Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 666–672

An unusual oxidation–dealkylation of 3,4-dihydropyrimidin-2(1*H*)-ones mediated by $Co(NO_3)_2 \cdot 6H_2O/K_2S_2O_8$ in aqueous acetonitrile

Pachaiyappan Shanmugam and Paramasivan T. Perumal*

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India

Received 20 April 2006; revised 17 October 2006; accepted 2 November 2006
Available online 27 November 2006

Abstract—4-Aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (DHPM) scaffolds of Biginelli type were oxidized using Co(II)/$S_2O_8^{2-}$ and the reaction afforded 6-unsubstituted pyrimidin-2(1*H*)-ones through an unprecedented dealkylation process. 4-Alkyl DHPMs under similar conditions afforded yet another unusual product, ethyl tetrahydropyrimidin-2,4(1*H*,3*H*)-dione-5-carboxylate.

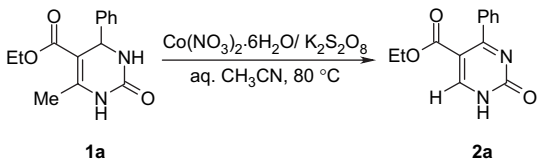
1. Introduction

The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) also called Biginelli compounds, has gained importance because they exhibit illustrious biological and medicinal applications.[1] Unlike facile oxidation of 1,4-dihydropyridines (DHPs) in vitro and in vivo,[2] structurally similar DHPMs, second generation lead compounds, are resistant to oxidants.[3] Furthermore, literature reported protocols are focused on the oxidation of DHPMs of selective type[4] and require the use of excess corrosive or harmful reagents in highly acidic conditions to yield the corresponding pyrimidines.[5] For instance, Eynde's procedure[6a,b] to oxidize DHPMs, involved the multistep synthesis of 1,4-dihydropyrimidines that were oxidized and hydrolyzed to furnish only moderate yields of the desired pyrimidines. $CuCl_2$/TBHP/K_2CO_3[6c] and Jones reagents[6d] have also been employed recently for the oxidation of DHPMs.

MKC-442, a HEPT(1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine) analogue finds application in clinical trials and similar compounds are also expected to inhibit the HIV virus.[7] 5-Methyl-2,4-diaminopyrimidines were found to inhibit exquisitely HIV and moloney murine sarcoma virus-induced cytopathicity in cell culture.[8] In addition, several nucleosides containing 5-substituted pyrimidine moiety have been shown to inhibit the growth of murine mammary carcinoma virus.[9] Itami et al.[10a] have reported that pyrimidine-cores with extended π-systems have interesting fluorescent properties and similar compounds are useful in the development of advanced electronic and photonic materials. Kang et al.[10b] have employed readily accessible multifunctionalized pyrimidine templates for diversity-oriented synthesis. Consequently it is of interest to synthesize structurally diverse pyrimidines by the oxidation of DHPMs.

2. Results and discussion

Oxidants such as PCC, $KMnO_4$/clay, DDQ, chloranil, CAN, and $NaNO_2$ are inefficient for the conversion of DHPMs to pyrimidines.[6a] We therefore, considered the $Co^{2+}/S_2O_8^{2-}$ couple,[11a–c] one of the most powerful oxidants,[12] for the dehydrogenation process. In a trial run, DHPM **1a** in aqueous acetonitrile was stirred with 2 mmol of $Co(NO_3)_2 \cdot 6H_2O$ and 1 mmol of $K_2S_2O_8$ mixture at 80 °C. Interestingly, the reaction yielded an unusual product through oxidation–dealkylation (Scheme 1); the ^1H NMR spectrum showed that the 6-methyl group has been replaced by a D_2O-unexchangeable H-atom resonating around 8.5 ppm. The disappearance of methyl group was further confirmed by mass spectrometry and elemental analysis. The NH proton (D_2O-exchangeable) of the product appeared in deshielded region (δ 10–12 ppm) and, for a few substrates, it was not observed at all.



1a **2a**

Scheme 1.

Keywords: Dehydrogenation; Cobalt; C–C cleavage reaction; Heterocycles.
* Corresponding author. Tel.: +91 44 2491 1386; fax: +91 44 2491 1589; e-mail: ptperumal@gmail.com

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.11.010

Oxidation of organic compounds with $Co^{2+}/S_2O_8^{2-}$ is often mediated by in situ generation of powerful oxidants such as Co^{3+} (emf 1.92 V) and $SO_4^{-\bullet}$ (emf 2.6 V). For the complete conversion of **1a** to **2a**, 4 equiv of Co^{2+} and 2 equiv of persulfate are needed as per stoichiometry.[13]

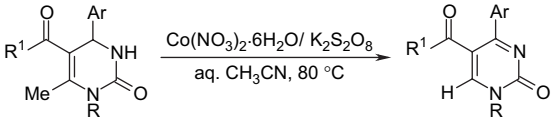
The reaction was optimized by using 5:2.5 equiv of $Co^{2+}/S_2O_8^{2-}$ and heating at 80 °C. Stirring the mixture at room temperature for 48 h gave no appreciable amount of product, but oxidation mediated by $K_2S_2O_8$ without $Co(NO_3)_2\cdot 6H_2O$ proceeded very slowly to furnish 5% of **2a**. Other metal ion-persulfate couples were also screened however, they were either unsuccessful ($AgNO_3/K_2S_2O_8$ and $FeSO_4/Na_2S_2O_3/K_2S_2O_8$) or afforded very low yields ($(CoOAc)_2\cdot 4H_2O/K_2S_2O_8$ and $FeSO_4/K_2S_2O_8$ at reflux) of **2a**. Table 1 shows the results obtained for the oxidation of **1a–l** to **2a–l** mediated by $Co^{2+}/K_2S_2O_8$.

DHPMs bearing naphthyl and biphenyl pendent groups (Table 1, Compounds **1f** and **1g**) invariably afforded comparable yields of **2f** and **2g** with respect to DHPMs bearing phenyl groups (Table 1, **2a** and **2l**). DHPMs with aryl groups containing electron-withdrawing and electron-releasing functionalities showed no resistance to oxidation and afforded the corresponding products in good yields (Compounds **1b–e**, **1h**, **1i**, and **1k**). The *N*-methyl DHPMs also afforded moderate to good yields, with the *N*-methyl group remaining intact throughout the oxidation. Of the oxidized compounds studied, **1d** afforded the highest yield of product, **2d**. The structure of the product (**2f**) was confirmed by X-ray crystallography (Fig. 1).[14]

For **1a**, **1b**, **1c**, and **1f**, the reaction also furnished small amounts (<5%) of 6-aryl-1,2,3,4-tetrahydropyrimidin-2,4(1*H*,3*H*)-diones as well (Fig. 2).

The C-4 carbons and substituted aromatic quaternary carbons of the products generally appeared with less intensity but were clearly detectable for *N*-methyl products, **2i–l**.

Table 1. Unprecedented oxidation of **1a–l** to **2a–l** mediated by $Co^{2+}/S_2O_8^{2-}$



1a-l **2a-l**

Compound	R	R^1	Ar	Time (h)	Yield[a,b]
1a	H	OEt	C_6H_5	3	76[b]
1b	H	OEt	2-Cl–C_6H_4	7	77[b]
1c	H	OEt	4-Cl–C_6H_4	6	71[c]
1d	H	OEt	2-NO_2–C_6H_4	8	84
1e	H	OEt	3-NO_2–C_6H_4	8	78
1f	H	OEt	1-Naphthyl	8	69[c]
1g	H	OEt	Biphenyl	6	74
1h	H	OEt	4-MeO–C_6H_4	6	83
1i	H	OMe	4-MeO–C_6H_4	4	81
1j	Me	OEt	C_6H_5	4	74
1k	Me	OEt	4-Cl–C_6H_4	4	81
1l	Me	Me	C_6H_5	8	77

[a] The reaction was conducted using 1 mmol of DHPM with 2.5 mmol of $K_2S_2O_8$ and 5 mmol of $Co(NO_3)_2$ in aqueous acetonitrile at 80 °C.
[b] Isolated yield.
[c] A small amount of 4-aryl-tetrahydropyrimidine-2,4(1*H*,3*H*)-diones (5%) was also formed.

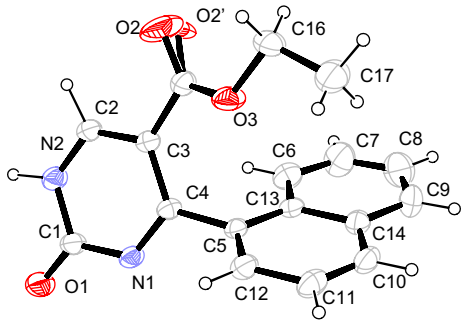
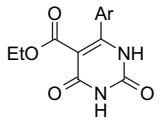


Figure 1. XRD of ethyl 4-(1-naphthyl)-pyrimidin-2(1*H*)-one-5-carboxylate, **2f**.



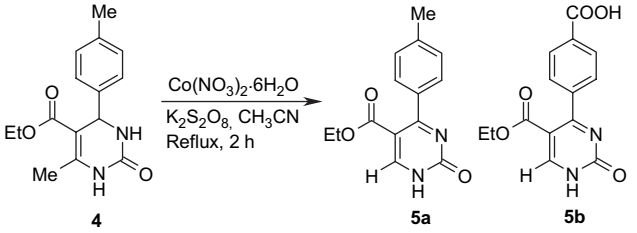
Ar = C_6H_5, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 1-Naphthyl

Figure 2. Structure of 6-aryl-1,2,3,4-tetrahydropyrimidine-2,4(1*H*,3*H*)-diones.

3. Mechanistic investigation on oxidative-dealkylation of DHPMs

The oxidation–dealkylation reaction of DHPM to give 6-unsubstituted pyrimidin-2(1*H*)-ones by $Co^{2+}/S_2O_8^{2-}$ is an uncommon organic transformation and therefore, necessitates some mechanistic investigation.

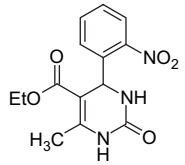
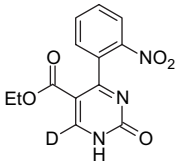
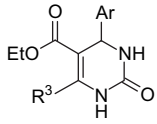
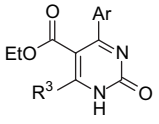
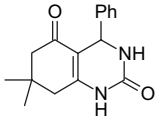
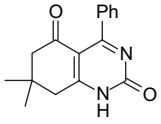
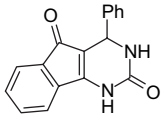
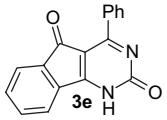
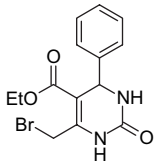
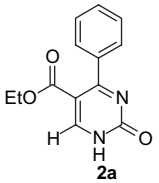
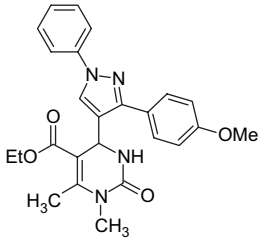
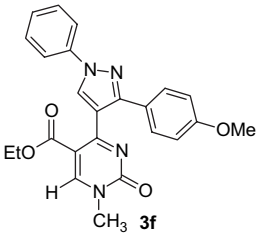
(i) Co^{2+}/O_2, used to oxidize toluene to benzene,[15a] did not demethylate **1a**. Formation of **2a** under anaerobic conditions confirmed that the atmospheric oxygen has no role during the oxidation.
(ii) We have also subjected 4-tolyl-6-methyl-DHPM, **4** to oxidation under typical $Co^{2+}/S_2O_8^{2-}$conditions (Scheme 2). The reaction yielded **5a** as the sole product without the formation of 4-(4-pyrimidyl)benzoic acid derivative, **5b**.[15a,b]



Scheme 2.

To trace the source of hydrogen at C(6) of the pyrimidin-2(1*H*)-ones, the oxidation of **1d** was conducted in D_2O instead of water. The height of the unexchangeable hydrogen of the product **3a**(CH(6)) was reduced by 70% in ^1H NMR spectra due to the formation of C–D bond (Table 2, Entry 1). Mass spectrometry also substantiated the observations that deuterium had been introduced at C(6) of the pyrimidin-2(1*H*)-one scaffold.

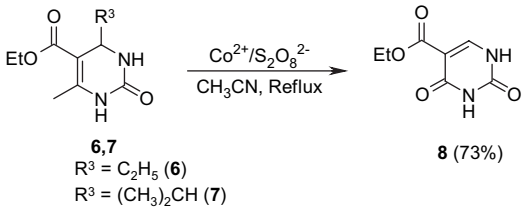
Table 2. Oxidation of structurally diverse DHPMs by $Co^{2+}/S_2O_8^{2-}$

Entry	Reactant	Product	Yield[a]
1		 **3a**	78[b]
2	 Ar=4-MeO–C_6H_4; R^3=C_6H_5	 **3b**	65[c]
3	Ar=4-MeO–C_6H_4; R^3=CF_3	**3c**	52[c]
4		 **3d**	45[c]
5		 **3e**	77[c]
6		 **2a**	65
7		 **3f**	71

[a] Isolated yield.
[b] The reaction conducted in D_2O–CH_3CN.
[c] $Co^{2+}/S_2O_8^{2-}$ of 2.5:1.3 equiv was used.

The incomplete introduction of deuterium at C(6) of the pyrimidin-2(1*H*)-one might be due to the competitive reaction of H_2O molecules (30 mmol in 5 mmol of $Co(NO_3)_2\cdot 6H_2O$) under the reaction conditions. Therefore, the source of hydrogen at position-6 need not be from 6-methyl group of DHPM. In order to obtain a completely deuteriated product, the reaction was conducted at 80 °C with $K_2S_2O_8$ alone in D_2O–CH_3CN. However, the reaction was too slow to isolate appreciable amounts of the product for characterization even after 48 h.

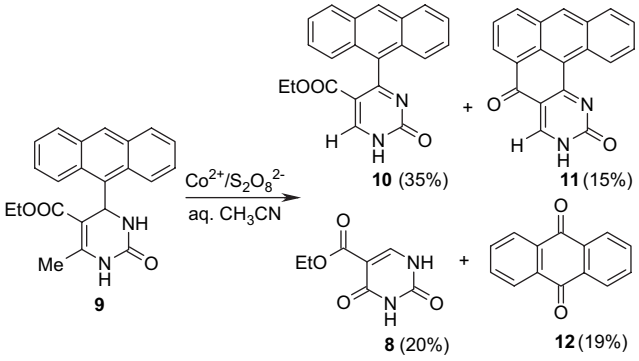
The above findings provide additional support to the indispensable role of Co^{2+} and the in situ generated oxidant, Co^{3+} (1.92 V). The aryl group at the C(4) of the pyrimidin-2(1*H*)-one was essential for the oxidative-dealkylation as 4-alkyl DHPMs **6** and **7** led to the formation of ethyl 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **8** (Scheme 3). The structure of **8** was confirmed by NMR spectroscopy, mass spectrometry, and elemental analysis.



Scheme 3.

The unprecedented dealkylation reaction was also unsuccessful for 6-phenyl substituted and cyclic DHPMs, which underwent simple dehydrogenation (Table 2, Products **3b**, **3d**, and **3e**). The reaction also afforded the desired product when one of the methyl hydrogens was substituted by a bromine atom (Table 2, Entry 6). Pyrazolyl DHPM provided reasonably good yield of the corresponding 6-unsubstituted pyrimidin-2(1*H*)-one (Table 2, Product **3f**). The dealkylation reaction was not observed during the oxidation of 6-trifluoromethyl DHPM (Table 2, Product **3c**).

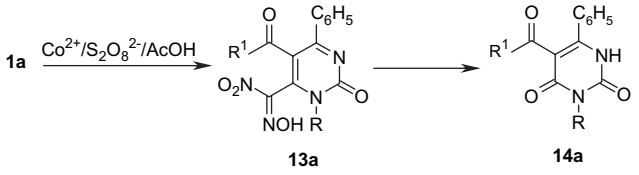
An interesting observation was made while subjecting **9** to typical $Co^{2+}/S_2O_8^{2-}$ oxidation. The reaction mixture upon careful separation through flash column yielded **10**, **11**, **12**, and **8** (Scheme 4). The typical oxidized product, **10** and its subsequent intra-molecular Friedel–Craft acylated product, **11**, accounted for 35% and 15% yield, respectively.



Scheme 4.

Additionally, the reaction afforded substantial amount of **8** (20%), yet another unusual product of the reaction. Compound **8** was the major oxidation product of 4-alkyl DHPMs, **6** and **7**. The formation of **8** from **9** could be rationalized as follows: the bulky anthryl group in **9** could be partially lost to form the 4-unsubstituted pyrimidin-2(1*H*)-one in situ that could be converted to **8**, in a reaction similar to the oxidations of **6** and **7** to **8** (cf. Scheme 3). The resultant anthryl radical was subsequently oxidized to 9,10-anthraquinone **12**. The oxidation of **9** corroborates that the 4-aryl group is mandatory for the unusual transformation of 6-methyl 4-aryl DHPMs (**1a–l**) into 6-unsubstituted 4-aryl pyrimidin-2(1*H*)-ones (**2a–l**).

Kappe et al.[5b] isolated nitrolic acid (**13**) during the oxidation of DHPMs with concd HNO_3. The hydrolysis of **13** under acidic conditions was expected to produce **14** (Scheme 5). To trace whether our reaction was proceeding through **13**, the oxidation of **1a** using $Co(NO_3)_2/K_2S_2O_8$/AcOH was conducted. Notably the reaction afforded **2a** as the major product. In addition, both $Co(OAc)_2/K_2S_2O_8$ and $FeSO_4/K_2S_2O_8$ mediated oxidations also furnished **2a** as the major product indicating that a pathway via **13** was unlikely.



Scheme 5.

In conclusion we have oxidized 4-aryl/4-alkyl, 6-methyl-DHPMs using $Co(NO_3)_2/K_2S_2O_8$ to unique rearranged products. The current procedure enabled the synthesis of structurally diverse pyrimidin-2(1*H*)-ones in moderate to good yields. The mechanistic investigation revealed that the conversion of a methyl group into a hydrogen atom on a pyrimidine scaffold was unprecedented. Ongoing studies in our laboratory are focused on further mechanistic details of the oxidation–dealkylation process.

4. Experimental section

4.1. General

Melting points were determined in open capillary tubes and are uncorrected. IR measurements were carried out using KBr pellets in FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR were recorded in 500, 400, 300 MHz high resolution NMR spectrometers with TMS as an internal standard. All NMR spectra of pyrimidin-2(1*H*)-ones were recorded in $CDCl_3$. Mass spectra were obtained in EI ionization mode at 70 eV. TLC was performed on precoated Polygram sheets. Column chromatography was carried out using 100–200 mesh silica gel or flash-column with 200–400 mesh silica gel and flushing out N_2 on the head of the column. Acetonitrile was distilled from P_2O_5 prior to use. DHPMs were prepared using reported literature procedures.[1d,3,16]

4.2. Experimental procedure for the cobalt nitrate and potassium persulfate mediated oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones

4.2.1. Typical procedure for the oxidative-dealkylation of 1a. A 50-mL round bottom flask containing magnetic bar was charged with 1 mmol (0.260 g) of **1a** and 10 mL acetonitrile. To this solution was added a mixture of cobalt(II) nitrate hexahydrate (5 mmol, 1.46 g) and potassium persulfate (2.5 mmol, 0.68 g) in 3 mL of water and the solution was stirred at 80 °C on an oil bath. The stirring was continued at 80 °C for 3 h (Table 1) and TLC showed the complete disappearance of **1a**. The reaction mixture was diluted with $CHCl_3$ (2×20 mL) and the supernatant was decanted. The residue was poured into 20 g of crushed ice and extracted with $CHCl_3$ (2×20 mL). The organic extracts were pooled up, washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford 0.23 g of crude product. The column purification of residue using 1:1 petroleum ether/ethyl acetate afforded 0.19 g of **2a** as yellow viscous compound, which crystallized to form yellow crystalline solid on cooling.

The same procedure was followed for redox couples, namely, $Ag^+/S_2O_8^{2-}$, $Fe^{2+}/S_2O_8^{2-}$, and $Fe^{3+}/S_2O_3^{2-}/S_2O_8^{2-}$ to oxidize **1a**. $Fe^{2+}/S_2O_8^{2-}$ mediated reaction under reflux conditions afforded 23% yield and rest of the redox couples were ineffective for the conversion.

The above procedure was also followed for the syntheses of **2b–l**, **3f**, **5**, **8**, **10**, **11**, and **12**. Characterization of the compounds by IR, ^{1}H NMR, and ^{13}C NMR spectroscopies, mass spectrometry, elemental analysis, and crystallographic analysis confirms the formation of the products.

4.2.2. Ethyl 4-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (2a). Yellow solid. Mp: 130–132 °C. IR (KBr): 1020, 1187, 1423, 1508, 1663, 1710, 3204 cm^{-1}. ^{1}H NMR (300 MHz): δ 0.94 (t, J=6.8 Hz, 3H), 3.96 (q, J=6.8 Hz, 2H), 7.39 (m, 5H), 8.50 (s, 1H, D_2O-unexchangeable), 11.50 (s, 1H). ^{13}C NMR (75 MHz): δ 12.8, 60.3, 107.9, 127.9, 127.9, 129.1, 130.5, 146.1, 155.7, 163.9, 174.1. MS (EI, *m*/*z*): 244 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.91; H, 4.89; N, 11.54.

4.2.3. Ethyl 4-(2-chlorophenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2b). Yellow solid. Mp: 155–157 °C. IR (KBr): 1013, 1165, 1422, 1506, 1738, 3151 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.08 (t, J=6.8 Hz, 3H), 4.09 (q, J=6.8 Hz, 2H), 7.23 (m, 4H), 8.84 (s, 1H, D_2O-unexchangeable), 11.51 (s, 1H). ^{13}C NMR (75 MHz): δ 13.8, 61.2, 108.6, 113.4, 128.1, 129.7, 130.7, 145.6, 152.3, 157.5, 162.1, 163.9, 173.2. MS (EI, *m*/*z*): 278 (M^+). Anal. Calcd for $C_{13}H_{11}ClN_2O_3$: C, 56.03; H, 3.98; N, 10.05. Found: C, 56.04; H, 3.99; N, 10.07.

4.2.4. Ethyl 4-(4-chlorophenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2c). Yellow solid. Mp: 154–155 °C. IR (KBr): 1424, 1627, 1636, 1699, 1721, 3320 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.11 (t, J=7.3 Hz, 3H), 4.08 (q, J=7.3 Hz, 2H), 7.42 (dd, J=8.3 and 9.3 Hz, 4H), 8.46 (s, 1H, D_2O-unexchangeable), 11.50 (s, 1H). ^{13}C NMR (75 MHz): δ 13.6, 60.5, 107.2, 127.6, 129.8, 131.8, 135.4, 145.6, 155.4, 163.3, 173.7. MS (EI, *m*/*z*): 278 (M^+). Anal. Calcd for $C_{13}H_{11}ClN_2O_3$: C, 56.03; H, 3.98; N, 10.05. Found: C, 56.04; H, 3.90; N, 10.06.

4.2.5. Ethyl 4-(2-nitrophenyl)-pyrimidin-2-(1*H*)-one-5-carboxylate (2d). Pale yellow crystalline solid. Mp: 140–141 °C. IR (KBr): 1420, 1616, 1630, 1695, 3430 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.89 (t, J=7.7 Hz, 3H), 3.87 (q, J=7.7 Hz, 2H), 7.42 (t, J=6.9 Hz, 2H), 7.67 (t, J=7.7 Hz, 1H), 8.17 (t, J=8.4 Hz, 1H), 8.61 (s, 1H, D_2O-unexchangeable). ^{13}C NMR (125 MHz): δ 14.0, 61.3, 107.1, 124.3, 129.9, 130.3, 130.8, 134.9, 146.6, 150.9, 155.6, 162.9, 174.3. MS (EI, *m*/*z*): 289 (M^+). Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.96; H, 3.82; N, 14.52.

4.2.6. Ethyl 4-(3-nitrophenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2e). Yellow solid. Mp: 151–153 °C. IR (KBr): 1421, 1615, 1638, 1694, 3429 cm^{-1}. ^1H NMR (500 MHz): δ 0.96 (t, J=7.5 Hz, 3H), 3.94 (q, J=7.5 Hz, 2H), 7.25 (t, J=8.0 Hz, 1H), 7.72 (d, J=6.9 Hz, 1H), 8.17 (m, 2H), 8.49 (s, 1H), 11.54 (s, 1H). ^{13}C NMR (125 MHz): δ 12.2, 59.3, 105.1, 121.8, 122.8, 127.4, 129.3, 133.1, 145.7, 149.8, 154.5, 161.4, 174.2. MS (EI, *m*/*z*): 289 (M^+). Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.96; H, 3.84; N, 14.51.

4.2.7. Ethyl 4-(1-naphthyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2f). Yellow solid. Mp: 155–157 °C. IR (KBr): 1199, 1320, 1372, 1421, 1613, 1654, 1711, 2872, 3084, 3251 cm^{-1}. ^1H NMR (500 MHz): δ 0.50 (t, J=7.7 Hz, 3H), 3.73 (q, J=7.7 Hz, 2H), 7.37 (m, 1H), 7.42 (q, J=3.1 and 3.9 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 7.71 (d, J=7.7 Hz, 1H), 7.87 (d, J=8.4 Hz, 1H), 8.89 (s, 1H, D_2O-unexchangeable), 11.52 (s, 1H). ^{13}C NMR (125 MHz): δ 13.2, 61.1, 110.5, 124.0, 125.0, 126.0, 126.4, 127.2, 128.7, 130.2, 130.4, 130.5, 133.0, 145.9, 157.8, 163.2, 172.6. MS (EI, *m*/*z*): 294 (M^+). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.32; H, 4.82; N, 9.43.

4.2.8. Ethyl 4-biphenyl-pyrimidin-2(1*H*)-one-5-carboxylate (2g). Yellow solid. Mp: 180–182 °C. IR (KBr): 1419, 1614, 1653, 1704, 3429 cm^{-1}. ^1H NMR (500 MHz): δ 0.97 (t, J=6.9 Hz, 3H), 3.90 (q, J=6.9 Hz, 2H), 7.34 (t, J=7.7 Hz, 1H), 7.43 (t, J=7.7 Hz, 2H), 7.50 (d, J=8.4 Hz, 2H), 7.66 (d, J=7.7 Hz, 2H), 7.69 (d, J=8.4 Hz, 2H), 8.56 (s, 1H, D_2O-unexchangeable), 11.52 (s, 1H). ^{13}C NMR (125 MHz): δ 14.1, 61.4, 108.1, 126.5, 127.3, 128.6, 129.6, 129.7, 139.6, 142.4, 145.7, 156.1, 158.91, 164.4, 173.6. MS (EI, *m*/*z*): 320 (M^+). Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.25; H, 5.01; N, 8.73.

4.2.9. Ethyl 4-(4-methoxyphenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2h). Yellow solid. Mp: 147–148 °C. IR (KBr): 1260, 1416, 1511, 1602, 1681, 1724, 2897, 2986, 3072, 3433 cm^{-1}. ^1H NMR (500 MHz): δ 1.07 (t, J=7.4 Hz, 3H), 3.80 (s, 3H), 4.10 (q, J=7.4 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 7.44 (d, J=8.8 Hz, 2H), 8.71 (s, 1H), 11.49 (s, 1H). ^{13}C NMR (125 MHz): δ 13.8, 58.2, 61.2, 108.6, 113.4, 130.7, 132.4, 143.2, 157.5, 162.1, 164.0, 172.8. MS (EI, *m*/*z*): 274 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.34; H, 5.15; N, 10.19.

4.2.10. Ethyl 4-(4-methoxyphenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2i). Yellow solid. Mp: 175–177 °C. IR (KBr): 1284, 1566, 1604, 1675, 1722, 2935, 3024, 3059, 3415 cm^{-1}. ^1H NMR (500 MHz): δ 3.72 (s, 3H), 3.84 (s, 3H), 6.94 (d, J=8 Hz, 2H), 7.52 (d, J=8 Hz, 2H), 8.80 (s, 1H), 11.54 (s, 1H). ^{13}C NMR (125 MHz): δ 52.3, 55.5, 108.8, 113.8, 120.2, 130.9, 146.3, 158.1, 162.5, 164.6, 174.1. MS (EI, *m*/*z*): 260 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.02; H, 4.67; N, 10.78.

4.2.11. Ethyl 1-methyl-4-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (2j). Yellow solid. Mp: 131–132 °C. IR (KBr): 1103, 1197, 1286, 1494, 1439, 1616, 1679, 1722, 2990 cm^{-1}. ^1H NMR (500 MHz): δ 1.03 (t, J=7.7 Hz, 3H), 3.36 (s, 3H), 4.07 (q, J=7.7 Hz, 2H), 7.35 (t, J=6.9 Hz, 2H), 7.41 (t, J=7.7 Hz, 1H), 7.49 (t, J=6.9 Hz, 2H), 8.41 (s, 1H). ^{13}C NMR (125 MHz): δ 13.8, 39.3, 61.5, 108.82, 127.9, 128.6, 130.6, 137.7, 153.5, 155.2, 164.1, 174.3. MS (EI, *m*/*z*): 258 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.09; H, 5.43; N, 10.88.

4.2.12. Ethyl 1-methyl-4-(4-chlorophenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2k). Colorless crystalline solid. Mp: 160–162 °C. IR (KBr): 1425, 1625, 1638, 1699, 1720, 3319 cm^{-1}. ^1H NMR (500 MHz): δ 1.12 (t, J=7.5 Hz, 3H), 3.67 (s, 3H), 4.14 (q, J=7.5 Hz, 2H), 7.36 (doublet of triplet, J=8.6 and 2.3 Hz, 2H), 7.47 (doublet of triplet, J=8.6 and 2.3 Hz, 2H), 8.44 (s, 1H, D_2O-unexchangeable). ^{13}C NMR (125 MHz): δ 14.0, 39.4, 61.7, 108.4, 128.1, 130.2, 136.0, 136.9, 153.6, 155.1, 163.7, 173.2. MS (EI, *m*/*z*): 292 (M^+). Anal. Calcd for $C_{14}H_{13}ClN_2O_3$: C, 57.44; H, 4.48; N, 9.57. Found: C, 57.25; H, 4.43; N, 9.71.

4.2.13. 5-Acetyl-1-methyl-4-phenyl-pyrimidin-2(1*H*)-one (2l). Yellow solid. Mp: 139–141 °C. IR (KBr): 1108, 1290, 1370, 1441, 1675, 1726, 2953 cm^{-1}. ^1H NMR (500 MHz): δ 3.67 (s, 6H), 7.39 (t, J=6.9 Hz, 2H), 7.45 (d, J=5.3 Hz, 1H), 7.52 (t, J=6.9 Hz, 2H), 8.41 (s, 1H, D_2O-unexchangeable). ^{13}C NMR (125 MHz): δ 39.3, 52.3, 108.4, 129.9, 128.6, 130.8, 137.4, 153.4, 155.1, 164.4, 174.2. MS (EI, *m*/*z*): 228 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.43; H, 5.33; N, 12.25.

4.3. Preparation of ethyl 6-deuterio-4-(2-nitrophenyl)-pyrimidin-2-(1*H*)-one-5-carboxylate (3a)

A 50-mL round bottom flask containing magnetic bar was charged with 1 mmol (0.308 g) of **1d** and 10 mL acetonitrile. To this solution was added a mixture of cobalt(II) nitrate hexahydrate (5 mmol, 1.46 g) and potassium persulfate (2.5 mmol, 0.68 g) in 3 mL of D_2O and the solution was stirred at 80 °C on an oil bath. The stirring was continued at 80 °C for 8 h (Table 2) and TLC showed the complete disappearance of **1d**. The reaction mixture was diluted with 20 mL of $CHCl_3$ and the supernatant was decanted. The residue was poured into 20 g of crushed ice and extracted with $CHCl_3$ (2×20 mL). The organic extracts were pooled up, washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford 0.290 g of crude product. The column purification of residue using 1:1 petroleum ether/ethyl acetate afforded 0.23 g of **3a** as pale yellow crystalline solid.

4.3.1. Ethyl 6-deuterio-4-(2-nitrophenyl)-pyrimidin-2-(1*H*)-one-5-carboxylate (3a). Pale yellow solid. Mp: 148–150 °C. IR (KBr): 1142, 1224, 1345, 1446, 1517, 1599, 1701, 1720, 2280, 2808, 2984, 3273 cm^{-1}. MS (EI, *m*/*z*): 290 (M^+). The intensity of CH(6) proton was reduced by 70%. Other spectral characterizations were similar to **2d**.

4.4. Experimental procedure for preparation of 3b–e

4.4.1. Typical procedure for the preparation of ethyl 4-(4-methoxyphenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (3b). A 50-mL round bottom flask containing

magnetic bar was charged with 1 mmol (0.352 g) of ethyl 4-(4-methoxyphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate and 10 mL acetonitrile. To this solution was added a mixture of cobalt(II) nitrate hexahydrate (2.5 mmol, 0.73 g) and potassium persulfate (1.3 mmol, 0.351 g) in 3 mL of H_2O and the solution was stirred at 80 °C on an oil bath. The stirring was continued at 80 °C for 4 h (Table 2) and TLC showed the complete disappearance of the starting material. The reaction mixture was diluted with 20 mL of $CHCl_3$ and the supernatant was decanted. The residue was poured into 20 g of crushed ice and extracted with $CHCl_3$ (2×20 mL). The organic extracts were pooled up, washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford 0.263 g of crude product. The column purification of residue using 1:1 petroleum ether/ethyl acetate afforded 0.227 g of **3b**. The same procedure was followed for the synthesis of **3d–e**.

4.4.2. Ethyl 4-(4-methoxyphenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (3b). Yellow solid. Mp: 153–154 °C. IR (KBr): 1163, 1238, 1328, 1446, 1517, 1599, 1668, 1709, 2280, 2808, 2984, 3213 cm^{-1}. ^1H NMR (500 MHz): δ 0.85 (t, J=6.9 Hz, 3H), 3.82 (s, 3H), 3.90 (q, J=6.9 Hz, 2H), 6.94 (d, J=9.2 Hz, 1H), 7.00 (d, J=8.5 Hz, 1H), 7.40 (sextet, J=7 and 7.7 Hz, 2H), 7.49 (d, J=3.8 Hz, 1H), 7.58 (t, J=8.5 Hz, 2H), 8.01 (q, J=8.5 and 9.2 Hz, 2H), 13.32 (s, 1H, D_2O-exchangeable). ^{13}C NMR (125 MHz): δ 13.5, 55.4, 61.9, 106.5, 114.2, 128.6, 129.2, 129.6, 130.2, 138.5, 139.7, 150.2, 158.2, 162.2, 162.9, 174.1. MS (EI, *m*/*z*): 350 (M^+). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.57; H, 5.17; N, 8.02.

4.4.3. Ethyl 4-(4-methoxyphenyl)-6-trifluoromethyl-pyrimidin-2(1*H*)-one-5-carboxylate (3c). Red viscous liquid crystallized to intense yellow solid. Mp: 136–138 °C. IR (KBr): 1017, 1127, 1162, 1210, 1299, 1509, 1605, 1699, 1739, 3188 cm^{-1}. ^1H NMR (500 MHz): δ 1.15 (t, J=6.9 Hz, 3H), 3.85 (s, 3H), 4.17 (q, J=6.9 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 11.50 (s, 1H). ^{13}C NMR (125 MHz): δ 13.7, 55.6, 62.8, 109.5, 114.9, 122.0 (q, J=275 Hz), 130.2, 138.6, 155.6 (q, J=34 Hz), 161.2, 163.2, 164.1, 174.2. MS (EI, *m*/*z*): 342 (M^+). Anal. Calcd for $C_{15}H_{13}F_3N_2O_4$: C, 52.64; H, 3.83; N, 8.18. Found: C, 52.65; H, 3.83; N, 8.19.

4.4.4. 7,7-Dimethyl-4-phenyl-7,8-dihydroquinazoline-2,5(1*H*,6*H*)-dione (3d). Pale yellow solid. Mp: 196–198 °C. IR (KBr): 1092, 1323, 1640, 1722, 2956, 3208 cm^{-1}. ^1H NMR (500 MHz): δ 1.35 (s, 6H), 2.58 (s, 2H), 2.88 (s, 2H), 7.01 (q, J=1.7 , 5.2, and 7.5 Hz, 2H), 7.40 (q, J=1.7 and 5.2 Hz, 3H), 11.83 (s, 1H). ^{13}C NMR (125 MHz): δ 25.4, 28.3, 32.1, 48.1, 54.1, 108.5, 126.6, 127.8, 128.0, 138.8, 152.3, 167.7, 172.2, 194.8. MS (EI, *m*/*z*): 268 (M^+). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.61; H, 6.02; N, 10.46.

4.4.5. 4-Phenyl-1*H*-indeno[1,2-*d*]pyrimidin-2,5-dione (3e). Colorless crystalline solid. Mp: 210–212 °C. IR (KBr): 1276, 1378, 1459, 1576, 1617, 1617, 1659, 1723, 2854, 2923, 3484 cm^{-1}. ^1H NMR (500 MHz): δ 7.6 (t, J=6.9 Hz, 2H), 7.65 (q, J=6.9 Hz, 2H), 7.71 (t, J=7.5 Hz, 1H), 7.82 (d, J=7.5 Hz, 1H), 7.89 (d, J=7.5 Hz, 2H), 8.11 (d, J=6.8 Hz, 1H). ^{13}C NMR (125 MHz): δ 106.2, 120.8, 121.5, 126.7, 128.3, 128.9, 130.1, 132.1, 133.7, 135.2, 143.5, 151.2, 157.4, 173.9, 187.5. MS (EI, *m*/*z*): 274 (M^+). Anal. Calcd for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.67; N, 10.21. Found: C, 74.46; H, 3.69; N, 10.20.

4.4.6. Ethyl 1-methyl-4-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolyl]-pyrimidin-2(1*H*)-one-5-carboxylate (3f). Yellow solid. Mp: 183–184 °C. IR (KBr): 1413, 1623, 1693, 1721, 2855, 3034, 3231 cm^{-1}. ^1H NMR (500 MHz): δ 0.96 (t, J=6.9 Hz, 3H), 3.66 (m, 5H), 3.80 (s, 3H), 6.86 (d, J=8.5 Hz, 2H), 7.30 (t, J=7.5 Hz, 1H), 7.43 (m, 4H), 7.81 (d, J=8.1 Hz, 2H), 8.22 (s, 1H, pyrazole-H), 8.55 (s, 1H, D_2O-unexchangeble). ^{13}C NMR (125 MHz): δ 13.7, 29.8, 55.6, 57.0, 105.1, 114.1, 119.2, 125.6, 129.0, 129.6, 129.9, 130.1, 131.2, 138.2, 139.6, 152.5, 156.0, 167.2, 168.2, 177.7. MS (EI, *m*/*z*): 430 (M^+). Anal. Calcd for $C_{24}H_{22}N_4O_4$: C, 66.97; H, 5.15; N, 13.02. Found: C, 66.98; H, 5.14; N, 13.03.

4.4.7. Ethyl 4-(4-tolyl)-pyrimidin-2(1*H*)-one-5-carboxylate (5a). Pale yellow crystalline solid. Mp: 160–162 °C. IR (KBr): 1183, 1425, 1512, 1666, 1712, 3213 cm^{-1}. ^1H NMR (500 MHz): δ 1.09 (t, J=6.9 Hz, 3H), 2.35 (s, 3H), 4.11 (q, J=6.9 Hz, 2H), 7.19 (d, J=8 Hz, 2H), 7.38 (d, J=8 Hz, 2H), 8.78 (s, 1H, D_2O-unexchangeable). ^{13}C NMR (125 MHz): δ 13.9, 21.7, 61.5, 109.0, 128.7, 128.8, 128.9, 131.6, 141.8, 157.8, 164.0, 169.4. MS (EI, *m*/*z*): 258 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.01; H, 5.38; N, 10.87.

4.4.8. Ethyl tetrahydropyrimidin-2,4(1*H*,3*H*)-dione-5-carboxylate (8). Colorless crystalline solid. Mp: 225–228 °C. IR (KBr): 1478, 1619, 1668, 1744, 2855, 3034, 3335 cm^{-1}. ^1H NMR (400 MHz): δ 1.15 (t, J=6.9 Hz, 3H), 4.09 (q, J=6.9 Hz, 2H), 8.08 (s, 1H, D_2O-exchangeable), 11.27 (s, 1H, D_2O-exchangeable), 11.57 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100 MHz): δ 14.7, 60.5, 103.6, 149.92, 151.1, 160.6, 163.6. MS (EI, *m*/*z*): 184 (M^+). Anal. Calcd for $C_7H_8N_2O_4$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.67; H, 4.39; N, 15.19.

4.4.9. Ethyl 4-(9-anthryl)-pyrimidin-2(1*H*)-one-5-carboxylate (10). Yellow solid. Mp: 180–182 °C. IR (KBr): 1142, 1230, 1459, 1648, 1698 cm^{-1}. ^1H NMR (400 MHz): δ 0.35 (t, J=6.9 Hz, 3H), 3.58 (doublet of quartet, J=6.9 Hz, 2H), 7.48 (t, J=6.9 Hz, 2H), 7.56 (d, J=6.9 Hz, 2H), 7.61 (t, J=7.7 Hz, 2H), 7.78 (q, J=3.8 and 2.3 Hz, 1H), 7.88 (d, J=9.2 Hz, 2H), 9.10 (s, 1H), 11.50 (s, 1H). ^{13}C NMR (100 MHz): δ 12.9, 61.4, 106.1, 121.8, 123.1, 124.9, 125.7, 127.3, 127.7, 127.9, 128.0, 128.9, 132.1, 133.7, 134.3, 144.7, 145.9, 150.9, 156.5, 163.1, 174.5. MS (EI, *m*/*z*): 344 (M^+). Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.24; H, 4.69; N, 8.12.

4.4.10. 3*H*-1,3-Diaza-naphtho[3,2,1-*de*]anthracene-2,5-dione (11). Yellow solid. Mp: 230–232 °C. IR (KBr): 1145, 1233, 1460, 1645, 1696 cm^{-1}. ^1H NMR (400 MHz): δ 7.95 (m, 1H), 8.23 (m, 1H), 8.39 (d, J=9.2 Hz, 1H), 8.43 (d, J=9.2 Hz, 2H), 8.58 (d, J=9.2 Hz, 1H), 8.66 (d, J=9.2 Hz, 2H), 8.79 (s, 1H, D_2O-unexchangeable), 11.52 (s, 1H). MS (EI, *m*/*z*): 298 (M^+). Anal. Calcd for

$C_{19}H_{10}N_2O_2$: C, 76.50; H, 3.38; N, 9.39. Found: C, 76.53; H, 3.40; N, 9.38.

Acknowledgements

One of the authors (P.S.) would like to thank the Council of Scientific and Industrial Research, New Delhi for financial support. We are grateful to Mr. D. Muralidharan and Dr. R. Sridhar, CLRI for meticulously correcting the manuscript.

References and notes

1. (a) 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, M. S. *J. Med. Chem.* **1995**, *38*, 119; (b) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043; (c) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879; (d) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1.
2. Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1142 and more references therein.
3. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
4. (a) Khanina, E. L.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1982**, 535; (b) Akhtar, M. S.; Seth, M.; Bhaduri, A. P. *Indian J. Chem.* **1987**, *26B*, 556; (c) Khanina, E. L.; Liepin'sh, E. E.; Mutsenietse, E. Kh.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1987**, 668.
5. (a) Slavinskaya, V. A.; Duburs, G.; Sile, D.; Kreile, D.; Khanina, E. L. U.S.S.R. Patent 632,695, 1978; *Chem. Abstr.* **1979**, *90*, 121631y; (b) Puchala, A.; Belaj, F.; Bergman, J.; Kappe, C. O. *J. Heterocycl. Chem.* **2001**, *38*, 1345.
6. (a) Vanden Eynde, J. J.; Audiart, N.; Canonne, V.; Michel, S.; Van Haverbeke, Y.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967; (b) Vanden Eynde, J. J.; Labuche, N.; Haverbeke, Y. V.; Vanden, L. T. *ARKIVOC* **2003**, 22; (c) Yamamoto, K.; Chen, Y. G.; Buono, F. G. *Org. Lett.* **2005**, *7*, 4673; (d) Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2003**, *68*, 6172.
7. Rizzo, R. C.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2001**, *44*, 145.
8. Hockova, D.; Holy, A.; Masojidkova, M.; Andrei, G.; Snoeck, R.; Clercq, E. D.; Balzarini, J. *J. Med. Chem.* **2003**, *46*, 5064.
9. Chen, C.; Wilcoxen, K. M.; Huang, C. Q.; Xie, Y.-F.; McCarthy, J. R.; Webb, T. R.; Zhu, Y.-F.; Saunders, J.; Liu, X.-J.; Chen, T.-K.; Bozigian, H.; Grigoriadis, D. E. *J. Med. Chem.* **2004**, *47*, 4787.
10. (a) Itami, K.; Yamazaki, D.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 12396; (b) Kang, F.-A.; Kodah, J.; Guan, O.; Li, X.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 1957.
11. (a) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 5069; (b) Lenka, S.; Dash, S. B. *J. Macromol. Sci., Chem. A* **1983**, *20*, 397; (c) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. O.; Shoa, R. H. *Tetrahedron Lett.* **2005**, *46*, 2775.
12. House, D. A. *Chem. Rev.* **1962**, *62*, 185.
13. Liang, C.; Bruell, C.; Marley, M. C.; Sperry, K. L. *Chemosphere* **2004**, *55*, 1213 and more references therein.
14. The crystallographic details were submitted in Cambridge Crystallographic Data Centre and CCDC number is CCDC 265949.
15. (a) Das, B. K.; Clark, J. H. *Chem. Commun.* **2000**, 605 and more references therein; (b) Sheldon, R. A.; Kochi, J. K. *Metal Ion Catalyzed Oxidation of Organic Compounds*; Academic: New York, NY, 1981; pp 315–339.
16. (a) Shanmugam, P.; Sabastein, C.; Perumal, P. T. *Indian J. Chem.* **2004**, *43 B*, 135; (b) Shanmugam, P.; Annie, G.; Perumal, P. T. *J. Heterocycl. Chem.* **2003**, *40*, 879; (c) Sivaprasad, G.; Perumal, P. T. *J. Heterocycl. Chem.* **2005**, *42*, 863.