Heterocyclic Letters
Vol. 10| No.4|537-542|Aug-Oct |2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

FACILE SYNTHESIS OF HIGHLY FUNTIONALIZED BUTYROLACTONES THROUGH AN UNPRECEDENTED BASE-CATALYZED CONDENSATION

Ashutosh Pal* and Bimal Krishna Banik*

[1]Raja Peary Mohan College, West Bengal, India; [2]Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Deanship of Research; Prince Mohammad Bin Fahd University, Al Khobar, Kingdom of Saudi Arabia; Email: ashupal33@gmail.com; bimalbanik10@gmail.com; bbanik@pmu.edu.sa

Abstract:
Oxo propionic acid such 2-oxo-3-phenyl propionic acid and their hydroxyl derivatives are useful building blocks for asymmetric synthesis and the preparation of biologically active butyrolactones. A new synthesis of three different types of hydroxyl butyrolactones (4, 5, 6) has been performed. A number of butyrolactones such as methyl 2-benzyl-2,5-dihydro-4-hydroxy-3-(hydroxyphenyl)-5-oxofuran-2-carboxylate, methyl 2-(4-hydroxyphenyl)-2,5-dihydro-4-hydroxy-5-oxo-3-phenylfuran-2-carboxylate, methyl 2-(4-hydroxyphenyl)-2,5-dihydro-4-hydroxy-3-(4-hydroxyphenyl)-5-oxofuran-2-carboxylate has been synthesized.

Key words: Oxo propionic acid, butyrolactones, condensation, X-ray

Introduction:

Functionalized butyrolactones have attracted substantial attention in present year because of their importance as their chiral building blocks and for the synthesis of alkaloids, macrocyclic antibiotics, lignans, lactones, pheromones, antileukemics, and flavor components.[1] The lactones have been synthesized by means of variety of methods including the transformation of chiral natural products,[2]microbal reduction of ketoacids,[3] enzymatic resolution,[4] and with chiral chemical reagents.[5] Among these, five-and six-membered lactones are especially useful either as core structures for biologically active molecules[6] or as ligands for asymmetric synthesis.[7, 8] Among five-membered heterocycles, functionalized 3-hydroxypyrrolidines are very useful moieties found in many biologically interesting compounds.[9,10]We have used a convergent base-catalyzed condensation reaction for the synthesis of highly functionalized lactones related to the biologically active compounds.

Results:

Treatment of pyruvic ester with substitution at the para position afforded symmetrical para-substituted lactone as the only product. Similar reaction of esters **2a and 2b** produced a mixture of unsymmetrical as well as para -substituted lactones.

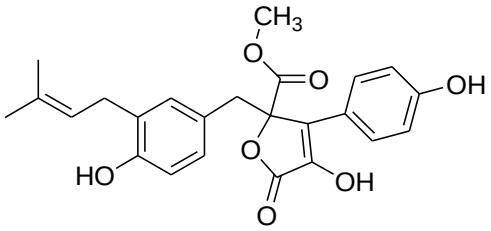


Figure 1: Butyrolactone I

Butyrolactone I with alkenyl chain, a natural product was isolated from *Aspergillus terreus* var. *africans* IFO 8835 in 1977.[11] Lactone I has been found to exhibit antiproliferative activity against colon and pancreatic carcinoma, human lung cancer [12] and prostatic cancer cell lines.[13]It also selectively inhibits CDK2 and CDK1 kinases, both of which play important roles in cell progression from G1 to S phase and from G2 phase to M phase, respectively. It shows little effect on mitogen-activated protein kinase, protein kinase C, cyclic-AMP dependent kinase, casein kinase II, casein kinase I or epidermal growth factor-receptor tyrosine kinase.[14] It behaves as an ATP competitive inhibitor. Due to the structural complexity of this compound, little is known about its binding mode to its target. Morishima *et al.*[15] studied and reported that suppression of the alkenyl chain does not markedly affect the anti-CDK1 activity of butyrolactone I.

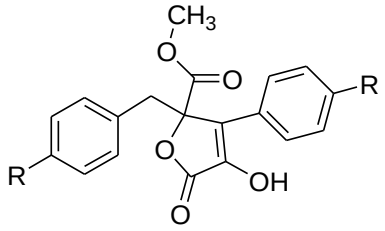
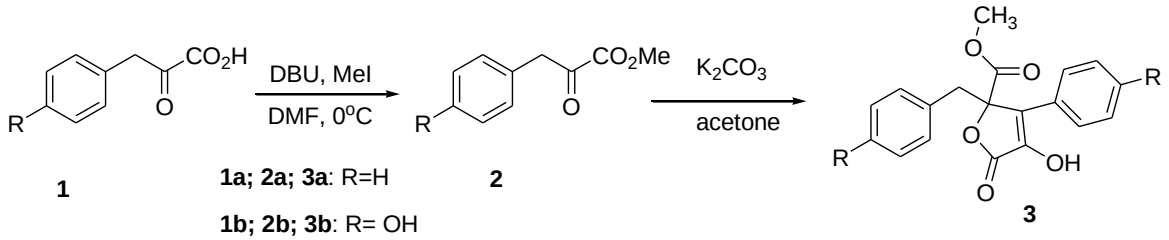


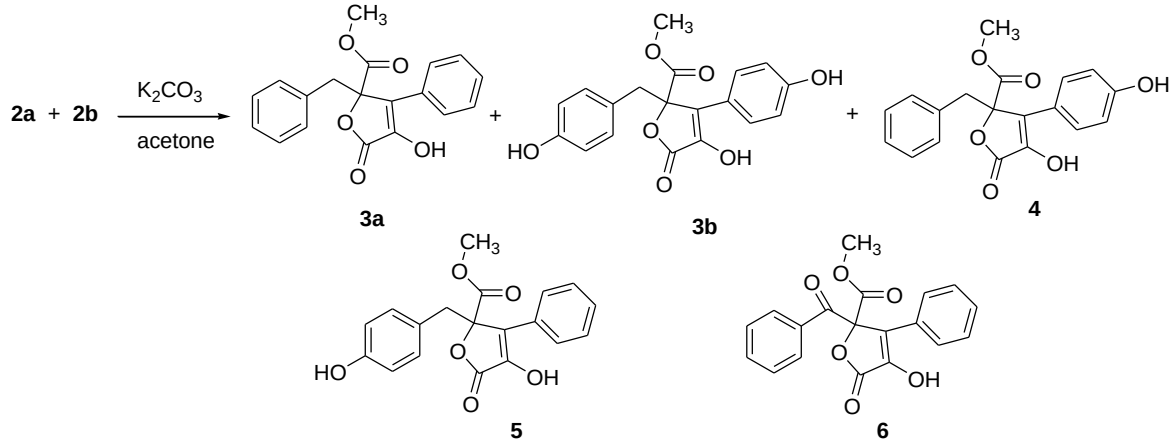
Figure 2 Butyrolactones where R = H, OH, Cl, NH_2, Bu^t, CF_3, OCH_3, CF_3

Figure 2 shows several examples of biologically active compounds containing various lactone structures.[16] Compounds **3a** and **3b** contain the 3-hydroxylactone core structure. The phenyl benzyl 3-hydroxylactones are ion channel modulating compounds and are also useful for the treatment of leukemia.[11]



Scheme 1: General procedure for the synthesis of butyrolactone

The acid group in compound **1** was esterified to produce the keto ester **2.** The reaction of **2** with potassium carbonate in acetone afforded lactone **3** in good yield (Scheme 1).



Scheme 2: Synthesis of butyrolactones

By following an identical sequence **2a** and **2b** produced **3a, 3b, 4, 5** and **6** (Scheme 2). The X-ray study had confirmed the structures of the lactones **5** and **6** (Figure 3 and 4).

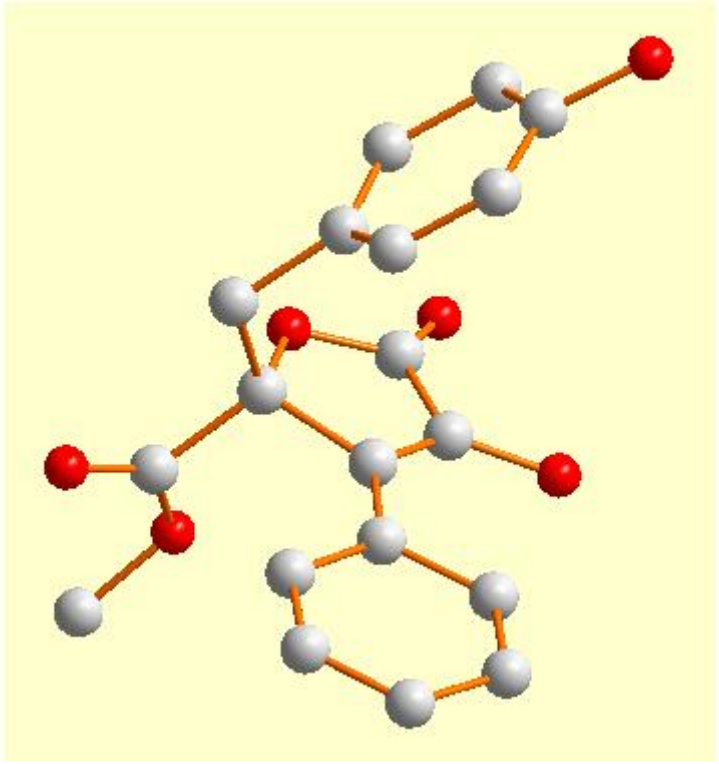


Figure 3: X-ray structures of compound **5**

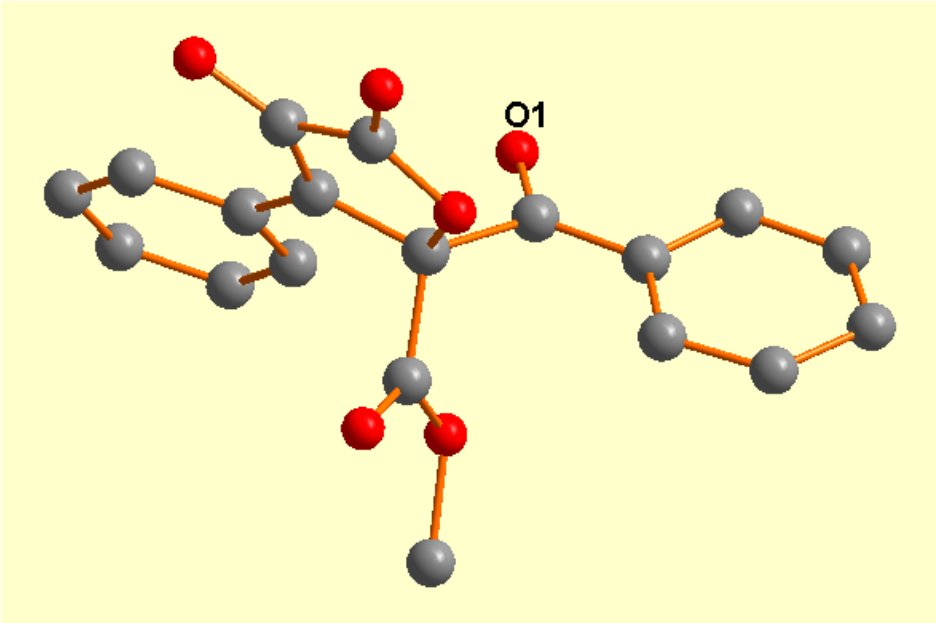
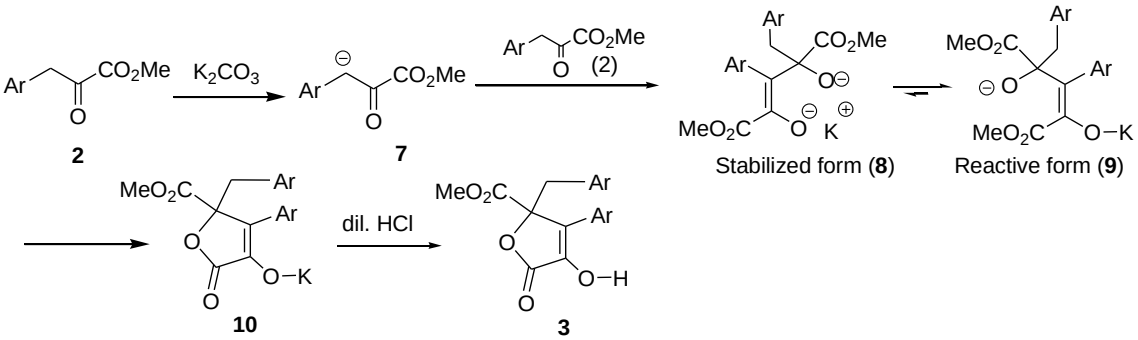


Figure 4: X-ray structures of compound **6**



Scheme 3: Plausible mechanism of the self-condensation products of phenylpyruvic esters

The keto ester **2** on the treatment of a base generates a carbanion **7** which on condensation with another molecule of **2** afforded two forms of dianions **8** and **9**. The dianion **9** on intramolecular cyclization produced the salt of the lactone. On acidification, free lactone **3** was obtained. Thus, using a simple linear activated keto ester, highly functionalized lactone can be obtained through a base-catalyzed intramolecular condensation reaction (Scheme 3).

Experimental

General Apparatus: Nuclear magnetic resonance spectra (^{1}H and ^{13}C) were recorded at ambient temperature on an IBM-Brucker Model NR/200 AF spectrometer in the Fourer transform model, in $CDCl_3$ using Me_4Si as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are in hertz (Hz). Melting points were determined on a Hoover capillary apparatus and are uncorrected. All reactions were carried out in dry glass were protected from atmospheric moisture. Solvents were dried over freshly activated (300^{o}C/1h) molecular sieves (type 4 A). The homogeneity of the products were determined by ascending TLC on silica-coated aluminium-backed plates (silica gel 60 F 254; Merck) using the flowing solvent mixtures: A, CH_3CN-H_2O (typically 8:2 to 6:4 v/v); Organic extracts of aqueous solutions were dried over anhydous Na_2SO_4. Solutions were concentrated under reduced pressure on a rotary evaporator.

General Procedure for the synthesis of butyrolactones

To a solution of ester **2a (**1.78 g, 10 mmol) and **2b (**1.94 g, 10 mmol) in acetone (50 mL) was added K_2CO_3 (50 mmol) and the mixture was stirred at room temperature overnight. After the

acetone was evaporated, 1 M HCl was added, and the solution was extracted with ether (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by reverse phase column chromatography with the mobile phase water-acetonitrile (9:1 to 8:2) mixture and produced all five butyrolactones overall 55% yield.

To a solution of ester **1a (**1.64 g, 10 mmol) and **1b (**1.80 g, 10 mmol) in acetone (50 mL) was added K_2CO_3 (50 mmol) and the mixture was stirred at room temperature overnight. After the acetone was evaporated, 1 M HCl was added, and the solution was extracted with ether (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by reverse phase column chromatography with the mobile phase acetonitrile-water (8:2) mixture and produced all five butyrolactones overall 55% yield.

Methyl-2 benzyl-4-hydroxy-5-oxo-3-phenyl-2H-furan-2-carboxylate (3a):

Yield is (260 mg); white crystalline solid; mp 157^{o}C; ^{1}H NMR (DMSO-d_6) δ7.62 (m, 2H), 7.42 (m, 3H), 7.12 (m, 3H), 6.82(m, 2H), 3.79 (s, 3H), 3.68 (d, *J* = 14.3 Hz, 1H), 3.58 (d, *J* = 14.3 Hz, 1H); ^{13}C NMR δ 169.4, 169.1, 138.9, 132.5, 130.3, 129.5, 129.2, 129.0, 127.9, 127.7, 127.6, 127.3, 86.0, 53.6, 39.1; MS ($C_{19}H_{16}O_5$) estimated 324.0998 found 325.2 (M+H).

Methyl-4-hydroxy-3-(4-hydroxyphenyl)-2-(4-hydroxyphenylmethyl)-5-oxo-2H-furan-2-carboxylate (3b):

Yield is (240 mg); white crystalline solid, mp 216^{o}C; ^{1}H NMR (DMSO-d_6) δ 7.61 (d, 2H, *J* = 8.5 Hz), 6.90 (d, 2H, *J* = 8.5 Hz), 6.67 (d, 2H, *J* = 8.5 Hz), 6.54 (d, 2H, *J* = 8.5 Hz), 3.80 (s, 3H), 3.48 (s, 2H); ^{13}C NMR δ 171.1, 168.9, 158.0, 156.1, 138.4, 131.2, 129.1, 129.0, 127.9, 123.9, 121.7, 115.4, 115.2, 114.2, 52.4, 38.1; MS ($C_{19}H_{16}O_7$) estimated 356.0896 found 357.2 (M+H).

Methyl-2-benzyl-4-hydroxyphenyl-2-(4-hydroxyphenylmethyl)-5-oxo-2H-furan-2-carboxylate (4):

Yield is (140 mg); white crystalline solid; mp 199^{o}C; ^{1}H NMR (DMSO-d_6) δ 7.47 (m, 5H), 6.64 (m, 2H), 6.54 (m, 2H), 3.81 (s, 3H), 3.50 (s, 2H); ^{13}C NMR δ 170.1, 168.6, 157.0, 141.0, 131.2, 130.8, 128.8, 128.7, 127.6, 127.0, 124.1, 114.6, 85.9, 52.9, 38.3; MS ($C_{19}H_{16}O_6$) estimated 340.0947 found 341.2 (M+H).

Methyl-2 benzyl-4-hydroxy-2-(4-hydroxyphenylmethyl)-5-oxo-2H-furan-2-carboxylate (5):

Yield is (125 mg); white crystalline solid; mp 190^{o}C; ^{1}H NMR (DMSO-d_6) δ 7.91 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.47 (m, 3H), 6.64 (m, 2H), 6.54 (m, 2H), 3.81 (s, 3H), 3.50 (s, 2H); ^{13}C NMR δ 170.4, 168.9, 156.6, 141.0, 131.5, 130.8, 128.8, 128.7, 127.6, 127.0, 124.1, 114.6, 85.9, 52.9, 38.3; MS ($C_{19}H_{16}O_6$) estimated 340.0947 found 341.2 (M+H).

Methyl-2 benzol-4-hydroxy-5-oxo-3-phenyl-2H-furan-2-carboxylate (6):

Yield is (50 mg); white crystalline solid; mp 182^{o}C; ^{1}H NMR (DMSO-d_6) δ 7.88 (m, 2H), 7.42 (m, 3H), 7.12 (m, 3H), 6.82 (m, 2H), 3.79 (s, 3H); ^{13}C NMR δ 194.6, 169.4, 169.1, 138.9, 132.5, 130.3, 129.5, 129.2, 129.0, 127.9, 127.7, 127.6, 127.3, 112.0, 53.6. MS ($C_{19}H_{14}O_6$) estimated 338.079 found 339.1 (M+H).

Conclusion:

The preparation of different kinds of structurally complex phenyl benzyl 3-hydroxylactones is possible using commercially available keto-ester through a single step. Physico-chemical data and X-ray confirmed their structures. These complex lactones may prove to be useful for further chemical modifications.

Acknowledgement:

BKB thanks Prince Mohammad Bin Fahd University for encouragement. AP sincere thanks Dr. William G. Bormann for his valuable advice.

References:

1. S.S. Cannon Koch, A.R. Chamberlin, *J.Org.Chem*. 1993, 58, 2725.
2. (a) J. Mulzer, N. Salimi, S. Hartl, *Tetrahedron: Asymmetry*, 1993, 4, 457.
   (b) T. Ebata, K. Mutsumoto, H. Yoshikoshi, K. Koseki, H. Kawakami, K. Okano, H. Matsushita, *Heterocycles*, 1993, 36, 1017
   (c) Y. Suzuki, W. Mori, H. Yishizone, K. Naito, T. Honda, *Tetrahedron Lett*., 1992, 33, 4931.
   (d) H. Yoda, K. Shirakawa, K. Takabe, *Chem. Lett*. 1991, 489.
   (e) H. Yoda, K. Shirakawa, K. Takabe, *Tetrahedron Lett.* 1991, 32, 3401.
3. (a) C.A.M. Afonso, M.T. Barros, L.S. Godinho, C.D. Maycock, Tetrahedron, 49, 4283.
   (b) S. Robin, H. Huet, *Tetrahedron Lett*. 1993, 34, 2945.
   (c) M. Aquino, S. Cardani, G. Fronza, C. Fuganti, R.P. Fernandez, A. Tagliani, *Tetrahedran*, 1991, 47, 7887.
   (d) A. Gopalan, R. Lucero, H. Jacobs, K. Berryman, *Syn. Commun*. 1991, 21, 1321.
4. (a) H.K. Jacbs, B.H. Mueller, A.s. Gopalan, *Tetrahedron*, 1992, 48, 8891.
   (b) M.P. Sibi, J.A. Gaboury, *Tetrahedron Lett*., 1992, 33, 5681.
   (c) T. Sugai, S. Osawa, H. Yamada, H. Ohta, Synthesis, 1990, 1112.
   (d) A.L. Gutman, K. Zuobi, T. Bravdo, *J.Org.Chem*., 1990, 55, 3546.
5. (a) T. Honda, N.J. Kimura, *Chem Soc. Chem. Commun*. 1994, 77
   (b) H.C. Brown, S.V. Kulkarni, U.S. Racherla, *J.Org.Chem*. 1994, 59, 365.
6. G. Wang, Curr. Med. Chem. Anti-infective Agents 2008, 7, 32.
7. L. M. Geary, P. G. Hultin, *Tetrahedron: Asymmetry* 2009, 20, 131.
8. M. P. Sibi, J. Ji, J. H. Wu, S. Guertler, N. A. Porter, *J. Am. Chem. Soc*. 1996, 118, 9200.
9. D. Fedida, G. N. Beatch, A. M. Ezrin, P. Orth, C. Hesketh, PCT Int. Appl. WO 2005018635 A2 20050303, 2005; *Chem. Abstr*. 2005, 142, 274013.
10. (a) F. Sternfeld, A. R. Guiblin, R. A. Jelley, V. G. Matassa, A. J. Reeve, P. A. Hunt, M. S. Beer, A. Heald, J. A. Stanton, B. J. Sohal, Med. Chem. 1999, 42, 677. (b) R. Baker, S. Bourrain, J. L. Castro Pineiro, M. S. Chambers, A. R. Guiblin, S. C. Hobbs, R. A. Jelley, A. Madin, V. G. Matassa, PCT A1 Int. Appl. WO 9604274 A1 19960215, 1996; *Chem. Abstr*. 1996, 125, 58520.
11. N. Kiriyama, K. Nitta, Y. Sakaguchi, Y. Taguchi and Y. Yamamoto, *Chem. Pharm. Bull.*, 1977, **25**, 2593–2601.
12. K. Nishio, T. Ishida, H. Arioka, H. Kurokawa, K. Fukuoka, T. Nomoto, H. Fukumoto, H. Yokote and N. Saijo, *Anticancer Res.*, 1996, **16**, 3387–3396.
13. M. Suzuki, Y. Hosaka, H. Matsushima, T. Goto, T. Kitamura and K. Kawabe, *Cancer Lett.*, 1999, **138**, 121–130.
14. M. Kitagawa, T. Okabe, H. Ogino, H. Matsumoto, I. Suzuki-Takahashi, T. Kokubo, H. Higashi, S. Saitoh and Y. Taya, *Oncogene*, 1993, **8**, 2425–2432.
15. H. Morishima, K. Fujita, M. Nakano, S. Atsumi, M. Ookubo, M. Kitagawa, H. Matsumoto, A. Okuyama and T. Okabe, (Banyu Pharma Co. Ltd.), Jpn. Kokai Tokkyo Koho 06 100, 445, 1994.
16. M. F. Braña, M. Luisa García, B López, B.de Pascual-Teresa, A. Ramos, J. M. Pozuelo, M. Teresa Domínguez, *Org. Biomol. Chem*. 2004, 2, 1864–1871.
17. V. Ya. Sosnovskikh, D. A. Vetyugova, A. V. Safrygin, O. S. Eltsov, P. A. Slepukhin, Mendeleev Communications, 2018, 28 (4), 434-436**.**