HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 715 - 726. © The Japan Institute of Heterocyclic Chemistry
Received, 28th March, 2008, Accepted, 1st May, 2008, Published online, 8th May, 2008. COM-08-S(N)68

OXIDATIVE CONVERSION OF FUNCTIONALIZED 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES TO THE CORRESPONDING PYRIMIDIN-2(1*H*)-ONES USING ACTIVATED CARBON—MOLECULAR OXYGEN SYSTEM

Ken-ichi Okunaga, Yukiko Nomura, Kenjiro Kawamura, Natsuki Nakamichi, Kazuo Eda, and Masahiko Hayashi*

Department of Chemistry, Graduate School of Science, Kobe University, Nada, Kobe 657-8501, Japan *E-mail: mhayashi@kobe-u.ac.jp

Abstract – Efficient synthesis of functionalized pyrimidin-2(1*H*)-ones was achieved by oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) using activated carbon—molecular oxygen (O_2) system. Various DHPMs were easily prepared by Biginelli reactions starting from aldehydes, β-ketoesters and urea. Therefore, the present method provides general and versatile protocol for the synthesis of a variety of functionalized pyrimidin-2(1*H*)-ones.

The functionalized pyrimidin-2(1*H*)-one moiety occurs in various natural and pharmaceutical structures.[1] Therefore, there have been several methods for the synthesis of functionalized pyrimidin-2(1*H*)-ones. For example, Zhong and his co-workers reported the method for the synthesis of functionalized pyrimidones *via* microwave-accelerated rearrangement reaction of substituted amidoximes with dimethyl acetylenedicarboxylate (DMAD).[2] On the other hand, the oxidative conversion of dihydrohetero-aromatic compounds to heteroaromatic compounds should be alternative and attractive methods, especially, for the synthesis of functionalized pyrimidin-2(1*H*)-ones, because DHPMs were easily prepared by Biginelli reaction, that is the condensation of a variety of aldehydes, β-ketoesters, and urea.[3] Actually, recently, Yamamoto and her co-workers reported oxidative dehydrogenation of dihydropyrimidinones and dihydropyrimidines with a catalytic amount of a Cu salt, K_2CO_3 and *tert*-butylhydroperoxide (TBHP) system.[4] Shanmugam and Perumal reported oxidation of DHPMs

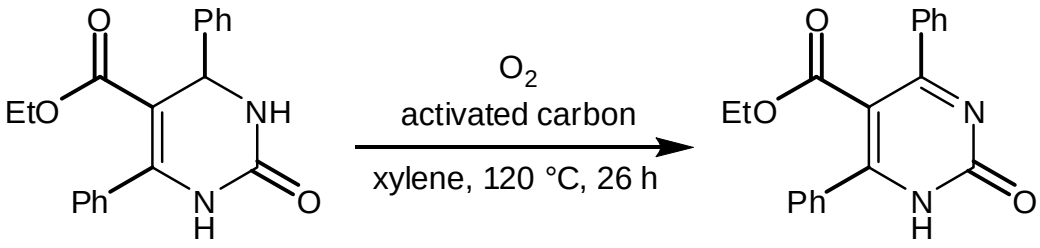
---

This paper is dedicated to Prof. Dr. Ryoji Noyori on the occasion of his 70th birthday.

to pyrimidin-2(1*H*)-ones using 3—5 equivalent of ceric ammonium nitrate (CAN).[5] They discussed the regioselectivity in dehydrogenation of DHPMs that was dependent on the reaction media and conditions.[5] More recently, the same authors reported the similar reaction mediated by $Co(NO_3)_2 \cdot 6H_2O/K_2S_2O_8$ system.[6] We recently reported oxidative aromatization using activated carbon—molecular oxygen (O_2) system. For examples, conversions of substituted pyrazolines to pyrazoles,[7] dihydropyridines to pyridines,[7] functionalized indolines to indoles[8] and 9,10-dihydroanthracenes to anthracenes[9] have been realized. Furthermore, direct synthesis of 2-arylbenzoxazoles,[10] 2-arylbenzimidazoles,[10] and 2-arylbenzothiazoles[11] by the reaction of substituted 2-aminophenols, 1,2-phenylenediamines, and 2-aminobenzenethiols with aryl aldehydes in the presence of activated carbon under oxygen or air atmosphere were also accomplished. Here, we report efficient synthesis of functionalized pyrimidin-2(1*H*)-ones by oxidative conversion of DHPMs using activated carbon—O_2 system.

At first, we examined the effect of the amount of activated carbon (Charcoal Activated, TOKYO CHEMICAL INDUSRTY CO., LTD (TCI)) in xylene at 120 °C for 26 h. As shown in entry 1 in Table 1, when the reaction was carried out in the absence of the activated carbon, only 32% of ethyl 4,6-diphenyl-pyrimidin-2(1*H*)-one-5-carboxylate (**1b**) was obtained from ethyl 4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (**1a**). The yield increased to 70% in the presence of 50 weight% (wt%) of activated carbon under the same reaction condition (entry 2). When 100 wt% of activated carbon was used, the product was obtained in 78% yield (entry 3).

Table 1. Effect of the amount of activated carbon



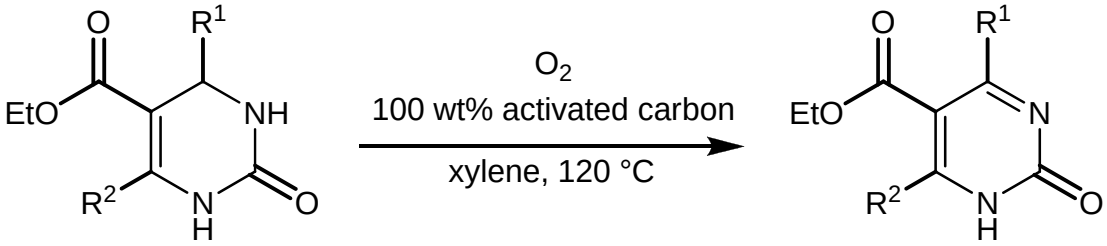
1a **1b**

entry	activated carbon/wt%[a]	yield/%[b]
1	0	32
2	50	70
3	100	78

[a] Charcoal Activated (TCI) was used. [b] Isolated yield after silica-gel column chromatography.

Therefore, other DHPMs were employed under O_2 atmosphere at 120 °C for 20—48 h using 100 wt% of activated carbon. A variety of DHPMs **1a**—**11a** were converted to the corresponding pyrimidin-2(1*H*)-ones **1b**—**11b** by the aid of activated carbon under oxygen atmosphere as shown in Table 2. The presence of aryl group at both of 4- and 6- positions (R^1 and R^2) is essential to obtain the oxidation product in high yield (entries 1—11).

Table 2. Oxidative conversion of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones to the corresponding pyrimidin-2(1*H*)-ones



1a—12a **1b—12b**

entry	R^1	R^2	time/h	yield/%[a]
1	C_6H_5	C_6H_5	26	78[b]
2	4-FC_6H_4	C_6H_5	24	85
3	4-ClC_6H_4	C_6H_5	20	84
4	2-ClC_6H_4	C_6H_5	48	96
5	4-BrC_6H_4	C_6H_5	24	83
6	4-$CF_3C_6H_4$	C_6H_5	22	92
7	4-NCC_6H_4	C_6H_5	22	84
8	4-$NO_2C_6H_4$	C_6H_5	26	80
9	4-MeC_6H_4	C_6H_5	24	95
10	4-$MeOC_6H_4$	C_6H_5	24	85
11	1-naphthyl	C_6H_5	20	97
12	*i*-Pr	Me	48	trace[c]

[a] Isolated yield after recrystallization unless otherwise noted. [b] Isolated yield after silica-gel column chromatography. [c] Starting material was recovered in 70% yield.

When DHPM having alkyl group at both of 4- and 6- positions (R^1 = *i*-Pr, R^2 = Me) was used, oxidation did not take place under the same condition (entry 12). The reaction of DHPM having one alkyl group

and one aryl group (R^1 = Ph, R^2 = Me) with molecular oxygen in the presence of activated carbon proceeded very slowly to give oxidation product in less than 30% yield (120 °C, 48 h) (data not shown in Table 2). As for the structure of the product, we confirmed the structure of ethyl 4,6-diphenyl-pyrimidin-2(1*H*)- one-5-carboxylate (**1b**) by single-crystal X-ray diffractometry, and we found that this compound has formed dimer by taking keto form utilizing the stabilization of hydrogen bond (Figures 1, 2 and Table 3). As for reaction mechanism, to clarify the mechanism, especially, to obtain the information concerning the role of activated carbon, we examined the efficiency of oxidation using more than ten kinds of activated carbons those have different surface areas, micropore volumes, and contents of oxygen functional group. At present, we revealed that the multiplier effects of surface area and contents of oxygen functional group evolved as CO in micropore played very important role to make the reaction proceed effectively. Anyway the detailed reaction mechanism of the activated carbon—O_2 system seems very complicated, so the mechanism, especially concerning the role of micropore in activated carbon in oxidation reaction will be discussed in near future.

In conclusion, the present oxidative synthesis of functionalized pyrimidin-2(1*H*)-ones from 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) was achieved using activated carbon—O_2 system. Various DHPMs were easily prepared by Biginelli reactions, therefore the present method provides general and versatile protocol for the synthetic method of a variety of functionalized pyrimidin-2(1*H*)-ones. This method has advantage from the viewpoints of operational simplicity, cost performance, and environmental friendliness.

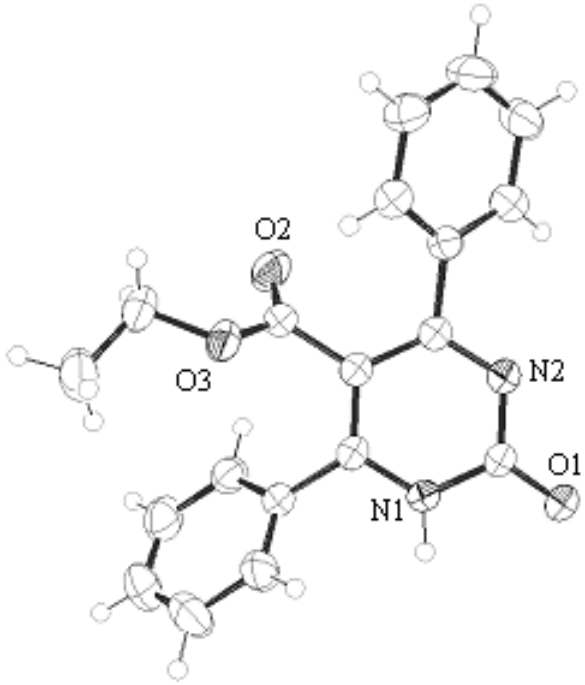


Figure 1. ORTEP diagram of **1b**. (50% thermal ellipsoids)

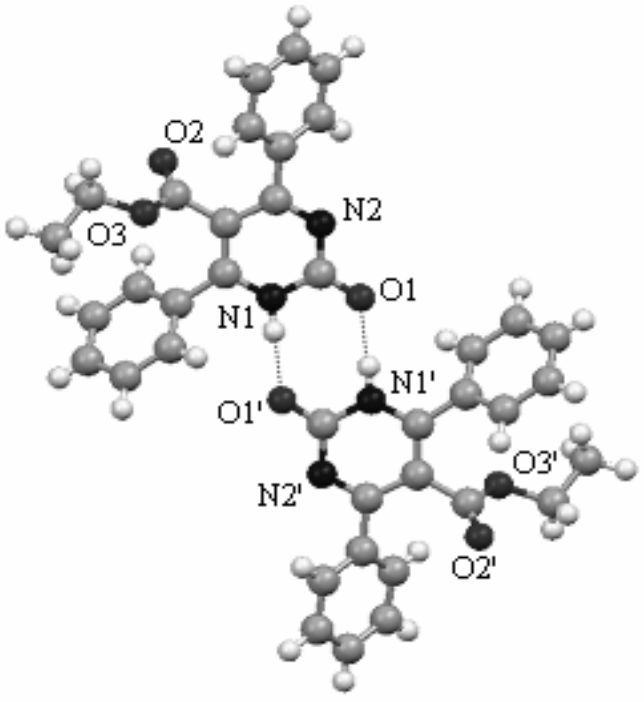


Figure 2. Dimer formation of **1b** in crystal phase.

Table 3. Crystal data and refinement details for 1b.

Formula	$C_{19}H_{16}N_2O_3$
formula weight	320.34
T (K)	294(2)
radiation	Mo-K α (λ = 0.71073 Å)
crystal system	Triclinic
space group	$P\bar{1}$
unit cell dimensions	
a (Å)	7.451(4)
b (Å)	10.627(6)
c (Å)	11.499(7)
α (°)	65.635(9)
β (°)	81.701(9)
γ (°)	80.672(10)
V (Å^3)	815.4(8)
Z	2
$D_{(calc)}$ (Mg/m^3)	1.305
F000	336
μ (MoKα) (mm^{-1})	0.09
crystal size (mm^3)	0.24 × 0.17 × 0.16
θ range	1.95–27.35
index ranges	$-8\leq h\leq 9$, $-13\leq k\leq 11$, $-14\leq l\leq 14$
no. of reflections measured	total: 4647 unique: 3204 (R_{int} = 0.0346)
structure solution	direct method
refinement	full-matrix least-squares on F^2
no. of variables	281
GOF	1.059
R_1 (F)	0.0545
wR_2 (F^2)	0.1597

EXPERIMENTAL

General: The structure of ethyl 4,6-diphenyl-pyrimidin-2(1*H*)-one-5-carboxylate (**1b**) was solved by direct methods and refined by full—matrix least-squares calculations on F^2 using SHELXL-97 program package.[12] All melting points were measured on a Yanaco MP-500D and uncorrected. IR spectra were measured on a PERKIN ELMER FT-IR Spectrometer SPECTRUM 1000. ^{1}H and ^{13}C NMR spectra (400.0 and 100.4 MHz, respectively) were recorded on a JEOL JNM-LA 400 using Me_4Si as the internal standard in $CDCl_3$ and DMSO-d_6. Elemental analyses were performed with a Yanaco CHN Corder MT-5. Mass spectra were measured on a Thermo Quest LCQ DECA XP^{Plus}. Preparative column chromatography was carried out on Fuji Silysia BW-820MH or YMC∗GEL Silica (6nm I-40-63 um).

Filtrations were carried out using nacalai tesque Celite®500 (grain size 1.5 μm) or nacalai tesque Hyflo Super-Cel® (grain size 7 μm). Thin-layer chromatography (TLC) was carried out on Merck 25 TLC aluminum Sheets silica gel 60 F_{254} (layer thickness 0.2 mm).

Preparation of PPE (Poly phosphate ester).[13] A three-necked flask was charged with P_2O_5 (16.5 g), anhydrous $CHCl_3$ (15 mL), and anhydrous Et_2O (30 mL) under an argon atmosphere using a balloon. The whole was warmed to reflux temperature and stirred for 4 days at this temperature. The mixture was transferred to a round-bottom flask, washed with Et_2O, then evaporated to give 25.7 g of PPE as a brown syrup.

General procedure for the PPE-mediated preparation of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones 1a—11a.[14] A three-necked flask was charged with anhydrous THF (10 mL), urea (54 mmol), β-ketoester (36 mmol), and appropriate aldehyde (36 mmol) under an argon atmosphere. PPE (5.4 g) was added slowly to this solution with stirring. The whole was refluxed and continued stirring for 24 h. After confirmation of the completion of the reaction by TLC analysis (hexane : EtOAc = 1 : 1), the reaction mixture was evaporated, and 40 mL of distilled water was added to the solution. The precipitate was filtered and washed with Et_2O and acetone. The obtained solid was vacuum-dried to give functionalized 3,4-dihydropyrimidin-2(1*H*)-ones **1a**—**11a**.

Ethyl 4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (1a). Colorless solid. mp 163—164 °C (lit.,[15] 157—159 °C, lit.,[16] 155—158 °C). IR (KBr): 3310, 3058, 2979, 1700, 1669, 1637, 1600, 1457, 1248, 1188 cm^{-1}. ^1H NMR (400.0 MHz, DMSO-d_6): δ 9.27 (s, 1H), 7.83 (s, 1H), 7.41—7.38 (m, 7H), 7.32—7.27 (m, 3H), 5.24 (d, J = 3.2 Hz, 1H), 3.71 (q, J = 7.1 Hz, 2H), 0.72 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.2, 152.7, 146.9, 143.4, 135.0, 129.5, 128.8, 128.2, 128.0, 127.9, 126.6, 102.4, 60.0., 55.8, 13.5. Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.45; H, 5.57; N, 8.63.

Ethyl 4-(4-fluorophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (2a). Colorless solid. mp 177—178 °C. IR (KBr): 3200, 3066, 2905, 1700, 1659, 1604, 1452, 1253, 1222, 1188, 837 cm^{-1}. ^1H NMR (400.0 MHz, DMSO-d_6): δ 9.31 (s, 1H), 7.85 (s, 1H), 7.41—7.39 (m, 5H), 7.31 (d, J = 6.8 Hz, 2H), 7.21 (t, J = 6.8 Hz, 2H), 5.24 (s, 1H), 3.71 (q, J = 6.9 Hz, 2H), 0.71 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.2, 163.6, 161.2, 152.7, 147.0, 139.4, 134.9, 129.6, 128.4, 128.3, 128.2, 128.0, 115.8, 115.6, 102.4, 60.1, 55.2, 13.5. Anal. Calcd for $C_{19}H_{15}FN_2O_3$: C, 67.05; H, 5.03; N, 8.23. Found: C, 67.24; H, 4.91; N, 8.26.

Ethyl 4-(4-chlorophenyl)-6-phenyl-3,4-dihdropyrimidin-2(1*H*)-one-5-carboxylate (3a). Colorless solid. mp 140—142 °C. IR (KBr): 3260, 3133, 2984, 1701, 1667, 1654, 1446, 1374, 1246, 1088, 832

cm^{-1}. ^{1}H NMR (400.0 MHz, DMSO-d_6): δ 9.33 (s, 1H), 7.87 (s, 1H), 7.47—7.37 (m, 7H), 7.30 (d, J = 8.0 Hz, 2H), 5.23 (d, J = 3.6 Hz, 1H), 3.71 (q, J = 7.0 Hz, 2H), 0.72 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.1, 152.6, 147.0, 141.9, 134.9, 133.9, 129.6, 129.0, 128.3, 128.0, 127.9, 102.2, 60.1, 55.3, 13.5. Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85 Found: C, 63.61; H, 4.89; N, 7.76.

Ethyl 4-(2-chlorophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (4a). Colorless solid. mp 216—218 °C. IR (KBr): 3225, 3103, 2942, 1700, 1685, 1640, 1573, 1448, 1260, 1252, 1111, 758 cm^{-1}. ^{1}H NMR (400.0 MHz, DMSO-d_6): δ 9.33 (s, 1H), 7.76 (s, 1H), 7.53 (d, J = 9.2 Hz, 1H), 7.46—7.30 (m, 8H), 5.72 (d, J = 3.2 Hz, 1H), 3.65 (q, J = 7.0 Hz, 2H), 0.69 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 164.7, 152.0, 148.8, 139.1, 134.8, 132.9, 130.1, 129.8, 129.5, 128.4, 128.0, 127.9, 127.6, 100.0, 60.1, 52.7, 13.5. Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85. Found: C, 63.78; H, 4.90; N, 8.10.

Ethyl 4-(4-bromophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (5a). Colorless solid. mp 148—149 °C. IR (KBr): 3254, 3100, 2984, 1700, 1667, 1653, 1628, 1446, 1247, 1087, 767 cm^{-1}. ^{1}H NMR (400.0 MHz, DMSO-d_6): δ 9.33 (s, 1H), 7.87 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.42—7.29 (m, 7H), 5.21 (d, J = 3.2 Hz, 1H), 3.71 (q, J = 7.0 Hz, 2H), 0.72 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.1, 152.6, 147.1, 142.4, 134.9, 131.9, 129.6, 128.3, 128.2, 127.9, 122.0, 102.1, 60.1, 55.3, 13.5. Anal. Calcd for $C_{19}H_{15}BrN_2O_3$: C, 56.87; H, 4.27; N, 6.98. Found: C, 56.43; H, 4.49; N, 6.82.

Ethyl 4-(4-trifluoromethylphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (6a). Colorless solid. mp 167—169 °C. IR (KBr): 3261, 3144, 3000, 1710, 1667, 1653, 1625, 1446, 1335, 1235, 1126, 848 cm^{-1}. ^{1}H NMR (400.0 MHz, DMSO-d_6): δ 9.40 (s, 1H), 7.95 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.43—7.38 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 5.32 (d, J = 3.2 Hz, 1H), 3.72 (q, J = 7.2 Hz, 2H), 0.71 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.0, 152.6, 147.4, 147.1, 134.8, 130.4, 130.1, 129.7, 128.3, 127.9, 126.9, 125.8, 101.9, 60.2, 55.4, 13.4. Anal. Calcd for $C_{20}H_{17}F_3N_2O_3$: C, 61.54; H, 4.39; N, 7.18. Found: C, 61.19; H, 4.47; N, 7.21.

Ethyl 4-(4-cyanophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7a). Colorless needles. mp 183—185 °C. IR (KBr): 3282, 3111, 2983, 2230, 1700, 1663, 1636, 1608, 1437, 1239, 1187, 832 cm^{-1}. ^{1}H NMR (400.0 MHz, DMSO-d_6): δ 9.41 (s, 1H), 7.96 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.43—7.38 (m, 3H), 7.31 (d, J = 6.4 Hz, 2H), 5.30 (d, J = 3.6 Hz, 1H), 3.71 (q, J = 7.2 Hz, 2H), 0.71 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.0, 152.7, 148.3, 147.7, 134.6, 132.7, 129.8, 128.3, 127.9, 127.4, 118.6, 111.9, 101.5, 60.3, 55.4, 13.5. Anal. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.03; H, 5.05; N, 12.02.

Ethyl 4-(4-nitrophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (8a). Colorless

solid. mp 177—179 °C. IR (KBr): 3260, 3111, 2984, 1707, 1700, 1656, 1622, 1597, 1515, 1239, 1087, 855 cm^{-1}. ^1H NMR (400.0 MHz, DMSO-d_6): δ 9.46 (s, 1H), 8.28 (d, J = 8.8 Hz, 2H), 8.01 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.41—7.39 (m, 3H), 7.33 (d, J = 1.2 Hz, 2H), 5.37 (d, J = 3.2 Hz, 1H), 3.72 (q, J = 7.0 Hz, 2H), 0.72 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 164.9, 152.0, 150.1, 147.7, 134.6, 130.0, 128.4, 127.8, 127.6, 124.2, 101.6, 60.4, 55.4, 13.5. Anal. Calcd for $C_{19}H_{15}N_3O_5$: C, 62.12; H, 4.66; N, 11.44. Found: C, 62.02; H, 5.00; N, 11.14.

Ethyl 4-(4-methylphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (9a). Colorless solid. mp 176—177 °C. IR (KBr): 3306, 3223, 3030, 2977, 2934, 1704, 1667, 1639, 1599, 1472, 1247, 1100, 819 cm^{-1}. ^1H NMR (400.0 MHz, DMSO-d_6): δ 9.24 (s, 1H), 7.79 (s, 1H), 7.44—7.36 (m, 3H), 7.31—7.26 (m, 4H), 7.18 (d, J = 8.0 Hz, 2H), 7.50-7.42 (m, 3H), 7.27 (d, J = 8.0 Hz, 2H), 5.20 (d, J = 3.6 Hz, 1H), 3.71 (q, J = 7.0 Hz, 2H), 2.29 (s, 3H), 0.72 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.2, 152.8, 146.8, 140.6, 137.6, 135.1, 129.4, 128.1, 128.0, 126.5, 102.5, 59.9, 55.5, 21.1, 13.5. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.37; H, 6.00; N, 8.44.

Ethyl 4-(4-methoxyphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (10a). Colorless solid. mp 166—167 °C. IR (KBr): 3314, 3088, 2979, 2841, 1700, 1678, 1608, 1588, 1444, 1338, 1087, 836 cm^{-1}. ^1H NMR (400.0 MHz, DMSO-d_6): δ 9.25 (s, 1H), 7.79 (s, 1H), 7.42—7.38 (m, 3H), 7.31—7.29 (m, 4H), 6.94 (d, J = 8.0 Hz, 2H), 5.18 (d, J = 3.6 Hz, 1H), 3.75 (s, 3H), 3.71 (q J = 7.2 Hz, 2H), 0.72 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.2, 159.3, 152.8, 146.6, 135.8, 135.1, 129.4, 128.1, 128.0, 127.8, 114.1, 102.7, 59.9, 55.3, 55.2, 13.5. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.05; H, 5.77; N, 7.93.

Ethyl 4-(1-naphthylphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (11a). Colorless solid. mp 219—221 °C. IR (KBr): 3404, 3086, 2976, 1599, 1708, 1685, 1642, 1599, 1452, 1248, 1109, 766, 699 cm^{-1}. ^1H NMR (400.0 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 7.1 Hz, 1H), 7.89 (d, J = 7.1 Hz, 1H), 7.82 (s, 1H), 7.66—7.54 (m, 4H), 7.44—7.40 (m, 5H), 6.14 (d, J = 3.2 Hz, 1H), 3.70 (q, J = 6.9 Hz, 2H), 0.57 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.0, 152.1, 147.6, 138.0, 135.0, 134.2, 130.3, 129.6, 129.1, 128.8, 128.3, 128.2, 127.9, 126.7, 125.7, 124.5, 122.2, 101.4, 59.9, 51.6, 13.4. Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.11; H, 5.46; N, 7.59.

General procedure for the synthesis of functionalized pyrimidin-2(1*H*)-ones 1b—11b. A mixture of various 3,4-dihydropyrimidin-2(1*H*)-ones (5 mmol), 100 wt% of activated carbon (Charcoal Activated, TOKYO CHEMICAL INDUSTRY CO., LTD (TCI)), and anhydrous xylene (20 mL) was placed in a three-necked flask under an oxygen atmosphere using a balloon. The whole was heated to 120 °C and stirred for 20—48 h at this temperature. After confirmation of the completion of the reaction by TLC

analysis (hexane : EtOAc = 1 : 2), activated carbon was filtered off using celite. The filtrate was evaporated then recrystalized with 2-propanol. The obtained solid was vacuum-dried to give functionalized pyrimidin-2(1*H*)-ones **1b**—**11b**.

Ethyl 4,6-diphenyl-pyrimidin-2(1*H*)-one-5-carboxylate (1b). Colorless needles. mp 220—222 °C. IR (KBr): 3435, 2973, 2933, 1974, 1731, 1657, 1596, 1571, 1454, 1420, 1286, 1123, 770, 697 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.00 (br s, 1H), 7.63—7.61 (m, 4H), 7.53—7.44 (m, 6H), 3.92 (q, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$):δ 166.3, 157.7, 131.1, 128.7, 128.0, 111.9, 61.8, 13.3. Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.05; H, 4.99; N, 8.70.

Ethyl 4-(4-fluorophenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (2b). Colorless solid. mp 209—211 °C. IR (KBr): 3203, 2902, 1916, 1729, 1670, 1604, 1572, 1437, 1287, 1231, 1158, 806 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.28 (br s, 1H), 7.67—7.60 (m, 4H), 7.52—7.46 (m, 3H), 7.15 (t, *J* = 8.4 Hz, 2H), 3.93 (q, *J* = 7.0 Hz, 2H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 166.2, 165.7, 163.2, 157.8, 131.3, 130.5, 130.4, 128.8, 128.0, 116.0, 115.8, 111.9, 61.9, 13.4. Anal. Calcd for $C_{19}H_{15}FN_2O_3$: C, 67.45; H, 4.47; N, 8.28. Found: C, 67.27; H, 4.45; N, 8.33.

Ethyl 4-(4-chlorophenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (3b). Colorless solid. mp 225—226 °C. IR (KBr): 3306, 2897, 1995, 1725, 1661, 1563, 1489, 1430, 1290, 1206, 1090, 848 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.27 (br s, 1H), 7.62—7.58 (m, 4H), 7.53—7.43 (m, 5H), 3.84 (q, *J* = 7.2 Hz, 2H), 0.75 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 166.1, 157.8, 131.4, 129.5, 128.9, 128.8, 128.0, 111.9, 62.0, 13.3. Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.10; H, 4.10; N, 7.83.

Ethyl 4-(2-chlorophenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (4b). Colorless solid. mp 183—185 °C. IR (KBr): 3417, 3071, 2903, 2361, 1738, 1648, 1598, 1587, 1447, 1417, 1289, 1203, 1111, 762 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.25 (br s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.52-7.37 (m, 7H), 3.84 (q, *J* = 7.2 Hz, 2H), 0.75 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 164.9, 157.5, 131.7, 131.3, 131.1, 129.6, 129.4, 128.6, 128.1, 126.8, 112.1, 61.5, 13.1. Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.07; H, 4.29; N, 7.84.

Ethyl 4-(4-bromophenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (5b). Colorless solid. mp 232—233 °C. IR (KBr): 3200, 3062, 2899, 2340, 1724, 1646, 1589, 1563, 1426, 1289, 1109, 1072, 846, 673 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.11 (br s, 1H), 7.60 (d, *J* = 8.0 Hz, 4H), 7.54—7.45 (m, 5H), 3.93 (q, *J* = 7.1 Hz, 2H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 166.1, 157.8, 131.9, 131.4, 129.7, 128.8, 128.0, 111.9, 62.0, 13.4. Anal. Calcd for $C_{19}H_{15}BrN_2O_3$: C, 57.16; H, 3.79; N, 7.02. Found: C, 57.09; H, 3.90; N, 6.93.

Ethyl 4-(4-trifluoromethylphenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (6b). Colorless

solid. mp 254—256 °C. IR (KBr): 3435, 3069, 2982, 1940, 1730, 1662, 1597, 1437, 1330, 1291, 1127, 807 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.22 (br s, 1H), 7.76—7.71 (m, 4H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.57—7.48 (m, 3H), 3.92 (q, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 166.1, 157.8, 131.9, 131.4, 129.7, 128.8, 128.0, 111.9, 62.0, 13.4. Anal. Calcd for $C_{20}H_{17}F_3N_2O_3$: C, 61.86; H, 3.89; N, 7.21. Found: C, 62.20; H, 3.93; N, 7.28.

Ethyl 4-(4-cyanophenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (7b). Colorless solid. mp 250—251 °C. IR (KBr): 3307, 3090, 2902, 2226, 1719, 1653, 1588, 1571, 1430, 1294, 1133, 811 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.16 (br s, 1H), 7.76—7.71 (m, 4H), 7.61—7.49 (m, 5H), 3.92 (q, *J* = 7.2 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.6, 157.5, 132.2, 131.8, 129.1, 128.8, 128.0, 118.0, 114.6, 111.9, 62.1, 13.3. Anal. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.34; H, 4.42; N, 12.07.

Ethyl 4-(4-nitrophenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (8b). Colorless solid. mp 258—260 °C. IR (KBr): 3210, 3068, 2857, 1941, 1730, 1663, 1594, 1549, 1437, 1351, 1289, 1202, 859 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.27 (br s, 1H), 8.30 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.62—7.49 (m, 5H), 3.92 (q, *J* = 7.2 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.5, 157.5, 149.1, 131.9, 129.2, 129.1, 128.0, 123.6, 111.9, 62.2, 13.3. Anal. Calcd for $C_{19}H_{15}N_3O_5$: C, 62.46; H, 4.14; N, 11.50. Found: C, 62.62; H, 4.17; N, 11.50.

Ethyl 4-(4-methylphenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (9b). Colorless solid. mp 166—168 °C. IR (KBr): 3271, 2880, 1984, 1717, 1658, 1596, 1507, 1450, 1286, 1115, 826 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.29 (br s, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.50—7.42 (m, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 3.93 (q, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 166.5, 157.9, 141.8, 130.9, 129.5, 128.6, 128.1, 128.0, 111.8, 61.8, 21.5, 13.4. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.45; N, 8.38. Found: C, 71.61; H, 5.48; N, 8.45.

Ethyl 4-(4-methoxyphenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (10b). Colorless solid. mp 187—188 °C (lit.,[5] 153—154 °C). IR (KBr): 3292, 2982, 2894, 2848, 2019, 1721, 1646, 1596, 1515, 1437, 1381, 1255, 1175, 839 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.14 (br s, 1H), 7.64—7.60 (m, 4H), 7.51—7.42 (m, 3H), 6.98 (d, *J* = 9.2 Hz, 2H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 166.7, 162.2, 157.9, 130.9, 130.1, 128.6, 127.9, 114.2, 111.6, 61.8, 55.4, 13.4. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.27; H, 5.15; N, 8.00.

Ethyl 4-(1-naphthylphenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (11b). Colorless solid. mp 191—192 °C. IR (KBr): 3292, 3064, 2892, 1955, 1726, 1653, 1602, 1570, 1452, 1287, 1199, 775, 698 cm^{-1}. ^1H NMR (400.0 MHz, $CDCl_3$): δ 13.16 (br s, 1H), 7.94 (t, *J* = 4.8 Hz, 1H), 7.86 (d, *J* = 7.6 Hz,

1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.53—7.42 (m, 7H), 3.55 (q, *J* = 7.2 Hz, 2H), 0.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 165.4, 157.5, 133.3, 131.2, 130.7, 130.1, 128.6, 128.5, 128.2, 127.1, 126.5, 126.4, 124.9, 124.6, 113.2, 61.4, 12.9. Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.16; H, 4.84; N, 7.56.

REFERENCES

1. D. J. Brown, "*The Pyrimidines*", Interscience, New York, NY, 1994; D. E. O'Brien, L. T. Weinstock, R. H. Springer, and C. C. Cheng, *J. Heterocycl. Chem*., 1967, **4**, 49; V. Summa, A. Petrocchi, V. G. Matassa, M. Taliani, R. Laufer, R. D. Francessco, S. Altamura, and P. Pace, *J. Med. Chem.*, 2004, **47**, 5336; I. Stansfield, S. Avolio, S. Colarusso, N. Gennari, F. Narjes, B. Pacini, S. Ponzi, and S. Harper, *Bioorg. Med. Chem. Lett*., 2004, **14**, 5085; H. F. Boyd, S. C. M. Fell, D. M. B. Hickey, R. J. Ife, C. A. Leach, C. H. Macphee, K. J. Milliner, I. L. Pinto, D. A. Rawlings, S. A. Smith, I. G. Stansfield, S. J. Stanway, C. J. Theobald, and C. M. Whittaker, *Bioorg. Med. Chem. Lett*., 2002, **12**, 51.
2. Y.-L. Zhong, H. Zhou, D. R. Gauthier, Jr., and D. Askin, *Tetrahedron Lett*., 2006, **47**, 1315 and references cited therein.
3. P. Biginelli, *Ber*., 1891, **24**, 2962; P. Biginelli, *Gazz. Chim. Ital*., 1893, **23**, 360. Recently reported improved Biginelli reaction; T. Jin, S. Zhang, and T. Li, *Synth. Commun*., 2002, **32**, 1847; G. Sabitha, G. S. K. K. Reddy, C. S. Reddy, and J. S. Yadav, *Synlett*, 2003. 858; G. Maiti, P. Kundu, and C. Guin, *Tetrahedron Lett*., 2003, **44**, 2757; N. -Y. Fu, Y. -F. Yuan, Z. Cao, S. -W. Wang, J. -T. Wang, and C. Peppe, *Tetrahedron*, 2002, **58**, 4801; J. Lu and H. R. Ma, *Synlett*, 2000, 63; K. Ramalinga, P. Vijayalakshmi, and T. N. B. Kaimal, *Synlett*, 2001, 863; J. S. Yadav, B. V. S. Reddy, R. Srinivas, C. Venugopal, and T. Ramalingam, *Synthesis*, 2001, 1341; R. Varala, M. M. Alam, and S. R. Adapa, *Synlett*, 2003, 67; G. Sabitha, G. S. K. K. Reddy, K. B. Reddy, and J. S. Yadav, *Tetrahedron Lett*., 2003, **44**, 6497 and references cited therein.
4. K. Yamamoto, Y. G. Chen, and F. G. Buono, *Org. Lett*., 2005, **7**, 4673. See also, F. -A. Kang, J. Kodah, Q. Guan, X. Li, and W. V. Murray, *J. Org. Chem*., 2005, **70**, 1957.
5. P. Shanmugam and P. T. Perumal, *Tetrahedron*, 2006, **62**, 9726.
6. P. Shanmugam and P. T. Perumal, *Tetrahedron*, 2007, **63**, 666.
7. N. Nakamichi, Y. Kawashita, and M. Hayashi, *Synthesis*, 2004, 1015; M. Hayashi and Y. Kawashita, *Lett. Org. Chem*., 2006, **3**, 571. See also, N. Nakamichi, Y. Kawashita, and M. Hayashi, *Org. Lett*., 2002, **4**, 3955.
8. Y. Nomura, Y. Kawashita, and M. Hayashi, *Heterocycles*, 2007, **74**, 629.
9. N. Nakamichi, H. Kawabata, and M. Hayashi, *J. Org. Chem*., 2003, **68**, 8272.
10. Y. Kawashita, N. Nakamichi, H. Kawabata, and M. Hayashi, *Org. Lett.*, 2003, **5**, 3713.

11. Y. Kawashita, C. Ueba, and M. Hayashi, *Tetrahedron Lett*., 2006, **47**, 4231.
12. G. M. Sheldrick, SHELXL-97, Programs for the Refinement Crystal Structure Analysis, University of Göttingen, Germany, 1997.
13. M. P. Cava, M. V. Lakshmikantham, and M. J. Mitchell, *J. Org. Chem*., 1969, **34**, 2665.
14. C. O. Kappe and S. F. Falsone, *Synlett*, 1998, 718; C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937; C. O. Kappe, *Acc. Chem. Res*., 2000, **33**, 879.
15. E. H. Hu, D. R. Sidler, and U. -H. Dolling, *J. Org. Chem*., 1998, **63**, 3454.
16. P. Salehi, M. Dabiri, M. A. Zolfigol, and M. Baghbanzadeh, *Heterocycles*, 2005, **65**, 1177.