Tetrahedron Letters 49 (2008) 6698–6700

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A novel combination of (diacetoxyiodo)benzene and *tert*-butylhydroperoxide for the facile oxidative dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones

Nandkishor N. Karade *, Sumit V. Gampawar, Jeevan M. Kondre, Girdharilal B. Tiwari

School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded 431 606, Maharashtra, India

ARTICLE INFO

Article history:
Received 7 July 2008
Revised 6 September 2008
Accepted 10 September 2008
Available online 13 September 2008

Keywords:
Biginelli reaction
Dehydrogenation
1,2-Dihydropyrimidine
Hypervalent iodine
(Diacetoxyiodo)benzene
tert-Butylhydroperoxide

ABSTRACT

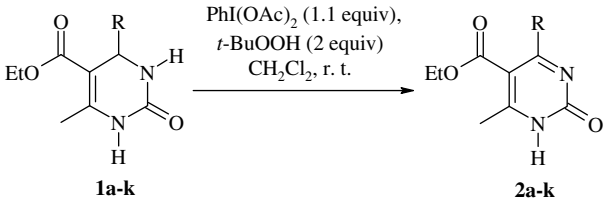
A clean and efficient oxidative dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones to 1,2-dihydropyrimidines has been achieved through a novel combination of (diacetoxyiodo)benzene and *tert*-butylhydroperoxide in CH_2Cl_2.

Multi-functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) obtained from the Biginelli reaction have been used as potent calcium channel blockers, antihypertensive agents, and neuropeptide Y antagonists.[1] The oxidative dehydrogenation of Biginelli DHPMs provides an efficient access to the corresponding 1,2-dihydropyrimidines. However, despite the fact that pyrimidines are found in a wide range of biologically active molecules,[2] there are few methods available to convert efficiently Biginelli DHPMs to 1,2-dihydropyrimidines.[3] In contrast to 1,4-dihydropyridines (DHPs) of the Hantzsch type, where aromatization to pyridines is typically an easy process, the dehydrogenation of Biginelli DHPMs is more difficult.[4] This is mainly due to the sensitivity of the methyl group at C-6 to oxidizing agents such as SeO_2.[5] The DHPM ring was also found to be inert to dehydrogenation using DDQ as an oxidizing agent.[6] The operationally less convenient electrochemical oxidation at a graphite electrode[7] and oxidation with CrO_3 in the presence of H_2SO_4, AcOH, and Ac_2O at 0–10 °C can be utilized for the dehydrogenation of DHPMs.[8] Another dehydrogenation method requires a high temperature of 230 °C involving oxidation with palladium on charcoal.[9] However, this method cannot be applied to the dehydrogenation of DHPMs with an ester functionality at the 5-position. The dehydrogenation of DHPMs is achieved effectively using 60% nitric acid[10] at 0 °C and using CAN/$NaHCO_3$.[11] Recently, a mild procedure for the oxidative dehydrogenation of DHPMs with catalytic amounts of a copper salt, K_2CO_3, and *tert*-butylhydroperoxide was reported.[12] A literature survey suggests that DHPMs have proven to be quite stable toward a variety of oxidizing agents yielding 1,2-dihydropyrimidines under typical reaction conditions. Thus, there is a need to develop a more efficient and practical method for the dehydrogenation of DHPMs.

There has been increasing interest from organic chemists in the oxidizing properties of hypervalent iodine compounds.[13] (Diacetoxyiodo)benzene [DIB, $PhI(OAc)_2$] is the parent member of the hypervalent iodine reagent family and is environmentally benign, easy to handle, and commercially available, and is similar in reactivity to heavy metal oxidants.[14] The oxidizing capacity of this versatile class of hypervalent iodine reagents has been investigated extensively for the dehydrogenation of Hantzsch 1,4-dihydropyridines,[15] 2-imidazolines,[16] and pyrazolines.[17] The reactions of DHPMs with hypervalent iodine reagents are hitherto unknown in the literature. In continuation of our work on hypervalent iodine,[18] herein we report a facile oxidative dehydrogenation of DHPMs using a combination of DIB with *tert*-butylhydroperoxide. Our results demonstrate that DIB alone was unable to induce dehydrogenation of DHMP in satisfactory yields due to lower nucleophilic nature of the N-3 nitrogen of the ring. However, the addition of *tert*-butylhydroperoxide (TBHP) as an additive facilitated the dehydrogenation of DHPMs under mild reaction conditions (Scheme 1).

* Corresponding author. Tel.: +91 2462 266999; fax: +91 2462 229245.
E-mail address: nnkarade@gmail.com (N. N. Karade).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.045



Scheme 1.

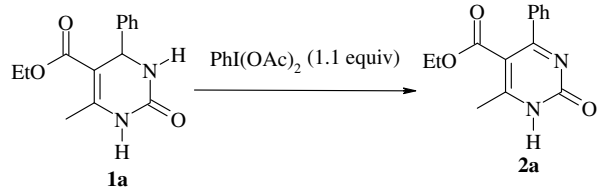
The reaction conditions were optimized by investigation of the model dehydrogenation of **1a** (R = C_6H_5) using DIB in various solvents with or without the use of additives. The results are summarized in Table 1. The reaction of **1a** with DIB in CH_3CN, MeOH, or CH_2Cl_2 did not produce **2a**. There is a report in the literature which describes that the oxidizing properties of hypervalent iodine reagents change remarkably on addition of certain additives.[19] Therefore, we decided to use hypervalent iodine reagents in combination with KBr or I_2. In these cases, the in situ-generated acetyl hypobromite or iodite (CH_3COOX, X = Br or I) was expected to be the active oxidant for bringing about dehydrogenation of the DHPMs.[20] However, we obtained relatively poor yields of the dehydrogenation products (Table 1, entries 4–8). Next, we used the combination of *tert*-butylhydroperoxide with DIB. To our delight, we observed facile oxidative dehydrogenation of **1a** to give **2a** in 84% yield.[21] In a blank experiment, *tert*-butylhydroperoxide alone did not oxidize **1a** to **2a.** The highest yield of **2a** was obtained in CH_2Cl_2 when a 1:2 molar ratio of DIB to *tert*-butylhydroperoxide was used.

Following the success in the oxidation of **1a** with the DIB/TBHP system, we extended this method to several DHPMs with aryl and alkyl substituents at C-4 and the results are summarized in Table 2. All the reactions were complete in less than 4 h under mild conditions, and high yields of the products were obtained. Both electron-donating and electron-withdrawing substituents on the precursors afforded the corresponding 1,2-dihydropyrimidine derivatives in good to excellent yields. Aliphatic substituents such as *iso*-propyl and *iso*-butyl at C-4 of the DHPMs (Table 2, entries 10 and 11) also gave clean oxidative dehydrogenation without the formation of any concomitant dealkylation product. The structures of all the products were established from IR, NMR, and mass spectral analysis (Supplementary data). The ^1H NMR spectra of all the products showed a characteristic broad signal due to the enolizable –OH or NH(1) protons around δ 12–13 ppm and the absence of CH(4) and NH(3) resonances around δ 5.2 and 8.2 ppm, respectively.[22] The tautomerization of NH(1) to N(3) in solution is reported in the literature[10,11] and therefore, the identity of C-4, C-6, and substituted aromatic carbons was difficult to locate in the ^{13}C NMR spectra of the dehydrogenated product.

Mechanistically, the ligand exchange reaction between *tert*-butylhydroperoxide and DIB forms intermediate **3**, which undergoes homolytic cleavage of the hypervalent iodine(III)-peroxy bond to form [9-I-2] iodanyl radical **4** and *tert*-butylhydroperoxy radical **5** (Scheme 2).[23] The dehydrogenation mechanism may involve abstraction of the hydrogen at C-4 of the DHPM by *tert*-butylhydroperoxy radical **5** to form the resonance stabilized radical **6**, which is further converted by single electron-transfer process to form the iminium ion **7**. Finally, a *tert*-butylhydroperoxy anion, acting as a base, can abstract a N–H proton from **7** to form the 1,2-dihydropyrimidine **2**.

In conclusion, a transition metal-free protocol for the facile oxidative dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones is reported using the novel combination of *tert*-butylhydroperoxide and (diacetoxyiodo)benzene. This is the first report describing the reactions of DHPMs with hypervalent iodine reagents. Mild reaction conditions, short reaction times, and easy isolation of the desired product make the present method convenient.

Table 1
Optimization of the reaction conditions



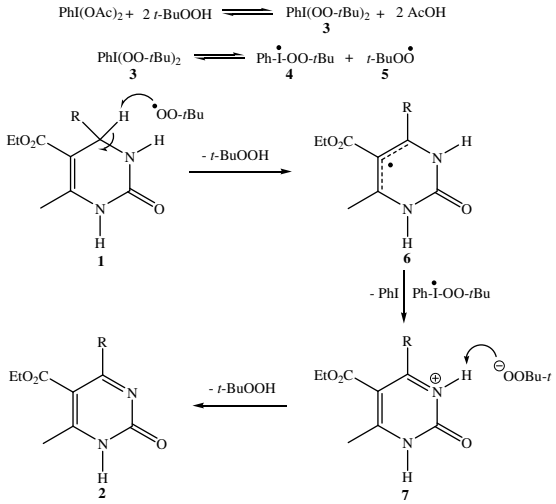
Entry	Additive	Solvent	Reaction time[a] (h)	Yield of **2a**[b] (%)
1	—	CH_3CN	24	0
2	—	CH_2Cl_2	24	0
3	—	CH_3OH	24	13
4	KBr (2 equiv)	CH_3CN	24	24
5	KBr (1 equiv)	CH_3OH	8	31
6	KBr (2 equiv)	CH_3OH	5	47
7	I_2 (1 equiv)	CH_3COOH	12	28
8	I_2 (1 equiv)	CH_2Cl_2	24	31
9	*t*-BuOOH (2 equiv)	CH_2Cl_2	4	84

[a] The reactions were carried out at room temperature.
[b] Isolated yield.

Table 2
Dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) with DIB and TBHP in CH_2Cl_2

Entry	DHPM	R	Product[a]	Yield[b] (%)
1	**1a**	C_6H_5–	**2a**	84
2	**1b**	4-$MeOC_6H_4$–	**2b**	83
3	**1c**	3-$MeOC_6H_4$	**2c**	79
4	**1d**	3,4-$(MeO)_2C_6H_3$–	**2d**	80
5	**1e**	4-MeC_6H_4–	**2e**	83
6	**1f**	4-ClC_6H_4–	**2f**	84
7	**1g**	3-BrC_6H_4	**2g**	79
8	**1h**	3-$O_2NC_6H_4$–	**2h**	83
9	**1i**	4-$O_2NC_6H_4$–	**2i**	79
10	**1j**	$(CH_3)_2CH$–	**2j**	73
11	**1k**	$(CH_3)_2CHCH_2$–	**2k**	72

[a] The structures of the products were confirmed from IR, NMR, and mass spectral analysis.
[b] Isolated yield.



Scheme 2.

Acknowledgments

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

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.045.

References and notes

1. (a) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629; (b) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806 and references cited therein.
2. (a) Itami, K.; Yamazaki, D.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 15396; (b) Kang, F.-A.; Kodah, J.; Guan, O.; Li, X.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 1957; (c) Wong, K.; Hung, T. S.; Lin, Y.; Wu, C.; Lee, G.; Peng, S.; Chou, C. H.; Su, Y. O. *Org. Lett.* **2002**, *4*, 513; (d) Rombouts, F. J. R.; Fridkin, G.; Lubell, W. D. *J. Comb. Chem.* **2005**, *7*, 589.
3. (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937; (b) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1142; (c) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291.
4. (a) Bagley, M. C.; Lubinu, M. C. *Synthesis* **2006**, *8*, 1283; (b) Han, B.; Liu, Z.; Liu, Q.; Yang, L.; Liu, Z. L.; Yu, W. *Tetrahedron* **2006**, *62*, 2492; (c) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 5069; (d) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955.
5. Khanina, E. L.; Duburs, G. *Khim. Geterotsikl. Soedin* **1982**, 535.
6. Eynde, J. J. V.; Audiart, N.; Canonne, V.; Michel, S.; Haverbeke, Y. V.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967.
7. (a) Kadis, V.; Stradins, J.; Khanina, E. L.; Duburs, G.; Muceniece, D. *Khim. Geterofsikl. Soedin* **1965**, 117; (b) Kadis, V.; Stradins, J.; Khanina, E. L.; Duburs, G. *Electrochim. Acta* **1989**, *34*, 899.
8. Slavinskaya, V. A.; Dubus, G.; Sile, D.; Krerle, D.; Khanrna, E. L. USSR Patent 632, 695, 1978; *Chem. Abstr.* **1979**, *90*, 121631y.
9. Kappe, C. O.; Roschger, P. *J. Heterocycl.* **1989**, *26*, 55–64.
10. Puchala, A.; Belaj, F.; Bergman, J.; Kappe, C. O. *J. Heterocycl. Chem.* **2001**, *38*, 1345.
11. Shanmugam, P.; Perumal, P. T. *Tetrahedron* **2006**, *62*, 9726.
12. Yamamoto, K.; Chen, Y. G.; Buono, F. G. *Org. Lett.* **2005**, *21*, 4673.
13. (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656; (b) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893; (c) Zhdankin, V. V.; Stang, P. *J. Chem. Rev.* **2002**, *102*, 2523.
14. Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997.
15. Varma, R. S.; Kumar, D. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 1755.
16. Ishihara, M.; Togo, H. *Synlett* **2006**, 227.
17. Singh, S. P.; Kumar, D.; Prakash, O.; Kapoor, R. P. *Synth. Commun.* **1997**, *27*, 2683.
18. (a) Karade, N. N.; Tiwari, G. B.; Shinde, S. V.; Gampawar, S. V.; Kondre, J. M. *Tetrahedron Lett.* **2008**, *49*, 3441; (b) Karade, N. N.; Gampawar, S. V.; Kondre, J. M.; Shinde, S. V. *Tetrahedron Lett.* **2008**, *49*, 4402; (c) Karade, N. N.; Tiwari, G. B.; Gampawar, S. V. *Synlett* **2007**, 1921; (d) Karade, N. N.; Tiwari, G. B.; Huple, D. B. *Synlett* **2005**, 2039; (e) Karade, N. N.; Gampawar, S. V.; Kondre, J. M.; Shinde, S. V. *ARKIVOC* **2008**, *xii*, 9.
19. (a) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1306; (b) Tohma, H.; Maegawa, T.; Kita, Y. *Synlett* **2003**, 723.
20. (a) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, *3*, 461; (b) Togo, H.; Sakuratani, K. *Synlett* **2002**, 1966.
21. *General experimental procedure:* To a stirred suspension of appropriate DHPM (2 mmol) and TBHP (5.0–6.0 M solution in decane, 0.45 mL, 0.360 g) in CH_2Cl_2 (10 mL) was added DIB (0.708 g, 2.2 mmol) at room temperature. The reaction mixture soon turned yellow in color and the progress of the reaction was monitored by TLC. After 3–4 h of stirring, the solution was concentrated under vacuum and the residue was purified by column chromatography (silical gel, petroleum ether–ethyl acetate) to give the corresponding 1,2-dihydropyrimidine in good yield.
22. Spectral data for new products:
Ethyl 1,2-dihydro-4-(3-methoxyphenyl) 6-methyl-2-oxopyrimidine-5-carboxylate (**2c**): Mp 102–104 °C; IR (KBr): ν = 2927, 2859, 1713, 1662, 1540, 1481, 1358, 1359, 1283, 1109, 1043, 800, 680 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, 3H, J = 7.2 Hz, CH_3), 2.58 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.07 (q, 2H, J = 7.16 Hz, OCH_2), 7.02 (m, 1H, ArH), 7.10 (d, 1H, J = 6.72 Hz, ArH), 7.16 (s, 1H, ArH), 7.31 (t, 1H, J = 7.92 Hz, ArH), 13.42 (br s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.24, 29.76, 55.54, 61.78, 100.05, 111.69, 112.90, 117.45, 120.39, 129.50, 138.02, 157.92, 159.69, 166.08. LCMS: m/z = 289 (M+1).
Ethyl 1,2-dihydro-4-(3,4-dimethoxyphenyl) 6-methyl-2-oxopyrimidine-5-carboxylate (**2d**): Mp 156–158 °C; IR (KBr): ν = 3028, 2841, 1716, 1670, 1593, 1518, 1437, 1369, 1319, 1271, 1151, 1099, 1022, 875, 792 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, 3H, J = 7.12 Hz), 2.58 (s, 3H), 3.93 (s, 6H), 4.12 (q, 2H, J = 7.12 Hz), 6.89 (d, 1H, J = 8.32 Hz), 7.20 (d, 1H, J = 8.36 Hz), 7.26 (s, 1H), 13.65 (br s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.82, 29.75, 56.08, 56.13, 61.81, 110.52, 111.36, 111.48, 121.77, 149.03, 151.74, 158.48, 166.75. LCMS: m/z = 319 (M+1).
Ethyl 1,2-dihydro-6-methyl-2-oxo-4-p-tolylpyrimidine-5-carboxylate (**2e**): Mp 183–185 °C; IR (KBr): ν = 2999, 2981, 1712, 1643, 1600, 1437, 1278, 1207, 1107, 1016, 964, 869, 802 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, 3H, J = 7.08 Hz, CH_3), 2.40 (s, 3H, $ArCH_3$), 2.59 (s, 3H, CH_3), 4.09 (q, 2H, J = 7.08 Hz, OCH_2), 7.23 (d, 2H, J = 8.04 Hz, ArH), 7.50 (d, 2H, J = 8.04 Hz, ArH), 13.57 (br s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.60, 21.52, 61.62, 65.89, 111.43, 128.17, 129.14, 141.47, 158.45, 166.43. LCMS: m/z = 273 (M+1).
Ethyl 4-(4-chlorophenyl)-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (**2f**): Mp 181–183 °C; IR (KBr): ν = 3090, 2982, 2904, 1707, 1645, 1597, 1435, 1367, 1282, 1211, 1087, 1014, 840, 798 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, 3H, J = 7.08 Hz, CH_3), 2.62 (s, 3H), 4.08 (q, 2H, J = 7.08 Hz, OCH_2), 7.41 (d, 2H, J = 8.56 Hz, ArH), 7.55 (d, 2H, J = 8.56 Hz, ArH), 13.73 (br s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.65, 29.75, 61.87, 111.38, 128.70, 129.56, 137.27, 158.34, 165.89. LCMS: m/z = 293 (M+1).
Ethyl 4-(3-bromophenyl)-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (**2g**): Mp 108–110 °C; IR (KBr): ν = 2926, 1719, 1600, 1560, 1438, 1367, 1278, 1103, 1103, 792, 684 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, 3H, J = 7.08 Hz, CH_3), 2.62 (s, 3H, CH_3), 4.11 (q, 2H, J = 7.2 Hz, OCH_2), 7.31 (t, 1H, J = 7.88 Hz, ArH), 7.52 (d, 2H, J = 7.72 Hz, ArH), 7.60 (d, 1H, J = 8.76 Hz, ArH), 7.77 (s, 1H, ArH).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.63, 29.74, 54.59, 61.86, 111.25, 122.54, 126.75, 130.03, 131.20, 134.04, 139.52, 158.01, 165.65. LCMS: m/z = 337 (M+1).
Ethyl 4-(3-nitrophenyl)-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (**2h**): Mp 165–167 °C; IR (KBr): ν = 3082, 2924, 1683, 1616, 1508, 1267, 1074, 794, 696 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, 3H, J = 7.08 Hz, CH_3), 2.69 (s, 3H, CH_3), 4.13 (q, 2H, J = 7.08 Hz, OCH_2), 7.64 (t, 1H, J = 7.96 Hz, ArH), 7.96 (d, 1H, J = 7.66 Hz, ArH), 8.36 (d, 1H, J = 8.16 Hz, ArH), 8.49 (s, 1H, ArH), 13.81 (br s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.71, 18.89, 54.65, 60.49, 62.06, 111.18, 123.32, 125.28, 129.49, 134.03, 148.06, 158.09, 165.21. LCMS: m/z = 304 (M+1).
Ethyl 1,2-dihydro-4-iso-butyl-6-methyl-2-oxopyrimidine-5-carboxylate (**2k**): Mp 131–132 °C; IR (KBr): ν = 2983, 1708, 1656, 1599, 1452, 1371, 1259, 1134, 1016, 964, 869, 804 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, 6H, J = 6.64 Hz, $2CH_3$), 1.38 (t, 3H, J = 7.2 Hz, CH_3), 2.12 (m, 1H, CH), 2.52 (s, 3H, CH_3), 2.73 (d, 2H, J = 7.32 Hz, CH_2), 4.37 (q, 2H, J = 7.16 Hz, OCH_2), 13.31 (br s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 14.22, 22.40, 28.88, 29.76, 31.99, 61.75, 112.02, 158.23, 165.77. LCMS: m/z = 239 (M+1).
23. Ochiai, M.; Sueda, T. *Tetrahedron Lett.* **2004**, *45*, 3557.