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Zhiwei Wang[a], Shaobai Li[a], Fulin Yan[a b] & Yulin Li[a]

[a] State Key Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou, 730000, P. R. China
[b] Department of Chemistry, Xinxiang Medical College

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SYNTHESIS OF (Z)-3-(2-HYDROXYBUTYLIDENE) PHTHALIDE

Zhiwei WANG Shaobai LI* Fulin YAN* * Yulin LI

State Key Laboratory of Applied Organic Chemistry and
Institute of Organic Chemistry, Lanzhou University,
Lanzhou 730000. P. R. China.

Abstract: The first synthesis of (Z)-3-(2-hydroxybutylidene)phthalide (**1**) is described, starting from phthalic anhydride (**2**). The key step in the synthesis is the condensation of the kinetic lithium enolate of butanone with **2**.

(Z)-3-(2-Hydroxybutylidene)phthalide (**1**, senkyunolide-E) was isolated from the commercial C. officinale rhizome[1]. The structure has been assigned on the basis of analytical and spectral data. Its synthesis, however, has not been achieved so far. In this paper we wish to describe the first synthesis of **1** starting from phthalic anhydride (**2**).

In our method phthalic anhydride (**2**) was treated with the kinetic lithium enolate (**3**), generated regioselectively *in situ* from butanone using

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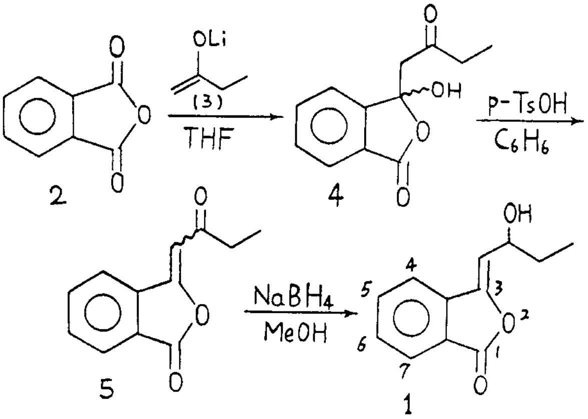
* To whom correspondence should be addressed.

* * Visiting scholar from Department of Chemistry, Xinxiang Medical College.

LDA in THF at −78℃ [2], to provide 3–hydroxy–3–(2–oxobutyl) phthalide (4) in 54% yield. Compound **5** was obtained by dehydration[3] of **4** with p–toluenesulphonic acid. Reduction of **5** was conducted in dry methanol with $NaBH_4$ to afford **1**. The chemical shift of =CH (δ 5.64 ppm) is an indication for the (*Z*)– configuration (*E*– : δ 5.85 ppm) [4].



Experimental

Melting point was measured on a Kofler hot stage and is uncorrected. IR spectra were recorded on a Nicolet 170 SX FT–IR spectrometer. ^{1}HNMR spectra were obtained with a FT–80A spectrometer using tetramethylsilane as internal standard. Mass spectra (70eV) were determined on a ZAB–HS spectrometer.

3–Hydroxy–3–(2–oxobutyl)phthalide(4)

To the solution of lithium diisopropylamide (LDA), prepared from diisopropylamide (1.85 mL, 13.2 mmol) and n–butyllithium (1.7M, 6.5 mL, 11.0 mmol) in THF (10 mL), was added 0.9 mL (10.0 mmol) of butanone at −78℃ under argon atomosphere. The thus obtained solution was stirred for 5 min and a solution of phthalic anhydride (2) (1.48 g, 10.0 mmol) in THF (20mL) was added . The reaction mixture was stirred for 15 min (monitored by TLC) at −78℃ and decomposed with water (25 mL). Tetrahydrofurane from the aqueous layer was evaporated under reduced pressure. The residual aqueous layer was acidified to pH = 1 ~ 2 with 10% HCl aq. and extracted with ether (4 × 30 mL). The ether layer was washed with water and brine respectively, dried (Na_2SO_4) and evaporated to give a residue. The residue was purified by flash column chromatography over silica gel (50 g, 200–300mesh) using ethyl acetate– petroleum ether (1:10) as an eluent to give a yellowish oil of **4** (1.19 g, 54%). R_f 0.11 (ethyl acetate–petroleum = 1:4). $\upsilon_{max}(cm^{-1})$: 3332(OH), 1772, 1722, 1604. δ_H(ppm): 1.15(3H, t, J=7.4Hz, CH_3), 2.6(2H, q, J=7.4Hz, CH_2CH_3), 3.09(2H, s, CH_2), 7.45–7.75(3H, m, 4–H, 5–H and 6–H), 7.85(1H, d, J=7.8Hz, 7–H). m / z (EI): 220(M^+, 1), 202($[M-18]^+$, 1), 191($[M-29]^+$, 4), 173(20), 149(100). R_f 0.12 (acetone: petroleum ether = 1:4).

3–(2–Oxobutylidene)phthalide (**5**)

p–Toluene sulphonic acid (30 mg) was added to a solution of **4** (0.59 g, 2.68 mmol) in benzene (20 mL) and the reaction mixture was refluxed in a 50mL round bottomed flask with a Dean–Stark apparatus for 1.5h. (benzene steam carried off water, monitored by TLC). The mixture was washed with water and brine, dried (Na_2SO_4) and evaporated to give a residue. The residue was purified by flash column chromatography over silica gel (25 g, 200–300 mesh) using ethyl acetate –petroleum ether (1:20) as an eluent to give **5** (0.28 g, 52%). R_f 0.30 (ethyl acetate–petroleum ether = 1:4). m. p. 105–106℃ . $\upsilon_{max}(cm^{-1})$: 1799, 1652. δ_H(ppm): 1.20(3H, t, J=7.0Hz, CH_3), 3.03(2H, q, J=7.0Hz, CH_2CH_3), 6.04(1H, s, =CH), 7.6–8.0(4H, m, Ar–H). m / z(EI): 202(M^+, 4), 173($[M-29]^+$, 100). R_f 0.31 (acetone: petroleum ether = 1:4).

3–(2–Hydroxybutylidene)phthalide (**1**)

Compound **5** (50 mg, 0.24 mmol) was dissolved in dry methanol (10 mL) and $NaBH_4$(10 mg, 0.26 mmol) was added . The reaction mixture was stirred for 5 min at 0℃ and decomposed with 10% HCl (1mL). The solvent was removed under reduced pressure. Water (15 mL) was added to the residue, the solution acidified with 10% HCl to pH$\approx$2 and extracted with ether (4× 10mL). The ether layer was washed with water and brine, dried (Na_2SO_4) and evaporated to give a residue. The residue was purified by flash chromatography over silica gel (5 g, 200–300 mesh) using ethyl acetate–petroleum ether (1:20) as an eluent to give pale–yellow oil of **1** (39 mg, 77%). R_f 0.18 (ethyl acetate–petroleum = 1:4). υ_{max}(cm^{-1}): 3422(OH), 1785(C=O), 1689, 1611. δ_H(ppm): 1.00(3H, t, J=7.3Hz, CH_3), 1.50–1.85(2H, m, CH_2CH_3), 3.16(1H, br, s, OH, D_2O exchangeable), 4.86(1H, dt, J=8.5, 7.0Hz, –CHOH), 5.64(1H, d, J=8.5Hz, =CH), 7.5–7.8(3H, m, 4–H, 5–H, 6–H), 7.92(1H, d, J=7.6Hz, 7–H). m/z(EI): 204(M^+, 12), 186(10), 175(100), 147(95), 133(11), 129(23). R_f 0.19 (acetone– petroleum ether= 1:4). The spectra data of **1** are consistent with those of the natural product[1,4]. The chemical shift (δ 5.64 ppm) is an indication for the (Z)–configuration (E– : δ 5.85 ppm)[4].

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