$(CH_3O)_2C_6H_3$	74	–
f	3,4,5—$(CH_3O)_3C_6H_2$	77	–
g	4—ClC_6H_4	76	–
h	3—$NO_2C_6H_4$	73	–
i	*i*—C_3H_7	–	69
j	$(CH_3)_2CHCH_2$	66	–
k	$CH_3(CH_2)_5$	63	–

[a] Isolated yields after chromatography.
[b] All the reactions were carried out at room temperature stirring of 1 h.

CONCLUSION

In summary we have developed a general and practical route for the oxidative aromatization of 4-substituted-1,4-dihydropyrimidine using (diacetoxyiodo)benzene as the safe oxidizing agent. The salient features of this methodology are: (a) mild reaction conditions, (b) transition metal-free protocol, (c) no excessive use of the oxidant, (d) short reaction time, and (e) an easy experimental procedure.

EXPERIMENTAL

General. All melting points are uncorrected. The glassware was routinely oven-dried at 110°C for a minimum of 4 h. Column chromatography was performed on silica gel 70–230 mesh. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 DPX spectrometer (^{1}H at 400 MHz and ^{13} C at 100 MHz) in $CDCl_3$ with TMS as the internal standard. FTIR spectra were determined on a PerkinElmer 100 FTIR spectrometer.

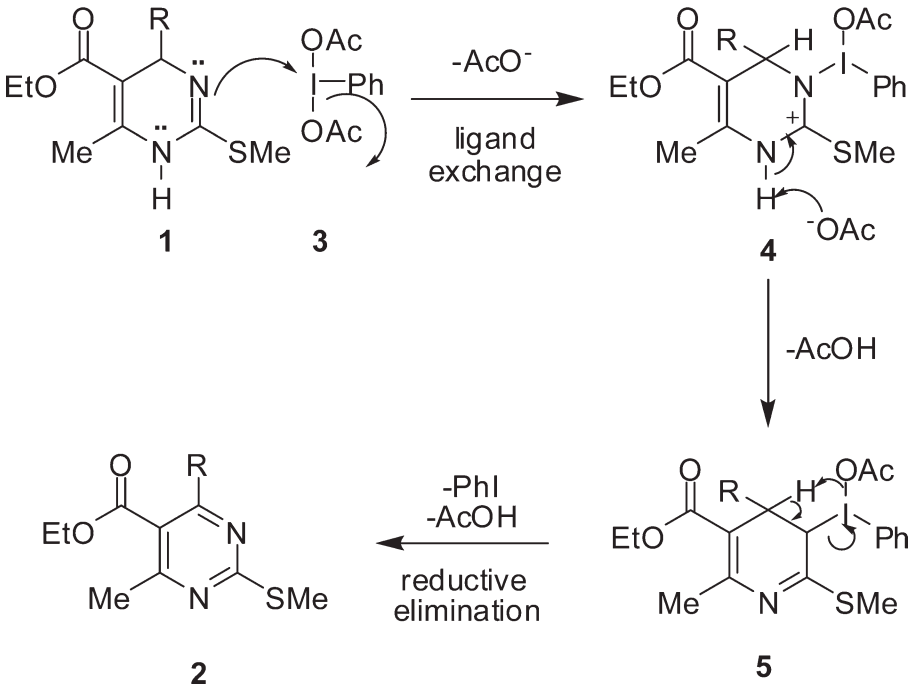
General procedure for the preparation of 4-substituted-3, 4-dihydropyrimidin-2(1H)-thione. A mixture of appropriate aldehyde (20 mmol), ethyl acetoacetate (20 mmol), thiourea (22 mmol), and HCl (2 mL) in EtOH (40 mL) was refluxed for 24 h. The reaction was monitored by TLC. After completion of reaction, the mixture was slowly poured to crushed ice and the resulting solid was filtered off. The crude Biginelli compound was recrystallized from ethanol to afford the product in excellent purity. The products were characterized by the comparison of melting points with the literature value.

General procedure for the preparation of 4-substituted-1, 4-dihydropyrimidines. A suspension of 4-substituted-3,4-dihydropyrimidin-2(1*H*)-thione (3 mmol) in acetone (15 mL) was treated with finely ground potassium carbonate (1.0 g, 7.25 mmol) and methyl iodide (3.5 mmol). The reaction was allowed to stir at room temperature overnight and was diluted with ethyl acetate. It was filtered and the filtrate was washed with water and brine and dried over magnesium sulfate. The solvent was evaporated and the residue was crystallized from ether-hexanes to provide 4-substituted-1,4-dihydropyrimidine as a colorless solid.

General procedure for the oxidation/aromatization of 4-substituted-1,4-dihydro-(2-methylthio)-pyrimidines. To a stirred solution of appropriate 4-substituted-1,4-dihydro-(2-methylthio)-pyrimidine (2 mmol) in CH_2Cl_2 (10 mL) was added (diacetoxyiodo)benzene (0.644 g, 2 mmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h. The progress of the reaction was monitored by TLC. After the completion of reaction, the solvent was removed under vacuum and the crude product was purified using column chromatography (silica gel, petroleum ether-ethyl acetate) to give the corresponding aromatized product in good yield.

Ethyl 4-methyl-2-(methylthio)-6-phenylpyrimidine-5-carboxylate (2a). IR (KBr): ν_{max} = 2926, 1722, 1582, 1534, 1225, 1080, 753, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, J = 9.2 Hz, 3H), 2.57 (s, 3H), 2.62 (s, 3H), 4.18 (q, J = 9.2 Hz, 2H), 7.46 (m, 3H), 7.62 (m, 2H). ^{13}C NMR (100 MHz,$CDCl_3$): δ 13.55, 14.13, 22.57, 61.64, 120.89, 128.27,

Scheme 3. Reaction mechanism.



128.39, 130.03, 137.72, 163.54, 165.42, 168.09, 172.45. LCMS (M+1) = 289.

Ethyl 4-methyl-2-(methylthio)-6-p-tolylpyrimidine-5-carboxylate (2b). IR (KBr): ν_{max} = 2925, 2853, 1722, 1613, 1574, 1532, 1224, 1078, 864, 793 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, *J* = 7.00 Hz, 3H), 2.35 (s, 3H), 2.54 (s, 3H), 2.60 (s, 3H), 4.18 (q, *J* = 7.00 Hz, 2H), 7.23 (d, *J* = 8.04 Hz, 2H), 7.56 (d, *J* = 8.28 Hz, 2H). ^{13}C NMR (100 MHz,$CDCl_3$): δ 13.72, 14.20, 21.44, 22.62, 61.74, 120.77, 128.34, 129.21, 134.83, 140.49, 163.39, 165.28, 168.40, 172.35. LCMS (M+1) = 303.

Ethyl 4-(3-methoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2c). IR (KBr): ν_{max} = 2928, 2851, 1723, 1601, 1536, 1429, 1223, 1122, 1046, 783, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, *J* = 7.08 Hz, 3H), 2.55 (s, 3H), 2.61 (s, 3H), 3.84 (s, 3H), 4.19 (q, *J* = 7.08 Hz, 2H), 7.01 (m, 1H), 7.19 (m, 2H), 7.33 (t, *J* = 7.88 Hz, 1H). ^{13}C NMR (100 MHz,$CDCl_3$): δ 13.67, 14.21, 22.63, 55.38, 61.77, 113.55, 116.08, 120.68, 121.06, 129.53, 139.03, 159.65, 163.37, 165.43, 168.15, 172.48. LCMS (M+1) = 319.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2d). IR (KBr): ν_{max} = 2928, 1721, 1608, 1580, 1531, 1509, 1402, 1255, 1224, 1079, 865, 797 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 9.6 Hz, 3H), 2.54 (s, 3H), 2.61 (s, 3H), 3.86 (s, 3H), 4.24 (q, *J* = 9.6 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 7.65 (d, *J* = 9.2 Hz, 2H). ^{13}C NMR (100 MHz,$CDCl_3$): δ 13.72, 14.07, 22.47, 55.31, 61.63, 113.83, 114.15, 129.98, 161.33, 162.59, 165.09, 168.48, 172.11. LCMS (M+1) = 319.

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2e). IR (KBr): ν_{max} = 2931, 2836, 1696, 1603, 1513, 1260, 1233, 1141, 1095, 795 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.08 Hz, 3H), 2.54 (s, 3H), 2.62 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 4.21 (q, *J* = 7.08 Hz, 2H), 6.91 (d, *J* = 8.32 Hz, 1H) 7.27 (m, 2H). ^{13}C NMR (100 MHz,$CDCl_3$): δ 13.49, 14.21, 19.99, 55.74, 59.77, 109.81, 110.35, 110.86, 118.72, 137.42, 148.15, 148.64, 166.77. LCMS (M+1) = 349.

Ethyl 4-(3,4,5-trimethoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2f). IR (KBr): ν_{max} = 2935, 2841, 1722, 1587, 1536, 1504, 1415, 1225, 1127, 1006, 797, 710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, *J* = 7.2 Hz, 3H), 2.55 (s, 3H), 2.71 (s, 3H), 3.89 (s, 9H), 4.19 (q, *J* = 7.2 Hz, 2H), 6.90 (s, 2H). ^{13}C NMR (100 MHz,$CDCl_3$): δ 13.78, 14.17, 22.50, 29.68, 56.19, 60.94, 61.83, 105.67, 120.94, 133.00, 139.81, 153.26, 163.06, 165.26, 168.37, 172.37. LCMS (M+1) = 379.

Ethyl 4-methyl-2-(methylthio)-6-(3-nitrophenyl)pyrimidine-5-carboxylate (2h). ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 7.2 Hz, 3H), 2.60 (s, 3H), 2.62 (s, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.92 Hz, 1H), 7.19 (m, 1H), 8.34 (m, 1H), 8.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):δ 13.75, 14.24, 22.85, 29.69, 62.12, 120.92, 123.46, 124.69, 129.58, 134.33, 139.28, 148.23, 161.00, 166.21, 167.40, 173.19. LCMS (M+1) = 334.

Ethyl 4-methyl-2-(methylthio)pyrimidine-5-carboxylate (2i). IR (KBr): ν_{max} = 2925, 1724, 1641, 1564, 1528, 1403, 1326, 1281, 1200, 1091, 1045 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.12 Hz, 3H), 2.59 (s, 3H), 2.84 (s, 3H), 4.39 (q, *J* = 7.24 Hz, 2H), 8.94 (s, 1H). LCMS (M+1) = 255.

Ethyl 4-isobutyl-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2j). IR (KBr): ν_{max} = 2958, 2928, 2869, 1725, 1542, 1430, 1274, 1240, 1184, 1100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 5.96 Hz, 6H), 1.39 (t, *J* = 7.1 Hz, 3H), 2.17 (m, 1H), 2.46 (s, 3H), 2.56 (s, 3H), 2.62 (d, *J* =

7.12 Hz, 3H), 4.41 (q, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz,$CDCl_3$): δ 14.05, 14.16, 22.48, 22.87, 28.33, 44.23, 61.62, 122.22, 164.52, 167.19, 167.77, 171.97. LCMS (M+1) = 269.

Ethyl 4-hexyl-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2k). IR (KBr): ν_{max} = 2956, 2928, 2856, 1725, 1652, 1541, 1402, 1228, 1102, 1078 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H), 1.29 (m, 8H), 1.36 (t, J = 7.16 Hz, 3H), 2.46 (s, 3H), 2.56 (s, 3H), 2.71 (t, J = 6.4 Hz, 2H), 4.37 (q, J = 7.16 Hz, 2H). LCMS (M+1) = 297.

Acknowledgment. The authors are thankful to the Department of Science and Technology (No. SR/FTP/CS-77/2005) and the University Grants Commission, New Delhi, India (No. MRP 32-245/2006 SR), for the financial support.

REFERENCES AND NOTES

[1] Kappe, C. O. Eur J Med Chem 2000, 35, 1043.

[2] Atwal, K.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. J Med Chem 1990, 33, 1510.

[3] 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.; Satah, F.; Morita, M.; Noguchi, T. J Med Chem 1989, 32, 2399.

[4] (a) Bocker, R.; Guengerich, F. P. J Med Chem 1986, 29, 1596; (b) Guengerich, F. P.; Brian, W. R.; Iwasaki, M.; Sari, M. A.; Baarnhielm, C.; Berntsson, P. J Med Chem 1991, 34, 1838.

[5] (a) Kuno, A.; Sugiyama, Y.; Katsuta, K.; Kamitani, T.; Takasugi, H. Chem Pharm Bull 1992, 6, 1452; (b) Kuno, A.; Sugiyama, Y.; Katsuta, K.; Kamitani, T.; Takasugi, H. Chem Pharm Bull 1992, 9, 2423.

[6] Matloobi, M.; Kappe, C. O. J Comb Chem 2007, 9, 275.

[7] Fang, X.; Liu, Y.-C.; Li, C. J Org Chem 2007, 72, 8608.

[8] Akhtar, M. S.; Seth, M.; Bhaduri, A. P. Ind J Chem 1987, 26B, 556.

[9] Yamamoto, K.; Chen, Y. G.; Buono, F. G. Org Lett 2005, 21, 4673.

[10] Wirth, T. Angew Chem Int Ed 2005, 44, 3656; (b) Moriarty, R. M. J Org Chem 2005, 70, 2893; (c) Zhdankin, V. V.; Stang, P. J Chem Rev 2002, 102, 2523; (d) Varvoglis, A. Hypervalent Iodine in Organic Synthesis; Academic Press: London, 1997.

[11] Varma, R. S.; Kumar, D. J Chem Soc Perkin Trans 1 1999, 12, 1755.

[12] Singh, S. P.; Kumar, D.; Prakash, O.; Kapoor, R. P. Synth Commun 1997, 27, 2683.

[13] Ishihara, M.; Togo, H. Synlett 2006, 2, 227.

[14] Karade, N. N.; Gampawar, S. V.; Kondre, J. M.; Tiwari, G. B. Tetrahedron Lett 2008, 49, 3441.

[15] Yadav, J. S.; Subba Reddy, B. V.; Sabitha, G.; Kiran Kumar Reddy, G. S. Synthesis 2000, 11, 1532.