Tetrahedron 67 (2011) 5615–5620

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient aerobic oxidative dehydrogenation of dihydropyrimidinones and dihydropyrimidines

Bing Han *, Run-Feng Han, Yu-Wei Ren, Xiao-Yong Duan, Yi-Chuan Xu, Wei Zhang

State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering, Lanzhou University, 222 Tianshui Rd., Gansu, Lanzhou 730000, People's Republic of China

ARTICLE INFO

Article history:
Received 11 January 2011
Received in revised form 17 May 2011
Accepted 24 May 2011
Available online 30 May 2011

Keywords:
Dihydropyrimidinones and dihydropyrimidines
N-Hydroxyphthalimide
Radical reaction
Aerobic oxidation
Dehydrogenation

ABSTRACT

4-Substituted dihydropyrimidinones and dihydropyrimidines were first efficient aerobic oxidized to the corresponding pyrimidinones and pyrimidines, respectively, in high yields by molecular oxygen in the presence of catalytic amount of *N*-hydroxyphthalimide (NHPI) and $Co(OAc)_2$ in a mild and environmental benign condition.

1. Introduction

Oxidation or oxygenation is a fundamental reaction in industrial production and organic synthesis.[1] Oxidative dehydrogenation of heterocycles is an important moiety in such reactions. Although a number of methods have been developed, most procedures require stoichiometric oxidants and/or rigorous reaction conditions.[2] Recently, the catalytic oxidative dehydrogenation of heterocycles using oxygen as terminal oxidant has been developed in view of green chemistry and atom economy.[3]

The dehydrogenation of multi-functionalized dihydropyrimidinones (DHPMs) and dihydropyrimidines has received great attention for its facile access via the Biginelli or Biginelli-like three-component-coupling reactions.[4] Furthermore, it also provides an efficient access to the corresponding pyrimidines, which are found in a wide range of biologically active molecules and shown biological and therapeutic activities, such as antitumoral agents[5] and HIV inhibitors.[6] However, in contrast to the quantitative dehydrogenation of Hantzsch type dihydropyridines (DPHs), the dehydrogenation of dihydropyrimidinones and dihydropyrimidines was found to be more difficult because of its highly stable structure.[7,8] Although TBHP/$CuCl_2$/K_2CO_3 (TBHP, *tert*-butyl hydroperoxide),[8a] CAN/$NaHCO_3$ (CAN, cerium ammonium nitrate),[8b] and TBHP/$PhI(OAc)_2$[8c] could give acceptable yield, stoichiometric or excess oxidants and base must be used. It is worth to note that catalytic aerobic oxidative dehydrogenation of DHPMs has not been reported yet. Herein, we wish to report an efficient and environmental benign oxidative dehydrogenation procedure of dihydropyrimidinones and dihydropyrimidines using oxygen as the terminal oxidant and NHPI (*N*-hydroxyphthalimide) with cobalt salt as the catalysts.

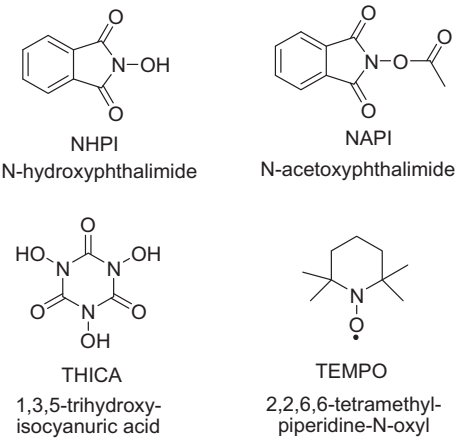
Aminoxyl radicals or its precursors, such as NHPI and TEMPO (2,2,6,6-tetramethyl-piperidine-*N*-oxyl) have been extensively studied on its application in the aerobic oxidation/oxygenation of hydrocarbons, alcohols and amines.[9] However, its application in the aerobic oxidation of heterocycles has scarcely been reported. Very recently, we reported its application in the aerobic oxidative dehydrogenation of Hantzsch dihydropyridines, pyrazolines and synthesis of benzoxazoles, benzothiazoles and benzimidazoles.[10]

2. Results and discussion

As a development of this chemistry, we attempted to dehydrogenate DHPMs by the aerobic oxidation procedure using aminoxyl radical as the catalyst. In view of the highly difficult aerobic oxidative dehydrogenation of DHPMs, four kinds of aminoxyl radicals or its precursors were used to accomplish the reaction (Scheme 1).

* Corresponding author. Fax: +86 930 891 2582; e-mail address: hanb@lzu.edu.cn (B. Han).

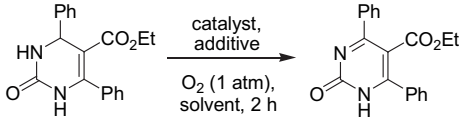
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.05.105



Scheme 1. Aminoxyl radical or precursor.

Initially, NHPI was chosen as the catalyst to accomplish the reaction because of its excellent performance in the dehydrogenation of DHPs.[10a] Various solvents were tested in the reaction, however, only 1,2-dichloroethane and acetonitrile gave >10% yield (HPLC analysis) (entries 1–5, Table 1). Next, NHPI-transition metal combined catalytic system was tested in the reaction. It was found by Ishii et al. that the presence of a small amount of transition metals, such as Mn^{II} and Co^{II}, could significantly enhance the oxidizing capacity of the NHPI–O_2 system in the oxygenation of hydrocarbons.[11] Accordingly, it was expected that the same effect could also be observed in the case for the oxidation of DHPMs. Indeed, when transition metal salts like $Co(OAc)_2$ or $Co(OBz)_2$ was added up to 0.5 mol % to the reaction system combined with 20 mol % NHPI it led to significant rate acceleration and gave much better conversion and yield than the case of absence of the metal salts (entries 6–10, Table 1). Moreover, halogen solvent $(CH_2Cl)_2$ gave the best conversion and yield, partly due to the good solubility of DHPMs. It is noteworthy that reduction of the usage amount of NHPI to 10 mol % did not affect the conversion, but the yield was a little bit lower (entry 8, Table 1).

Table 1
Effect of catalyst and solvent[a]



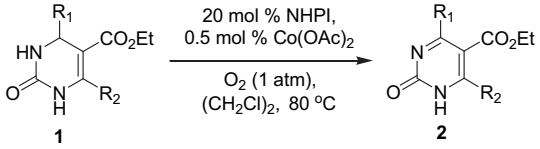
Entry	Catalyst (mol %)	Solvent	Conv.[b] (area %)	Yield[b] (area %)
1	NHPI (20)	CH_3CN	19	15
2	NHPI (20)	Acetone	—	Trace[c]
3	NHPI (20)	DCE	28	25
4	NHPI (20)	$MeCO_2Et$	9	5
5[d]	NHPI (20)	HOAc	10	9
6	NHPI/$Co(OAc)_2$ (20/0.5)	CH_3CN	97	60
7[d]	NHPI/$Co(OAc)_2$ (20/0.5)	HOAc	93	78
8	NHPI/$Co(OAc)_2$ (10/0.5)	DCE	96	90
9	NHPI/$Co(OAc)_2$ (20/0.5)	DCE	96	95
10	NHPI/$Co(O_2CPh)_2$ (20/0.5)	DCE	94	87
11[d]	NAPI/$Co(OAc)_2$ (10/0.5)	HOAc	—	Trace[c]
12	THICA/$Co(OAc)_2$ (5/0.5)	CH_3CN	—	Trace[c]
13[d]	THICA/$Co(OAc)_2$ (5/0.5)	HOAc	—	Trace[c]
14[d]	THICA/$Co(OAc)_2$/$Mn(OAc)_2$ (5/0.5/0.5)	HOAc	58	50
15	TEMPO (10)	CH_3CN	—	Nd.[c]
16	TEMPO/CuCl (10/0.5)	CH_3CN	—	Trace[c]

[a] A mixture of substrate **1** (1 mmol), catalyst, and solvent (4 mL) was stirred in a 25 mL three-necked flask under an oxygen atmosphere (1 atm) at 80 °C for 2 h.
[b] HPLC analysis unless other notes.
[c] TLC analysis.
[d] At 100 °C.

Furthermore, in order to reduce the usage amount of the catalyst and pursue the higher catalytic performance, analogues, such as *N*-acetoxyphthalimide (NAPI) and 1,3,5-trihydroxy-isocyanuric acid (THICA) were used instead of NHPI in the case, which performed better than NHPI in the aerobic oxidation of hydrocarbons.[12] Unexpectedly, such kind of analogues is inefficient in this reaction (entries 11–14, Table 1). TEMPO and TEMPO/CuCl were also used to accomplish the reaction, neither were effective (entries 15 and 16, Table 1). Finally, the optimal catalytic system NHPI (20 mol %)–$Co(OAc)_2$ (0.5 mol %)–$(CH_2Cl)_2$ was used in the following reactions based on its best yield (entry 9, Table 1).

4-Aryl with a range of electronic properties and 4-alkyl substituted DHPMs were aerobic oxidative dehydrogenated to the corresponding pyrimidinones in high yields as shown in Table 2. In the present case, however, no reaction occurred in the absence of NHPI, demonstrating that only Co^{II} salt could not directly catalyze the oxidation of DHPMs (entry 13, Table 2).

Table 2
Aerobic oxidative dehydrogenation of dihydropyrimidinones catalyzed by NHPI/Co^{II} system[a]

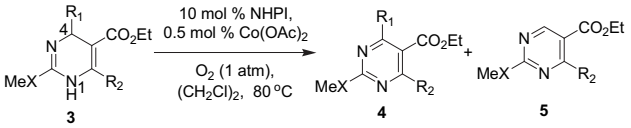


Entry	Sub.	R_1	R_2	Time (h)	Yield [b] (%)
1	**1a**	Ph	Ph	2	88 (**2a**)
2	**1b**	4-Cl–Ph	Ph	2	85 (**2b**)
3	**1c**	4-F–Ph	Ph	2.5	93 (**2c**)
4	**1d**	2-Br–Ph	Ph	1	93 (**2d**)
5	**1e**	*i*-Pr	Ph	2	80 (**2e**)
6	**1f**	Ph	Me	1.5	75 (**2f**)
7	**1g**	4-MeO–Ph	Me	2	73 (**2g**)
8	**1h**	3,4,5-Trimethoxy-Ph	Me	2.5	70 (**2h**)
9	**1i**	4-Cl–Ph	Me	1.5	81 (**2i**)
10	**1j**	4-F–Ph	Me	2	85 (**2j**)
11	**1k**	*i*-Pr	Me	2.5	75 (**2k**)
12	**1l**	Heptyl	Me	2.5	60 (**2l**)
13[c]	**1a**	Ph	Ph	3	0 (**2a**)

[a] A mixture of dihydropyrimidinone **1** (1 mmol), NHPI (0.2 mmol, 33 mg), and $Co(OAc)_2 \cdot 4H_2O$ (0.005 mmol, 1 mg) in $(CH_2Cl)_2$ (4 mL) was stirred in a 25 mL three-necked flask under an oxygen atmosphere (1 atm) at 80 °C for several hours.
[b] Isolated yields by silica gel column chromatography.
[c] In the absence of NHPI.

While having successfully achieved the aerobic oxidative dehydrogenation of DHPMs, we expanded the catalytic system to the oxidative dehydrogenation of dihydropyrimidines. In the case, the reaction could complete efficiently in the same condition using whether 10 mol % of NHPI or 20 mol % of NHPI combined with 0.5 mol % of $Co(OAc)_2$ (entries 1 and 2, Table 3). Excellent yields were obtained with most substrates except **3d**, **3e**, and **3h**. In the case of **3d** and **3h**, in addition to the normal dehydrogenation products **4d** and **4h**, 4-dealkylation products **5d** and **5h** were also obtained in 50% and 57% yield, respectively (entries 7 and 12, Table 3). In the case of **3e**, 4-dealkylation product (**5d**) was obtained in 65% yield and the normal dehydrogenation product (**5e**) was not observed (entry 8, Table 3). Similar dealkylation has also been observed previously in the TBHP/$CuCl_2$/K_2CO_3 oxidative dehydrogenation of dihydropyrimidines,[8a] as well as in the aromatization of DHPs catalyzed by NHPI.[10a] Interestingly, the corresponding dihydropyrimidinones (entries 5 and 11, Table 2) did not show this lability. Otherwise, the reaction could also complete even at room temperature with prolonged time using acetonitrile as the solvent since its good solubility of substrate **3**, NHPI and Co^{II} salt in this condition (entries 3, 5, and 10, Table 3).

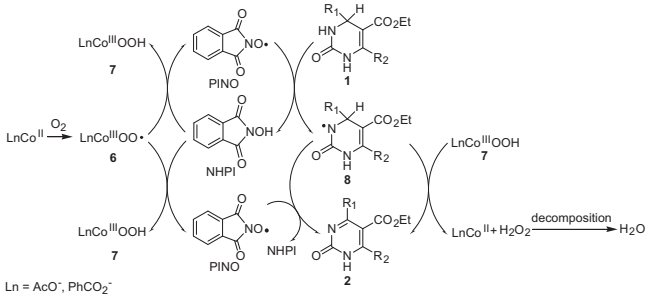
Table 3
Aerobic oxidative dehydrogenation of dihydropyrimidines catalyzed by NHPI/Co^{II} system[a]



Entry	Sub.	X	R_1	R_2	Time (h)	Yield[b] (%)
1	**3a**	S	Ph	Me	1	97 (**4a**)
2[c]	**3a**	S	Ph	Me	0.5	97 (**4a**)
3[d]	**3a**	S	Ph	Me	8	95 (**4a**)
4	**3b**	S	4-MeO–Ph	Me	1	95 (**4b**)
5[d]	**3b**	S	4-MeO–Ph	Me	7	93 (**4b**)
6	**3c**	S	4-Cl–Ph	Me	1	83 (**4c**)
7	**3d**[e]	S	*i*-Pr	Me	1	36, 50 (**4d**, **5d**)
8	**3e**[e]	S	*t*-Bu	Me	1.5	0, 65 (**4e**, **5d**)
9	**3f**	S	Heptyl	Me	1.5	94 (**4f**)
10[d]	**3f**	S	Heptyl	Me	10	85 (**4f**)
11	**3g**	S	4-F–Ph	Ph	2	94 (**4g**)
12	**3h**[e]	S	*i*-Pr	Ph	0.5	35, 57 (**4h**, **5h**)
13	**3i**[e]	O	4-NO_2–Ph	Me	3	86 (**4i**)
14	**3j**[e]	O	4-NO_2–Ph	Ph	2.5	88 (**4j**)
15[f]	**3a**	S	Ph	Me	3	5 (**4a**)

[a] A mixture of dihydropyrimidine **3** (1 mmol), NHPI (0.1 mmol, 16 mg), and $Co(OAc)2\cdot 4H_2O$ (0.005 mmol, 1 mg) in $(CH_2Cl)_2$ (4 mL) was stirred in a 25 mL three-necked flask under an oxygen atmosphere (1 atm) at 80 °C for several hours.
[b] Isolated yields by silica gel column chromatography.
[c] NHPI (0.2 mmol) used.
[d] In MeCN at room temperature.
[e] Mixture of (1,4-dihydro-**3**) and (3,4-dihydro-**3**) double bond isomers.
[f] In the absence of NHPI.

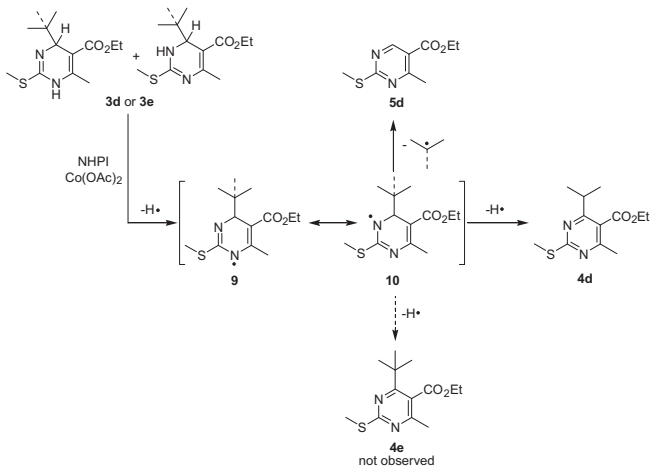
The NHPI catalyzed aerobic oxidation of DHPMs was supposed to be following a free radical chain process, similar to that proposed previously by literature.[13] The initiation step was the generation of phthalimide-*N*-oxyl radical (PINO) by the hydrogen transfer from NHPI to O_2. Co^{II} could accelerate this step by binding with O_2 to form a Co^{III}–O_2 radical complex **6**, which can abstract the hydrogen from NHPI much more effectively than oxygen to produce PINO radical and Co^{III}–O_2H complex **7** (Scheme 2). In the subsequent propagation step, PINO abstracted hydrogen from N–H of DHPMs **1** to produce radical **8**, which process is different from the hydrogen abstraction from C–H of hydrocarbons. The C–H versus N–H reactivity of heterocycles has been recently reported and the conclusion is that in the reactions with oxyl radical the N–H reactivity can be much larger than the C–H reactivity in spite of the lower BDE of the C–H bond (about 11 kcal/mol).[14] Similar phenomenon was also observed that the hydrogen transfer rate constants of the phenolic O–H are 10 times lager than it of the benzylic C–H in the reactions with PINO radical despite the BDE of the phenolic O–H bond is calculated to be as much as 5.3 kcal/mol lager than the C–H bond of the benzylic CH_2OH.[15] This consistency of whether heterocyclic N–H or phenolic O–H is more reactive than benzylic C–H with oxyl radical can be ascribed to the different mechanism of the hydrogen atom abstraction that the former might take place proton



Scheme 2. A proposed radical mechanism of dehydrogenation of dihydropyrimidinones.

coupled electron transfer (PCET), which suggested by Mayer rather than a classical hydrogen atom transfer (HAT) occurred in the latter.[16] Thus, in DHMPs H-atom transfer from N–H is strongly preferred over H-atom transfer from benzylic CH_2. The strong driving force of aromatization made the second hydrogen abstraction from radical **8** by PINO and/or Co^{III}–O_2 complex **6**/**7** very effective. Therefore, the pyrimidinone derivatives **2** formed exclusively. Complex **7** would be reduced by NHPI or intermediate **8** to release Co^{II} and yield hydrogen peroxide, which would decompose to water under this condition. Consequently, the whole process was remarkably accelerated in the presence of Co^{II}, as demonstrated by the present result, as well as those observed by others (Scheme 2).[11]

The oxidative dehydrogenation of dihydropyrimidines and the cleavage of isopropyl or *tert*-butyl group can also be explained by the general mechanism shown in Scheme 2. PINO abstracted hydrogen from dihydropyrimidine **3d** to produce radical **9**/**10**, which would further lose hydrogen radical, giving compound **4d**. Alternatively, loss of a propyl radical from **9**/**10** would give **5d** (Scheme 3). However, in the case of **3e**, loss of a *tert*-butyl radical from **9**/**10** was privileged due to the stability of the *tert*-butyl radical and would give **5d** exclusively. Therefore, the *tert*-butyl group preserved compound **4e** was not observed (Scheme 3).



Scheme 3. A proposed radical mechanism of dehydrogenation of dihydropyrimidine and isopropyl and *tert*-butyl cleavage.

3. Conclusion

In conclusion, the oxidative dehydrogenation of 4-substituted dihydropyrimidinones and dihydropyrimidines bearing various alkyl or aryl groups was achieved efficiently by using molecular oxygen as the terminal oxidant with NHPI and $Co(OAc)_2$ as the catalysts in the environmental benign condition. Extension of this method to the preparation of other heterocyclic compounds is under way in this laboratory.

4. Experimental

4.1. General information

All reagents and solvents purchased from commercial suppliers and used without further purification. Flash chromatography was carried out with silica gel (200–300 mesh). Analytical TLC was performed with silica gel GF_{254} plates, and the products were visualized by UV light (254 nm) detection. ^1H NMR and ^{13}C NMR (300 or 400 MHz and 75 or 100 MHz, respectively) spectra were recorded in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are reported in parts per million using TMS as internal standard, and spin-spin coupling constants (J) are given in hertz. Low resolution EI-MS spectra and

ESI-MS were measured on an HP 5988A spectrometer by direct inlet at 70 eV and Bruker Daltonics Esquire6000, respectively. The high-resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEX II 47e spectrometer by ESI. Analytical HPLC was routinely performed on Waters600 for reaction monitoring with the following conditions: column=S/N C1808–1299 250×φ4.6 mm, flow rate=1 mL/min, detector 220 nm, injection volume 5 μL, column temperature=room temperature. Mobile phase solvent: MeOH/H_2O (60:40).

4.2. General procedure for the Biginelli three-component-coupling for the preparation of compounds 1a–l

Compounds **1a**–**l** were prepared according to the literature.[4b] A typical procedure is as the following: A round bottom flask was charged with methanol (20 mL), 4-methoxybenzaldehyde (6.810 g, 50 mmol, 1 equiv), ethyl acetoacetate (6.507 g, 50 mmol, 1 equiv), and urea (4.504 g, 75 mmol, 1.50 equiv). To the mixture was added $CeCl_3 \cdot 7H_2O$ (1.863 g, 5 mmol, 0.1 equiv) and the batch was heated under reflux. The solution became heterogeneous within 2–3 h. After heating at reflux for 24 h, the mixture was cooled to room temperature and the product was isolated by filtration. The wet cake was washed twice with large amounts of water and once with methanol. Then the cake was recrystallized with methanol and dried under reduced pressure at 40 °C for 10 h. Dihydropyrimidinone (**1g**) was obtained as a white solid (12.773 g, 44 mmol, 88%).

4.3. General procedure for the base-catalyzed Biginelli-like three-component-coupling

Compounds **3a**–**j** were prepared according to the literature procedure.[4c] A typical procedure is as follows: A solution of ethyl 3-phenyl-3-oxopropanoate (576 mg, 3 mmol), *O*-methylisourea hydrogen sulfate (516 mg, 3 mmol), and 4-nitrobenzaldehyde (453 mg, 3 mmol) in 3 mL of dry DMF under nitrogen at room temperature was treated with sodium bicarbonate (756 mg, 9 mmol) and heated at 75 °C for 3–4 h. The reaction mixture was cooled to room temperature, then transferred into water (7 mL) with ice-bath cooling over 1 h, during, which time the product solidified out from the solution. Stirring was continued at room temperature for >3 h, and the product was filtered. The cake was washed with water (10 mL) and dried under vacuum until constant weight was obtained. Compound **3j** (800 mg, 2.1 mmol, 70%) was obtained as a pale-yellow solid. Purification was accomplished by chromatography after the standard extractive workup with EtOAc when the product is not sufficiently crystalline.

4.4. A typical procedure for the NHPI/Co^{II} system catalyzed aerobic oxidation of dihydropyrimidinones 1

A mixture of dihydropyrimidinone **1a** (322 mg, 1 mmol), NHPI (33 mg, 20 mol %), and $Co(OAc)_2 \cdot 4H_2O$ (1 mg, 0.5 mol %) was placed in a 25 mL three-necked flask in $(CH_2Cl)_2$ (4 mL) and stirred at 80 °C under oxygen atmosphere for 2 h. When the starting materials were consumed completely monitored by TLC, the reaction mixture was concentrated by vacuum and then the product was isolated by silica gel column chromatography to give a pale-yellow crystalline solid **2a** 282 mg (yield: 88%).

*4.4.1. Ethyl 1,2-dihydro-2-oxo-4,6-diphenylpyrimidine-5-carboxylate (**2a**).* Pale yellow solid; mp 210–211 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 3H, J=7.2 Hz), 3.91 (q, 2H, J=7.2 Hz), 7.43–7.53 (m, 6H), 7.60–7.63 (m, 4H), 12.99 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2, 61.7, 111.8, 127.3, 127.9, 128.3, 128.6, 131.0, 157.8, 166.2; EI-MS *m*/*z* (relative intensity, %): 320 (31.1), 291 (100.0), 275 (34.5), 149 (23.3), 104 (29.7), 57 (31.7), 43 (35.9); ESI-HRMS: *m*/*z* calcd for $C_{19}H_{16}N_2O_3+H^+$: 321.1234, found 321.1235.

*4.4.2. Ethyl 4-(4-chlorophenyl)-1,2-dihydro-2-oxo-6-phenylpyrimidine-5-carboxylate (**2b**).* White solid; mp 214–215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, J=7.2 Hz), 3.93 (q, 2H, J=7.2 Hz), 7.42–7.55 (m, 5H), 7.57–7.63 (m, 4H), 12.70 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.3, 61.9, 111.9, 127.9, 128.8, 128.9, 131.3, 133.4, 137.5, 157.8, 166.1; EI-MS *m*/*z* (relative intensity, %): 356 (11.1), 354 (36.5), 327 (33.8), 325 (100.0), 311 (13.8), 309 (41.3), 138 (38.6), 140 (12.4), 104 (76.8), 77 (63.8), 51 (41.3), 43 (32.9); ESI-HRMS: *m*/*z* calcd for $C_{19}H_{15}ClN_2O_3+H^+$: 355.0844, found 355.0845.

*4.4.3. Ethyl 4-(4-fluorophenyl)-1,2-dihydro-2-oxo-6-phenylpyrimidine-5-carboxylate (**2c**).* White solid; mp 219–220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, J=7.2 Hz), 3.93 (q, 2H, J=7.2 Hz), 7.15 (dd, 2H, J=8.4 Hz, J=8.4 Hz), 7.45–7.54 (m, 3H), 7.60–7.67 (m, 4H), 13.07 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.3, 61.9, 111.9, 115.8 (d, J=22 Hz), 127.9, 128.7, 130.4 (d, J=9 Hz), 131.3, 157.8, 164.4 (d, J=253 Hz), 166.2; EI-MS *m*/*z* (relative intensity, %): 338 (11.1), 309 (23.5), 149 (23.8), 97 (36.0), 69 (58.8), 57 (73.8), 44 (100); ESI-HRMS: *m*/*z* calcd for $C_{19}H_{15}FN_2O_3+H^+$: 339.1139, found 339.1148.

*4.4.4. Ethyl 4-(3-bromophenyl)-1,2-dihydro-2-oxo-6-phenylpyrimidine-5-carboxylate (**2d**).* White solid; mp 189–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 3H, J=7.2 Hz), 3.95 (q, 2H, J=7.2 Hz), 7.33 (t, 1H, J=8.0 Hz), 7.47–7.57 (m, 4H), 7.60–7.63 (m, 3H), 7.75 (dd, 1H, J=1.6 Hz, J=1.6 Hz), 13.08 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.4, 62.00, 111.9, 122.5, 126.6, 128.0, 128.9, 130.1, 131.1, 131.5, 133.9, 157.7, 165.9; EI-MS *m*/*z* (relative intensity, %): 400 (35.6), 398 (35.0), 371 (96.5), 369 (100), 355 (35.1), 353 (33.5), 172 (21.3), 149 (33.6), 104 (45.0), 77 (26.0), 57 (23.0); ESI-HRMS: *m*/*z* calcd for $C_{19}H_{15}BrN_2O_3+H^+$: 399.0339, found 399.0347.

*4.4.5. Ethyl 1,2-dihydro-4-isopropyl-2-oxo-6-phenylpyrimidine-5-carboxylate (**2e**)*[8a]. Pale yellow solid; mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, 3H, J=6.8 Hz), 1.43 (d, 6H, J=7.2 Hz), 3.29 (m, 1H), 4.04 (q, 2H, J=6.8 Hz), 7.43–7.45 (m, 3H), 7.59 (d, 2H, J=6.4 Hz), 13.00 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.4, 20.6, 31.8, 61.7, 110.9, 127.8, 128.5, 130.7, 158.2, 166.5; EI-MS *m*/*z*: 286 ([M+H$^+$], 287).

*4.4.6. Ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**2f**)*[8c]. Pale yellow solid; mp 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, 3H, J=7.2 Hz), 2.62 (s, 3H), 4.05 (q, 2H, J=7.2 Hz), 7.41–7.51 (m, 3H), 7.60 (d, 2H, J=7.2 Hz), 13.66 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.4, 19.2, 61.5, 111.4, 127.9, 128.3, 130.7, 137.0, 158.3, 166.0; EI-MS *m*/*z* (relative intensity, %): 258 (27.2), 229 (100), 213 (54.3), 185 (25.6), 104 (46.6), 77 (29.4), 42 (34.7).

*4.4.7. Ethyl 1,2-dihydro-4-(4-methoxyphenyl)-6-methyl-2-oxo-pyrimidine-5-carboxylate (**2g**)*[8c]. Pale yellow solid; mp 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (t, 3H, J=7.2 Hz), 2.59 (s, 3H), 3.86 (s, 3H), 4.13 (q, 2H, J=7.2 Hz), 6.94 (d, 2H, J=8.8 Hz), 7.62 (d, 2H, J=8.8 Hz), 12.77 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.6, 19.3, 55.3, 61.5, 111.1, 113.7, 130.0, 158.3, 162.0, 166.5; EI-MS *m*/*z* (relative intensity, %): 288 (54.8), 259 (100), 243 (47.9), 215 (24.3), 134 (25.7), 77 (23.2), 42 (52.7); ESI-HRMS: *m*/*z* calcd for $C_{15}H_{16}N_2O_4+H^+$: 289.1183, found 289.1186.

*4.4.8. Ethyl 1,2-dihydro-4-(3,4,5-trimethoxyphenyl)-6-methyl-2-oxo-pyrimidine-5-carboxylate (**2h**).* Yellow solid; mp 164–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, 3H, J=7.2 Hz), 2.61 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 4.11 (q, 2H, J=7.2 Hz), 6.88 (s, 2H), 13.65 (br s, 1H,

NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.6, 18.6, 56.2, 60.9, 61.7, 105.4, 111.6, 113.7, 140.4, 153.1, 158.3, 166.4; EI-MS *m*/*z* (relative intensity, %): 348 (3.8), 290 (28.6), 197 (58.2), 169 (57.4), 84 (100), 43 (67.9); ESI-HRMS: *m*/*z* calcd for $C_{17}H_{20}N_2O_6$+H^+: 349.1394, found 349.1388.

*4.4.9. Ethyl 4-(4-chlorophenyl)-1,2-dihydro-6-methyl-2-oxo-pyrimidine-5-carboxylate (**2i**)*[8c]. Pale yellow solid; mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, 3H, *J*=7.2 Hz), 2.63 (s, 3H), 4.10 (q, 2H, *J*=7.2 Hz), 7.42 (d, 2H, *J*=8.4 Hz), 7.56 (d, 2H, *J*=8.4 Hz), 13.70 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.5, 18.9, 61.7, 111.3, 128.7, 129.4, 137.2, 158.2, 165.8; EI-MS *m*/*z* (relative intensity, %): 294 (14.0), 292 (41.6), 263 (100), 247 (62.1), 219 (25.9), 138 (36.9), 110 (23.6), 75 (26.0), 42 (78.5); ESI-HRMS: *m*/*z* calcd for $C_{14}H_{13}ClN_2O_3$+H^+: 293.0687, found 293.0692.

*4.4.10. Ethyl 4-(4-fluorophenyl)-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (**2j**).* Pale yellow solid; mp 170–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, 3H, *J*=6.8 Hz), 2.62 (s, 3H), 4.10 (q, 2H, *J*=6.8 Hz), 7.13 (dd, 2H, *J*=8.8 Hz, *J*=8.4 Hz,), 7.63 (dd, 2H, *J*=5.2 Hz, *J*=8.8 Hz), 13.66 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.6, 19.0, 61.7, 111.3, 115.4, 115.5 (*J*=22 Hz), 130.3 (*J*=8 Hz), 158.2, 163.1, 164.4 (*J*=250 Hz), 165.9; EI-MS *m*/*z* (relative intensity, %): 276 (40.9), 247 (100), 203 (28.5), 190 (25.8), 122 (25.1), 42 (14.5); ESI-HRMS: *m*/*z* calcd for $C_{14}H_{13}FN_2O_3$+H^+: 277.0983, found 277.0985.

*4.4.11. Ethyl 1,2-dihydro-4-isopropyl-6-methyl-2-oxopyrimidine-5-carboxylate (**2k**).* Pale yellow solid; mp 164–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (d, 6H, *J*=6.4 Hz), 1.39 (t, 3H, *J*=7.2 Hz), 2.52 (s, 3H), 3.20 (m, 1H), 4.37 (q, 2H, *J*=7.2 Hz), 13.62 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 21.0, 33.4, 61.7, 111.6, 158.8, 165.9; EI-MS *m*/*z* (relative intensity, %): 224 (20.9), 209 (46.5), 195 (62.6), 179 (35.3), 124 (39.5), 110 (32.0), 67 (35.2), 42 (100); ESI-HRMS: *m*/*z* calcd for $C_{11}H_{16}N_2O_3$+Na^+: 247.1053, found 247.1056.

*4.4.12. Ethyl 4-hexyl-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (**2l**).* Pale yellow solid; mp 75–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J*=6.4 Hz), 1.28–1.40 (m, 6H), 1.39 (t, 3H, *J*=7.2 Hz), 1.70 (m, 2H), 2.54 (s, 3H), 2.81(t, 2H, *J*=8.0 Hz), 4.37 (q, 2H, *J*=7.2 Hz), 13.59 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.9, 14.1, 22.4, 28.8, 29.1, 31.4, 61.6, 111.4, 158.3, 165.5; ESI-MS: *m*/*z* 266 ([M+H^+], 267); ESI-HRMS: *m*/*z* calcd for $C_{14}H_{22}N_2O_3$+H^+: 267.1703, found 267.1708.

4.5. A typical procedure for the NHPI/Co^{II} system catalyzed aerobic oxidation of dihydropyrimidines 3

A mixture of dihydropyrimidine **3a** (290 mg, 1 mmol), NHPI (16 mg, 10 mol %), and $Co(OAc)_2 \cdot 4H_2O$ (1 mg, 0.5 mol %) was placed in a 25 mL three-necked flask in $(CH_2Cl)_2$ (4 mL) and stirred at 80 °C under oxygen atmosphere for 1 h. When the starting materials were consumed completely monitored by TLC, the reaction mixture was concentrated by vacuum and then the product was isolated by silica gel column chromatography to give white oil **4a** 278 mg (yield: 97%).

*4.5.1. Ethyl 4-methyl-2-(methylthio)-6-phenylpyrimidine-5-carboxylate (**4a**).* White oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, 3H, *J*=7.2 Hz), 2.57 (s, 3H), 2.61 (s, 3H), 4.15 (q, 2H, *J*=7.2 Hz), 7.43–7.46 (m, 3H), 7.63–7.65 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.6, 14.1, 22.5, 61.6, 120.9, 128.3, 128.4, 130.0, 137.8, 163.6, 165.4, 168.1, 172.5; EI-MS *m*/*z* (relative intensity, %): 288 (100), 259 (62.0), 243 (31.0), 159 (37.0), 115 (46.0), 77 (72.0), 67 (91.2), 45 (88.0); ESI-HRMS: *m*/*z* calcd for $C_{15}H_{16}N_2O_2S$+H^+: 289.1005, found 289.1006.

*4.5.2. Ethyl 4-(4-methoxyphenyl)-6-methyl-2-(methylthio)-pyrimidine-5-carboxylate (**4b**).* White oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, 3H, *J*=7.2 Hz), 2.53 (s, 3H), 2.60 (s, 3H), 3.85 (s, 3H), 4.21 (q, 2H, *J*=7.2 Hz), 6.93–6.96 (m, 2H), 7.63–7.66 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.7, 14.1, 29.6, 55.3, 61.6, 113.9, 120.4, 129.96, 130.02, 161.4, 162.6, 165.1, 168.5, 172.2; EI-MS *m*/*z* (relative intensity, %): 318 (100), 289 (22.0), 243 (11.0), 199 (17.0), 159 (20.0), 103 (18.0), 67 (37.0), 45 (50.0); ESI-HRMS: *m*/*z* calcd for $C_{16}H_{18}N_2O_3S$+H^+: 319.1111, found 319.1118.

*4.5.3. Ethyl 4-(4-chlorophenyl)-6-methyl-2-(methylthio)-pyrimidine-5-carboxylate (**4c**).* Pale yellow solid; mp 60–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, 3H, *J*=7.2 Hz), 2.56 (s, 3H), 2.61 (s, 3H), 4.19 (q, 2H, *J*=7.2 Hz), 7.42 (d, 2H, *J*=8.4 Hz), 7.59 (d, 2H, *J*=8.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.7, 14.1, 22.6, 61.8, 120.7, 128.7, 129.7, 136.1, 136.4, 162.2, 165.6, 167.9, 172.6; EI-MS *m*/*z* (relative intensity, %): 322 (100), 294 (29.8), 277 (15.8), 248 (15.5), 195 (14.8), 163 (10.1), 67 (10.4); ESI-HRMS: *m*/*z* calcd for $C_{15}H_{15}ClN_2O_2S$+H^+: 323.0616, found 323.0611.

*4.5.4. Ethyl 4-isopropyl-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (**4d**).* White oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, 6H, *J*=6.8 Hz), 1.39 (t, 3H, *J*=7.2 Hz), 2.45 (s, 3H), 2.57 (s, 3H), 3.06 (m, 1H), 4.40 (q, 2H, *J*=7.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 14.1, 21.6, 22.6, 33.4, 61.6, 121.1, 164.2, 167.9, 171.9, 172.2; EI-MS *m*/*z* (relative intensity, %): 254 (96.1), 225 (69.8), 211 (37.5), 154 (42.2), 67 (100), 39 (75.4); ESI-HRMS: *m*/*z* calcd for $C_{12}H_{18}N_2O_2S$+H^+: 255.1162, found 255.1167.

*4.5.5. Ethyl 4-methyl-2-(methylthio)pyrimidine-5-carboxylate (**5d**).* White solid; mp 59–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, 3H, *J*=7.2 Hz), 2.60 (s, 3H), 2.77 (s, 3H), 4.38 (q, 2H, *J*=7.2 Hz), 8.94 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.2, 24.4, 61.2, 118.4, 158.7, 164.9, 168.7, 175.3; EI-MS *m*/*z* (relative intensity, %): 212 (100), 184 (60.6), 167 (22.5), 138 (41.5), 53 (11.6); ESI-HRMS: *m*/*z* calcd for $C_9H_{12}N_2O_2S$+H^+: 213.0692, found 213.0696.

*4.5.6. Ethyl 4-hexyl-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (**4f**).* Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J*=6.8 Hz), 1.25–1.37 (m, 6H), 1.39(t, 3H, *J*=7.2 Hz), 1.70 (m, 2H), 2.47 (s, 3H), 2.56 (s, 3H), 2.72 (t, 2H, *J*=7.6 Hz), 4.40 (q, 2H, *J*=7.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.88, 13.94, 22.4, 22.8, 28.6, 29.00, 29.05, 31.5, 35.8, 61.5, 121.5, 164.5, 167.6, 168.0, 172.0; ESI-MS *m*/*z* requires 298, found ([M+H^+], 299); ESI-HRMS: *m*/*z* calcd for $C_{15}H_{24}N_2O_2S$+H^+: 297.1631, found 297.1638.

*4.5.7. Ethyl 4-(4-fluorophenyl)-2-(methylthio)-6-phenylpyrimidine-5-carboxylate (**4g**).* White solid; 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 3H, *J*=7.2 Hz), 2.65 (s, 3H), 4.04 (q, 2H, *J*=7.2 Hz), 7.12–7.17 (m, 2H), 7.43–7.49 (m, 3H), 7.66–7.72 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.4, 14.2, 61.8, 115.5 (d, *J*=21.1 Hz), 120.6, 128.3, 128.4, 130.1, 130.5 (d, *J*=8.0 Hz), 133.4 (d, *J*=3.0 Hz), 137.3, 163.0, 163.9 (d, *J*=250.5 Hz), 164.4, 168.0, 172.7; EI-MS *m*/*z* (relative intensity, %): 368 (100), 339 (35.5), 273 (36.0), 216 (43.1), 149 (73.8), 95 (58.3), 43 (63.1); ESI-HRMS: *m*/*z* calcd for $C_{20}H_{17}FN_2O_2S$+H^+: 369.1068, found 369.1063.

*4.5.8. Ethyl 4-isopropyl-2-(methylthio)-6-phenylpyrimidine-5-carboxylate (**4h**)*[8a]. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, 3H, *J*=7.2 Hz), 1.32 (d, 6H, *J*=6.8 Hz), 2.62 (s, 3H), 3.20 (m, 1H), 4.14 (q, 2H, *J*=7.2 Hz), 7.41–7.45 (m, 3H), 7.62–7.65 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.6, 14.2, 21.6, 33.1, 61.6, 120.4, 128.2, 128.4, 129.9, 137.9, 163.6, 168.2, 172.5, 172.9; EI-MS *m*/*z* (relative intensity, %): 316 (100), 287 (42.7), 216 (17.4), 129 (12.4), 77 (5.4), 41 (3.2).

*4.5.9. Ethyl 2-(methylthio)-6-phenylpyrimidine-5-carboxylate (**5h**)*[8a]. White solid; mp 57–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, 3H, *J*=7.2 Hz), 2.63 (s, 3H), 4.20 (q, 2H, *J*=7.2 Hz), 7.44–7.49

(m, 3H), 7.58–7.60 (m, 2H), 8.91 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.7, 14.3, 61.5, 119.3, 128.1, 128.3, 130.1, 137.5, 158.8, 166.0, 166.1, 175.0; EI-MS *m*/*z* (relative intensity, %): 274 (100), 245 (57.8), 200 (24.9), 155 (15.0), 77 (8.4), 53 (8.5).

*4.5.10. Ethyl 2-methoxy-6-methyl-4-(4-nitrophenyl)-pyrimidine-5-carboxylate (**4i**).* Pale yellow solid; mp 84–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, 3H, *J*=7.2 Hz), 2.62 (s, 3H), 4.09 (s, 3H), 4.18 (q, 2H, *J*=7.2 Hz), 7.80 (dd, 2H, *J*=7.2 Hz, *J*=2.0 Hz), 8.30 (dd, 2H, *J*=7.2 Hz, *J*=2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.7, 23.0, 55.3, 62.0, 120.1, 123.6, 129.4, 144.0, 148.7, 164.4, 164.6, 167.4, 169.7; EI-MS *m*/*z* (relative intensity, %): 317 (78.5), 288 (100), 272 (45.3), 242 (41.0), 196 (20.1), 150 (10.5), 67 (10.3); ESI-HRMS: *m*/*z* calcd for $C_{15}H_{15}N_3O_5+H^+$: 318.1084, found 318.1074.

*4.5.11. Ethyl 2-methoxy-4-(4-nitrophenyl)-6-phenylpyrimidine-5-carboxylate (**4j**).* Pale yellow solid; mp 104–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J*=7.2 Hz), 4.04 (q, 2H, *J*=7.2 Hz), 4.15 (s, 3H), 7.45–7.53 (m, 3H), 7.69 (ddd, 2H, *J*=7.2, 4.0, 2.0 Hz), 7.86 (ddd, 2H, *J*=9.2, 4.0, 2.4 Hz), 8.32 (ddd, 2H, *J*=9.2, 4.0, 2.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.4, 55.4, 62.0, 119.9, 123.5, 128.2, 128.5, 129.5, 130.4, 137.0, 143.4, 148.6, 164.6, 165.0, 167.6, 167.9; EI-MS *m*/*z* (relative intensity, %): 379 (19.3), 350 (100), 316 (41.7), 288 (60.3), 226 (25.8), 129 (31.4), 69 (49.0), 43 (75.1); ESI-HRMS: *m*/*z* calcd for $C_{20}H_{17}N_3O_5+H^+$: 380.1241, found 380.1233.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Grant No. 20902040) and the Fundamental Research Funds for the Central Universities (Grant No. lzujbky-2009-74) for financial support. We also thank Dr. Wei Yu for helpful discussions.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.05.105.

References and notes

1. (a) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990; (b) *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., De Jonge, C. R. H. I., Eds.; Plenium: New York, NY, 1986; (c) Bäckvall, J.-E. *Modern Oxidation Methods*; Wiley-VCH: Weinheim, 2004; (d) Ingold, K. U.; MacFaul, P. A. In *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*; Meunier, B., Ed.; Imperial College: London, 2000; pp 45–89.
2. A related oxidative dehydrogenation of dihydropyridines and pyrazolines: (a) Yadav, J. S.; Subba Reddy, B. V.; Sabitha, G.; Kiran Kumar Reddy, G. S. *Synthesis* **2000**, 1532–1534; (b) Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. *J. Org. Chem.* **1997**, *62*, 3582–3585; (c) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 5069–5073; (d) Zhu, X.-Q.; Zhao, B.-J.; Cheng, J.-P. *J. Org. Chem.* **2000**, *65*, 8158–8163; (e) Gladstone, W. A. F.; Norman, R. O. C. *J. Chem. Soc., Chem. Commun.* **1966**, 1536–1540; (f) Sabitha, G.; Reddy, G. S.; Reddy, C. S.; Fatima, N.; Yadav, J. S. *Synthesis* **2003**, 1267–1271; (g) A related oxidative synthesis of benzoxazoles: Chang, J.; Zhao, K.; Pan, S. *Tetrahedron Lett.* **2002**, *43*, 951–954; (h) Praveen, C.; Kumar, K. H.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2369–2374.
3. A related aerobic oxidative dehydrogenation of dihydropyridines and pyrazolines: (a) Mashraqui, S. H.; Karnik, M. A. *Tetrahedron Lett.* **1998**, *39*, 4895–4898; (b) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955–3957; (c) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis* **2004**, 1015–1020; (d) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. *Tetrahedron Lett.* **2005**, *46*, 2775–2777; (e) A related aerobic oxidative synthesis of benzoxazoles: Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713–3715; (f) Kidwai, M.; Bansal, V.; Saxena, A.; Aerryb, S.; Mozumdar, S. *Tetrahedron Lett.* **2006**, *47*, 8049–8053.
4. (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888; (b) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587–590; (c) Kappe, C. O.; Roschger, P. *J. Heterocycl. Chem.* **1989**, *26*, 1555–1560.
5. (a) Carraro, F.; Pucci, A.; Naldini, A.; Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Brullo, C.; Fossa, P.; Menozzi, G.; Mosti, L.; Manetti, F.; Botta, M. *J. Med. Chem.* **2004**, *47*, 1595–1598; (b) Manetti, F.; Santucci, A.; Locatelli, G. A.; Maga, G.; Spreafico, A.; Serchi, T.; Orlandini, M.; Bernardini, G.; Caradonna, N. P.; Spallarossa, A.; Brullo, C.; Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Hoffmann, O.; Bologna, M.; Angelucci, A.; Botta, M. *J. Med. Chem.* **2007**, *50*, 5579–5588.
6. (a) Mugnaini, C.; Alongi, M.; Togninelli, A.; Gevariya, H.; Brizzi, A.; Manetti, F.; Bernardini, C.; Angeli, L.; Tafi, A.; Bellucci, L.; Corelli, F.; Massa, S.; Maga, G.; Samuele, A.; Facchini, M.; Clotet-Codina, I.; Armand-Ugón, M.; Esté, J. A.; Botta, M. *J. Med. Chem.* **2007**, *50*, 6580–6595; (b) Mai, A.; Artico, M.; Rotili, D.; Tarantino, D.; Clotet-Codina, I.; Armand-Ugon, M.; Ragno, R.; Simeoni, S.; Sbardella, G.; Nawrozkij, M. B.; Samuele, A.; Maga, G.; Este, J. A. *J. Med. Chem.* **2007**, *50*, 5412–5424.
7. Eynde, J. J.; Audiart, N.; Canonne, V.; Michel, S.; Haverbeke, Y. V.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967–1978.
8. (a) Yamamoto, K.; Chen, Y. G.; Buono, F. G. *Org. Lett.* **2005**, *7*, 4673–4676; (b) Shanmugam, P.; Perumal, P. T. *Tetrahedron* **2006**, *62*, 9726–9734 and references therein; (c) Karade, N. N.; Gampawar, S. V.; Kondre, J. M.; Tiwari, G. B. *Tetrahedron Lett.* **2008**, *49*, 6698–6700.
9. For reviews, see: (a) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393–427; (b) Sheldon, R. A.; Arends, I. W. C. E.; Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774–781; (c) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051–1071; (d) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800–3842; (e) Galli, C.; Gentili, P.; Lanzalunga, O. *Angew. Chem., Int. Ed.* **2008**, *47*, 4790–4796; (f) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979–1993; (g) Piera, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506–3523.
10. (a) Han, B.; Liu, Q.; Liu, Z.-G.; Mu, R.-Z.; Zhang, W.; Liu, Z.-L.; Yu, W. *Synlett* **2005**, 2333–2334; (b) Han, B.; Liu, Z.-G.; Liu, Q.; Yang, L.; Liu, Z.-L.; Yu, W. *Tetrahedron* **2006**, *62*, 2492–2496; (c) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330–9333.
11. (a) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520–4526; (b) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem* **1997**, *62*, 6810–6813.
12. (a) Hirai, N.; Kagayama, T.; Tatsukawa, Y.; Sakaguchib, S.; Ishii, Y. *Tetrahedron Lett.* **2004**, *45*, 8277–8280; (b) Hirai, N.; Tatsukawa, Y.; Kameda, M.; Sakaguchib, S.; Ishii, Y. *Tetrahedron* **2006**, *62*, 6695–6699.
13. (a) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. *J. Org. Chem.* **1995**, *60*, 3934–3935; (b) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Org. Process Res. Dev.* **2000**, *4*, 94–97; (c) Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 222–224; (d) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1120–1123.
14. Mulder, P.; Litwinienko, G.; Lin, S.; MacLean, P. D.; Barclay, L. R. C.; Ingold, K. U. *Chem. Res. Toxicol.* **2006**, *19*, 79–85.
15. Baciocchi, E.; Gerini, M. F.; Lanzalunga, O. *J. Org. Chem.* **2004**, *69*, 8963–8966.
16. (a) Mayer, J. M.; Hrovat, D. A.; Thomas, J. L.; Borden, W. T. *J. Am. Chem. Soc.* **2002**, *124*, 11142–11147; (b) Rhile, I. J.; Mayer, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 12718–12719; (c) Mayer, J. M. *Annu. Rev. Phys. Chem.* **2004**, *55*, 363–390.