Oxidation of Biginelli Reaction Products: Synthesis of 2-Unsubstituted 1,4-Dihydropyrimidines, Pyrimidines, and 2-Hydroxypyrimidines

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Abstract: We have devised a new route toward 2-unsubstituted pyrimidine derivatives from the Biginelli product, dihydropyrimidin-2(1*H*)-thiones in two steps: Oxidation of dihydropyrimidin-2(1*H*)-thiones using oxone on wet alumina or hydrogen peroxide in the presence of catalytic amount of vanadyl sulfate provided 1,4-dihydropyrimidine, which was further oxidized to 2-unsubstituted pyrimidines by the treatment of $KMnO_4$. Oxidation of dihydropyrimidin-2(1*H*)-ones by $KMnO_4$ formed 2-hydroxypyrimidine in excellent yield, whereas attempted direct desulfurative aromatization of dihydropyrimidin-2(1*H*)-thiones by $KMnO_4$ resulted in the formation of 2-hydroxypyrimidines, the same products obtained in the oxidation of dihydropyrimidin-2(1*H*)-one.

Key words: Biginelli reaction, desulfurative oxidation, 2-unsubstituted pyrimidine, 1,4-dihydropyrimidine, 2-hydroxypyrimidine

Multicomponent reactions have received wide attention due to the high efficiency of making multiple bonds in a one-pot manner and the facile generation of diversity. As one such reaction, the Biginelli reaction which forms dihydropyrimidinone derivatives from the reaction of aldehyde, keto ester, and urea or thiourea has attracted renewed interest due to the prominent pharmacological activity of these products.[1] Accordingly, the original harsh reaction conditions using strong acid were modified by employing mild Lewis or Brønsted acids to enhance the yield and to broaden functional-group tolerance significantly: use of $InCl_3$,[2] $InBr_3$,[3] $CeCl_3 \cdot 7H_2O$,[4] $BiCl_3$,[5] heteropoly acid,[6] $LiClO_4$,[7] TMSCl,[8] TMSI,[9] $FeCl_3 \cdot 6H_2O$,[10] phenylpyruvic acid,[11] $LaCl_3$ with catalytic HCl,[12] and $BF_3 \cdot OEt_2$/CuCl[13] are representative examples to date.

Although there have been intensive investigations on the reaction itself, postmodification of the Biginelli product to a useful intermediate such as a pyrimidine derivative is limited. Earlier examples of the oxidation of 3,4-dihydropyrimidin-2(1*H*)-one to 2-hydroxylpyrimidine using HNO_3,[14] DDQ,[15] and Pd/C[16] as well as electrochemical oxidation[17] could not be used in general due to low functional-group tolerance caused by harsh reaction conditions, discharge of environmentally toxic effluent, and requirement of special equipment. These shortcomings were improved significantly by the recent discovery of oxidation using a combination of *tert*-butylhydroperoxide with either copper(II) catalyst[18] or stoichiometric (diacetoxyiodo)benzene.[19] In contrast to the established oxidation of the Biginelli product, dihydropyrimidin-2(1*H*)-one to 2-hydroxypyrimidine, there is no report on the oxidation of dihydropyrimidin-2(1*H*)-thiones, which might provide a new route towards the valuable pharmacophore of 2-unsubstituted pyrimidines via desulfurative oxidation. This class of compounds has only been accessible from the condensation of β-alkoxy-α-acylacrylates with amidines in poor yield of 10–60%.[20] Herein, we report the development of a new route towards 2-unsubstituted pyrimidine from the oxidation of dihydropyrimidin-2(1*H*)-thione and facile oxidation of dihydropyrimidin-2(1*H*)-one and -thione to 2-hydroxypyrimidine.

We were intrigued by the feasibility of the desulfurative oxidation of the Biginelli product, pyrimidin-2(1*H*)-thione as a route to 2-unsubstituted pyrimidine derivatives[21] on the basis of our early protocol used for the desulfurization of 2-mercaptoimidazole.[22] Thus, when dihydropyrimidin-2-thione **1a** was treated with hydrogen peroxide in the presence of catalytic amount of vanadyl sulfate, dihydropyrimidine **2a** was obtained in moderate yield of 48% (entry 1, Table 1). The structure of **2a** was assigned as 1,4-dihydropyrimidine instead of tautomeric 3,4-dihydropyrimidine on the basis of the singlet proton (δ = 5.40 ppm) at the C-4 position in the ^{1}H NMR spectrum – this proton should appear as a doublet through coupling with the N–H proton in 3,4-dihydropyrimidine. These conditions are generally applicable to various substrates to provide dihydropyrimidines in moderate yield, and the results are gathered in Table 1. To improve the yield we tested various oxidizing reagents. *m*-Chloroperoxybenzoic acid led to complex mixture without any sign of the formation of the desired product, whereas Oxone on wet alumina[23] converted 2-thiones into their 1,4-dihydropyrimidine derivatives in slightly better yields (entries 1 and 3) than that using hydrogen peroxide.[24] Major side product of this reaction was found to be dihydropyrimidin-2(1*H*)-one, which is formed presumably from the cyclic sulfite intermediate **9** as illustrated in Scheme 1. Further oxidation by $KMnO_4$[25] aromatized **2a–e** to pyrimidine **3a–e** in good yields[26] as shown in Table 1.

From the successful aromatization of **2** to **3** by $KMnO_4$, we anticipated that dihydropyrimidin-2(1*H*)-one could be oxidized by $KMnO_4$ to 2-hydroxypyrimidine as well. Delightedly, treatment of dihydropyrimidin-2(1*H*)-one with

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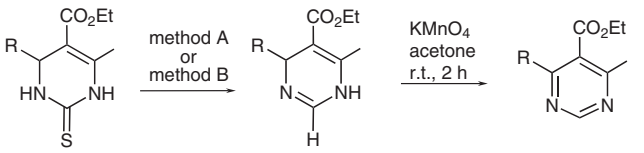
Table 1 Synthesis of 1,4-Dihydropyrimidines and 2-Unsubstituted Pyrimidines



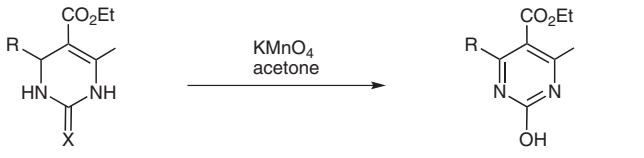
1a–e **2a–e** **3a–e**

Entry	R		Product	Yield (%)	Product	Yield (%)
1	**1a**	Ph	**2a**	48[a] (60[b])	**3a**	73
2	**1b**	4-EtC_6H_4	**2b**	43[a]	**3b**	73
3	**1c**	*n*-C_5H_{11}	**2c**	35[a] (50[b])	**3c**	81
4	**1d**	$PhCH_2CH_2$	**2d**	73[a]	**3d**	87
5	**1e**	4-FC_6H_4	**2e**	50[a]	**3e**	76

[a] Yield using Method A: 30% H_2O_2 (3.7 equiv), $VOSO_4 \cdot xH_2O$ (0.002 equiv), H_2O–EtOH, 50 °C, 8–12 h.
[b] Yield using Method B: Oxone (3.2–3.7 equiv), wet Al_2O_3, $CHCl_3$, r.t., 5–8 h.

$KMnO_4$ (2.5 equiv) provided 2-hydroxypyrimidine in good yield (Table 2).[27] With facile oxidation of 1,4-dihydropyrimidine and dihydropyrimidin-2(1*H*)-one by $KMnO_4$ in hands, we were intrigued by the possibility of direct desulfurative oxidation of dihydropyrimidin-2(1*H*)-thione to 2-unsubstituted pyrimidine. However, contrary to our expectation, oxidation of thiones by $KMnO_4$ (4.5 equiv) resulted in the exclusive formation of 2-hydroxypyrimidine, the same product formed from the oxidation of dihydropyrimidin-2-one (Table 2).

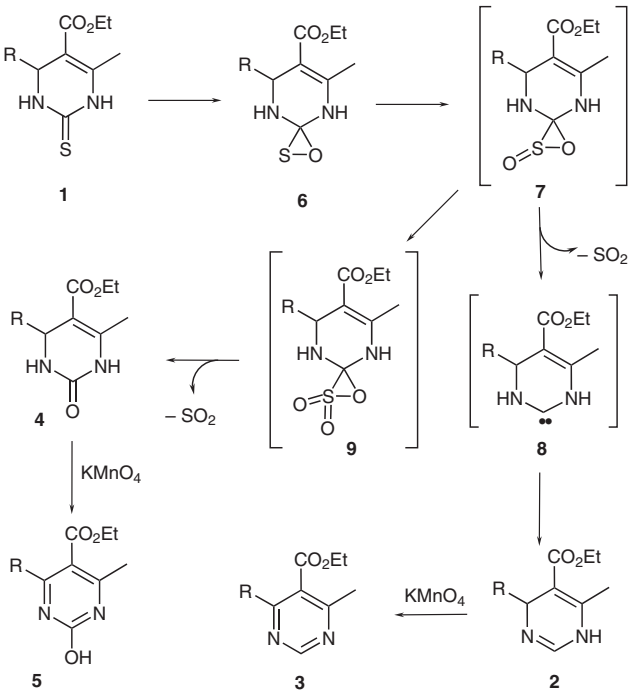
Table 2 Oxidation of Dihydropyrimidin-2(1*H*)-ones and -thiones by $KMnO_4$



4a–e X = O
1a–e X = S
5a–e

Entry	R	Product	Yield (%) from **4a–e**	Yield (%) from **1a–e**
1	Ph	**5a**	81	68
2	4-EtC_6H_4	**5b**	62	44
3	*n*-C_5H_{11}	**5c**	79	73
4	$PhCH_2CH_2$	**5d**	63	35
5	4-FC_6H_4	**5e**	79	65

On the basis of these observations, we tentatively postulated the mechanism of the oxidation reaction as in Scheme 1. When using mild oxidant such as hydrogen peroxide/vanadyl sulfate or Oxone on wet alumina, the thione group of **1** was oxidized to the cyclic sulfinate **7** which loses sulfur dioxide to form transient N-heterocyclic carbene species **8**, and its spontaneous rearrangement provides the dihydropyrimidine **2** as a major product. On the other hand, when strong oxidant such as $KMnO_4$ was used, the cyclic sulfinate intermediate **7** is rapidly oxidized to its sulfite **9**, which loses sulfur dioxide to form dihydropyrimidin-2-one and its further oxidation resulted in the exclusive formation of 2-hydroxypyrimidine **5**.



Scheme 1 Proposed mechanism

In conclusion, we have devised a new route toward 2-unsubstituted pyrimidine derivatives from the Biginelli product, dihydropyrimidin-2(1*H*)-thiones, in two steps. Oxidation of dihydropyrimidin-2(1*H*)-thiones using oxone on wet alumina or hydrogen peroxide in the presence of catalytic amount of vanadyl sulfate provided 1,4-dihydropyrimidine, which was further oxidized to 2-unsubstituted pyrimidines by the treatment of $KMnO_4$. Oxidation of dihydropyrimidin-2(1*H*)-ones by $KMnO_4$ formed 2-hydroxypyrimidine products in excellent yield, whereas attempted direct desulfurative aromatization of dihydropyrimidin-2(1*H*)-thiones by $KMnO_4$ resulted in the formation of 2-hydroxypyrimidines, the same products obtained in the oxidation of dihydropyrimidin-2(1*H*)-one.

References and Notes

(1) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.
(2) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.

(3) Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002**, *58*, 4801.
(4) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587.
(5) Ramalinga, K.; Vijayalakshmi, P.; Kaimala, T. N. B. *Synlett* **2001**, 863.
(6) Rafiee, E.; Jafari, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2463.
(7) Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341.
(8) Zhu, Y. L.; Huang, S. L.; Pan, Y. J. *Eur. J. Org. Chem.* **2005**, 2354.
(9) Sabitha, G.; Reddy, G. K. K.; Reddy, C. S.; Yadav, J. S. *Synlett* **2003**, 858.
(10) Lu, J.; Ma, H. *Synlett* **2000**, 63.
(11) Abelman, M. M.; Smith, S. C.; James, D. R. *Tetrahedron Lett.* **2003**, *44*, 4559.
(12) Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075.
(13) Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454.
(14) Mitsushita, A.; Oda, M.; Kawachi, Y.; Chika, J.-i. WO 03006437, **2003**.
(15) Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437.
(16) Kappe, C. O.; Roschger, P. *J. Heterocycl. Chem.* **1989**, *26*, 1555; this Pd/C dehydrogenation without the use of oxidant requires rigorous conditions (210 °C) in Ph_2O.
(17) Kadis, V.; Strandins, J.; Khanina, E. L.; Duburs, G. *Electrochim. Acta* **1989**, *34*, 899.
(18) Yamamoto, K.; Chen, Y. G.; Buono, F. G. *Org. Lett.* **2005**, *7*, 4673.
(19) Karade, N. N.; Gampawar, S. V.; Kondre, J. M.; Tiwari, G. B. *Tetrahedron Lett.* **2008**, *49*, 6698.
(20) (a) Kress, T. J. *Heterocycles* **1994**, *38*, 1380. (b) Draper, R. W. WO 2005007608, **2005**. (c) Palani, A.; Shapiro, S.; Clader, J. W.; Greenlee, W. J.; Vice, S. F.; McCombie, S.; Cox, K.; Stizki, J.; Baroudy, B. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 709. (d) McCombie, S. W.; Tagat, J. R.; Vice, S. F.; Lin, S.-I.; Steensma, R.; Palani, A.; Neustadt, B. R.; Baroudy, B. M.; Strizki, J. M.; Enders, M.; Cox, K.; Dan, N.; Chou, C.-C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 567.
(21) (a) Khanina, E. L.; Zolotoyabko, R. M.; Muceniece, D.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1989**, 1076. (b) Kanina, E. L.; Mucenice, D.; Kadysh, V. P.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1986**, 1223; in these references, pyrimidin-2-thione or its thioether derivative was reduced by Raney nickel to provide 1,4-dihydropyrimidine.
(22) Chang, J. H.; Lee, K. W.; Nam, D. H.; Kim, W. S.; Shin, H. *Org. Process Res. Dev.* **2002**, *6*, 674.
(23) Greenhalgh, R. P. *Synlett* **1992**, 235.
(24) **General Procedure for the Preparation of 1,4-Dihydropyrimidines 2a–e**
To a stirred mixture of **1a** (1 g, 3.62 mmol) and a catalytic amount of vanadium sulfate (0.0072 g, 10 mol%) in EtOH (2.5 mL) and H_2O (2.5 mL) was added dropwise 30% H_2O_2 (1.52 g, 13.38 mmol) over 1 h maintaining the reaction temperature at about 50 °C. After 8–12 h, the mixture was cooled and volatiles were evaporated under vacuum. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (30 mL). The separated organic layer was dried with $MgSO_4$, filtered, and concentrated to afford crude **2a**. Column chromatography with EtOAc–*n*-hexane gave **2a** as a white solid (397 mg, 48%).
Spectroscopic Data
Compound **2a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.30 (s, 1 H), 7.30–7.16 (m, 5 H), 5.40 (s, 1 H), 3.97 (q, *J* = 4.0 Hz, 2 H), 2.22 (s, 3 H), 1.12 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 145.6, 143.3, 128.9, 127.7, 127.6, 100.7, 60.2, 58.0, 19.3, 14.6. ESI-MS: *m/z* = 245.3 [M + 1].
Compound **2b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (br s, 1 H), 7.26–6.92 (m, 4 H), 5.48 (s, 1 H), 4.08 (q, *J* = 4.0 Hz, 2 H), 2.62 (q, *J* = 4.0 Hz, 2 H), 2.22 (s, 3 H), 1.26–1.15 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 145.6, 144.4, 143.9, 142.8, 128.4, 127.5, 101.0, 60.2, 57.2, 28.9, 18.8, 15.8, 14.6. ESI-MS: *m/z* = 273.4 [M + 1].
Compound **2c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13 (s, 1 H), 9.91 (s, 1 H), 4.83 (t, *J* = 4.0 Hz, 1 H), 4.26 (m, 2 H), 2.48 (s, 3 H), 1.79–1.14 (m, 11 H), 0.87 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 161.1, 142.7, 107.4, 61.7, 52.5, 51.7, 47.0, 36.9, 31.6, 23.3, 22.7, 17.9, 14.6, 14.3. ESI-MS: *m/z* = 239.3 [M + 1].
Compound **2d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 1 H), 7.28–7.14 (m, 5 H), 4.63 (t, *J* = 4.0 Hz, 1 H), 4.18 (m, 2 H), 2.80–2.67 (m, 2 H), 2.28 (s, 3 H), 1.91–1.82 (m, 2 H), 1.26 (t, *J* = 3.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 165.8, 165.7, 144.5, 141.1, 128.9, 128.7, 126.5, 103.2, 103.1, 60.8, 60.4, 52.3, 38.3, 30.9, 18.6, 14.7. ESI-MS: *m/z* = 271.4 [M + 1].
Compound **2e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–6.99 (m, 4 H), 5.57 (s, 1 H), 5.40 (d, *J* = 4.0 Hz, 1 H), 4.09 (m, 2 H), 2.31 (s, 3 H), 1.20 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 162.5 (d, *J* = 250.0 Hz), 145.1, 142.6, 141.4, 129.2 (d, *J* = 10.0 Hz), 115.6 (d, *J* = 20.0 Hz), 115.5, 101.2, 60.3, 57.4, 19.5, 14.6. ESI-MS: *m/z* = 263.3 [M + 1].
(25) (a) Girke, W. P. K. *Chem. Ber.* **1979**, *112*, 1. (b) de Bie, D. A.; Nagel, A.; van der Plas, H. C.; Koudijs, A. *Tetrahedron Lett.* **1979**, 649.
(26) **General Procedure for the Preparation of 2-Unsubstituted Pyrimidines 3a–e**
To a stirred solution of **2a** (100 mg, 0.41 mmol) in acetone (2 mL) was added $KMnO_4$ (87 mg, 0.55 mmol). After the complete consumption of **2a**, excess of $KMnO_4$ was decomposed by the addition of 2-PrOH. The reaction mixture was filtered through Celite and washed thoroughly with acetone (10 mL). Removal of solvent afforded product **3a** (72mg, 73%) as a white solid.
Spectroscopic Data
Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1 H), 7.68–7.43 (m, 5 H), 4.24 (q, *J* = 4.0 Hz, 2 H), 2.57 (s, 3 H), 1.10 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 164.7, 162.9, 157.8, 137.2, 131.8, 131.5, 129.9, 128.3, 128.0, 125.7, 61.7, 22.3, 13.4. ESI-MS: *m/z* = 243.4 [M + 1].
Compound **3b**: ^{1}H NMR(400 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 7.60 (d, *J* = 4.0 Hz, 2 H), 7.37 (d, *J* = 4.0 Hz, 2 H), 4.26 (q, *J* = 4.0 Hz, 2 H), 2.73 (q, *J* = 4.0 Hz, 2 H), 2.62 (s, 3 H), 1.28 (t, *J* = 2.7 Hz, 3 H), 1.13 (t, *J* = 2.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 165.2, 163.6, 158.4, 147.2, 135.8, 128.8, 128.6, 126.2, 62.3, 29.1, 22.9, 15.8, 14.1. ESI-MS: *m/z* = 271.3 [M + 1].
Compound **3c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (s, 1 H), 4.48 (q, *J* = 4.0 Hz, 2 H), 2.79 (t, *J* = 4.0 Hz, 2 H), 2.54 (s, 3 H), 1.77–1.22 (m, 9 H), 0.92 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 167.7, 164.2, 158.3, 62.2, 36.1, 31.9, 28.9, 22.9, 22.7, 14.4, 14.2. ESI-MS: *m/z* = 237.3 [M + 1].
Compound **3d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.02 (s, 1 H), 7.40–7.00 (m, 5 H), 4.44 (q, *J* = 4.0 Hz, 2 H), 3.11–3.02 (m, 4 H), 2.54 (s, 3 H), 1.40 (t, *J* = 3.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 166.8, 164.6, 158.5, 128.9, 128.8, 127.2, 126.7, 62.4, 38.2, 35.3, 23.2, 14.6. ESI-MS: *m/z* = 271.4 [M + 1].

Compound **3e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 7.70–7.65 (m, 2 H), 7.21–7.11 (m, 2 H), 4.27 (q, *J* = 4.0 Hz, 2 H), 2.63 (s, 3 H), 1.18 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 164.4 (d, d, *J* = 230.0 Hz), 164.0, 162.4, 158.5, 134.0, 131.0 (d, *J* = 10.0 Hz), 126.2, 116.2 (d, *J* = 20.0 Hz), 62.5, 23.0, 14.1. ESI-MS: *m/z* = 261.3 [M + 1].

(27) **General Procedure for the Preparation of 2-Hydroxypyrimidines 5a–e**

To a stirred solution of **4a** (1.0 g, 3.84 mmol) in acetone (20 mL) was added $KMnO_4$ (1.52 g, 9.60 mmol). After the complete consumption of **4a**, the excess $KMnO_4$ was decomposed by the addition of 2-PrOH. The reaction mixture was filtered through Celite and washed thoroughly with acetone (30 mL). Removal of solvent afforded product **5a** (670mg, 81%) as a white solid.

Spectroscopic Data

Compound **5a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.41 (m, 5 H), 4.05 (q, *J* = 4.0 Hz, 2 H), 2.62 (s, 3 H), 0.94 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 164.7, 162.9, 157.8, 137.2, 131.8, 131.7, 131.5, 129.9, 128.3, 128.0, 125.7, 61.7, 22.3, 13.4. ESI-MS: *m/z* = 259.3 [M + 1].

Compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.13 (m, 4 H), 4.80–4.26 (m, 2 H), 3.01 (q, *J* = 4.0 Hz, 2 H), 2.84 (s, 1 H), 2.69–2.45 (m, 2 H), 2.30 (s, 3 H), 1.26 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 141.0, 140.4, 129.0, 128.8, 128.7, 126.9, 126.8, 62.2, 38.8, 31.8, 31.0, 30.7, 30.1, 25.5, 14.6. ESI-MS: *m/z* = 287.3 [M + 1].

Compound **5c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.42 (q, *J* = 2.0 Hz, 2 H), 2.80 (t, *J* = 2.0 Hz, 2 H), 2.53 (s, 3 H), 1.73–1.26 (m, 9 H), 0.90 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 158.7, 111.8, 62.1, 32.0, 31.8, 31.5, 22.8, 14.6, 14.29, 14.26. ESI-MS: *m/z* = 253.3 [M + 1].

Compound **5d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.13 (m, 5 H), 4.80–4.26 (m, 2 H), 3.01 (q, *J* = 4.0 Hz, 2 H), 2.84 (s, 1 H), 2.69–2.45 (m, 2 H), 2.30 (s, 3 H), 1.26 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 165.8, 165.7, 144.5, 141.1, 128.9, 128.7, 126.5, 103.2, 103.1, 60.8, 52.3, 38.3, 30.9, 18.6, 14.7. ESI-MS: *m/z* = 287.3 [M + 1].

Compound **5e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–6.97 (m, 4 H), 4.11 (q, *J* = 4.0 Hz, 2 H), 2.62 (s, 3 H), 1.02 (t, *J* = 2.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 162.4 (d, *J* = 250.0 Hz), 146.4, 139.7, 139.6, 128.4 (d, *J* = 10.0 Hz), 115.5 (d, *J* = 20.0 Hz), 101.4, 60.1, 55.0, 18.5, 14.2. ESI-MS: *m/z* = 277.3 [M + 1].