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Efficient Synthesis of Thalifoline and Its Analogs

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Abstract: Thalifoline (**1**) and its analogs were synthesized from methyl 3-hydroxy-4-methoxy benzoate by prenyl etherification, Claisen rearrangement, oxidation, imine formation, reductive amination and intramolecular amidation. The last three steps, imine formation, reductive amination, and intramolecular amidation, were completed in one pot at room temperature.

Keywords: Claisen rearrangement, intramolecular amidation, isoquinolinone, one-pot method, thalifoline

Isoquinolinone derivatives are present in a wide variety of natural products[1] and exhibit a broad spectrum of biological activities.[2] Thalifoline (**1a**), with a skeleton of 3,4-dihydroisoquinolin-1-one, was first isolated from *Thalictrum minus* L. var. adiantifolium Hort in 1969 by Doskotch et al.[3] and was reported to possess vasorelaxing activity.[4] So far, a few synthetic routes have been developed to thalifoline. The initial chemical synthesis of thalifoline reported was achieved as a by-product in a photolysis reaction.[5] Another one is through oxidative cleavage reaction of substituted benzylisoquinolines.[6] In 2002, Wang and Georeghiou[7] developed an eight-step approach for the synthesis of thalifoline within 37% overall yield from vanillin using modified Bischler–Napieralski cyclization. These approaches, however, are limited by the application of special starting materials, poor selectivity, or multiple steps. Here we report an efficient approach to the total synthesis

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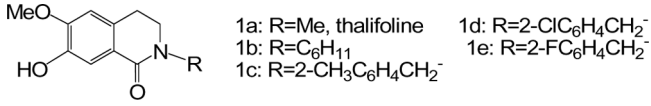
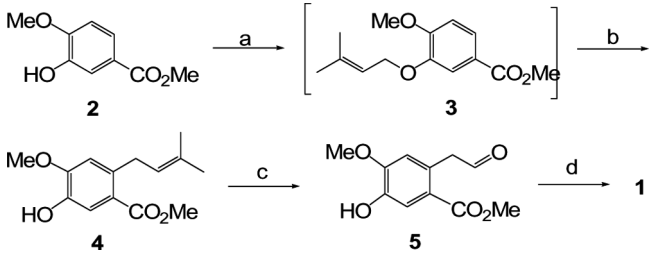


Figure 1. Structure of thalifoline (**1a**) and its analogs.

of thalifoline (**1a**, Fig. 1) and its analogs **(1b–e)** from methyl 3-hydroxy-4-methoxy benzoate (**2**). The synthetic route is outlined in Scheme 1.

The refluxing of **2** with prenyl bromide in the presence of anhydrous K_2CO_3 in acetone quantitatively afforded prenyl ether **3**. A solution of **3** in N,N-dimethylaniline was heated to reflux for 8 h to give the desired methyl 5-hydroxy-4-methoxy-2-prenylbenzoate **4** in a yield of 75%.[8] The prenyl group was moved into the *para*-position of hydroxyl in this Claisen rearrangement process. The oxidation of **4** with $OsO_4/NaIO_4$[9] produced aldehyde **5**, which is a key intermediate for the synthesis of the target compounds. The reaction of **5** with methylamine or other fatty amines, followed by reduction with $NaBH(OAc)_3$,[10] directly gave thalifoline (**1a**) and its analogs (**1b–e**). Actually, **1** was produced by intramolecular amidation of ester after reductive amination. The three steps, imine formation, reduction, and intramolecular amidation, were completed in one pot at room temperature. When R in Fig. 1 is an aromatic group, the nucleophilic property of an aromatic second amine is too weak to undergo smoothly an intramolecular amidation of ester at room temperature, so alkylamines were employed to synthesize thalifoline's analogs. This approach is mild in condition and short in steps compared to the previously reported synthetic routes. The methodology reported herein appears to be a general one and can be applied to the synthesis of 2-substituted-3,4-dihydroisoquinolin-1-ones.



Scheme 1. Route for synthesis of thalifoline. Reagents and conditions: (a) prenyl bromide, K_2CO_3, acetone, reflux, 3 h, quantitative; (b) N,N-dimethylaniline, N_2, reflux, 8 h, 75%; (c) OsO_4, $NaIO_4$, acetone/H_2O/t-BuOH, rt, 12 h, 41.9%; (d) RNH_2/EtOH, $NaBH(OAc)_3$, CH_2Cl_2, rt, 8 h, 55–80%.

EXPERIMENTAL

All melting points were determined on a Beijing micromelting-point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 300-MHz instrument in $CDCl_3$ solution with tetremethylsilane (TMS) as an internal standard. Mass spectra were performed on a Shimadzu GC-MS-QP2010 instrument. Infrared (IR) spectra were recorded on an Avatar 330 (Fourier transform FT)-IR instrument. Purification of reagents and solvents was done according to standard methods. Flash–column chromatography was performed on silica gel.

Methyl 5-Hydroxy-4-methoxy-2-prenylbenzoate (4)

Prenyl bromide (4.25 mL, 32.88 mmol) was added to a mixture of **2** (5.00 g, 27.4 mmol), anhydrous K_2CO_3 (11.36 g, 82.3 mmol), and acetone (80 mL). The resulting mixture was refluxed for 3 h with stirring, cooled to room temperature, and filtered. The filtrate was evaporated under vacuum, and the residue was dissolved in ethyl acetate (100 mL). The solution was washed with 1 M NaOH solution (2×25 mL), water (2×25 mL), and brine (2×25 mL); dried over anhydrous Na_2SO_4; and then filtered. The evaporation of solvent quantitatively afforded **3** as light yellow oil, which was used for the next step without further purification. A solution of **3** (4.00 g, 16.0 mmol) in N,N-dimethylaniline (20 mL) was refluxed under nitrogen for 8 h, cooled to room temperature, and was added to ethyl acetate (200 mL). The mixture was washed with 2 M HCl (6×25 mL), saturated $NaHCO_3$(2×25 mL), and brine (2×25 mL); dried over anhydrous Na_2SO_4; filtered; and concentrated. Flash chromatography of the residue over silica gel using petroleum ether–ethyl acetate (8:1) gave **4** (3.00 g, 75%) as a white solid. Recrystallization of the solid in ethyl acetate gave colorless prismatic crystals. Mp 78.0–79.0°C. ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.73 [6H, s, $C(CH_3)_2$], 3.66 (2H, d, CH_2, $J = 6.49$ Hz), 3.90 (3H, s, OCH_3), 4.05 (3H, s, CO_2CH_3), 5.26 (1H, t, C_H=), 5.50 (1H, s, *OH*), 6.71 (1H, s, *H*-5), 7.50 (1H, s, *H*-2); EI-MS m/z (%) 250.0 (M^+, 80), 218.0 (100); IR (KBr) 3400–3100, 3091, 2969, 2911, 2850, 1687, 1595, 1521 cm^{-1}. Anal. calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.21; H, 7.06.

Methyl 2-(2-Oxoethyl)-5-hydroxy-4-methoxybenzoate (5)

OsO_4 (50 mg, 5 mol%) was added to a stirred solution of **4** (2.00 g, 7.99 mmol) in 3:1:1 acetone–t-BuOH–H_2O (60 mL). After the stirred solution was kept from light at room temperature for 30 min, $NaIO_4$

(5.13 g, 23.97 mmol) was added in one portion. Stirring was continued for 12 h. The reaction mixture was filtered through diatomite (1 cm) and washed with acetone. The filtrate was concentrated in vacuo at room temperature, added to CH_2Cl_2 (150 mL), washed with water (2×25 mL) and brine (2×25 mL), dried, and concentrated. Flash chromatography of the residue over silica gel using petroleum ether–ethyl acetate (2:1) gave **5** (0.75 g, 41.9%) as a white solid. Mp 112.5–113.5°C. ^{1}H NMR (300 MHz, $CHCl_3$) δ 3.94 (3H, s, OC*H*$_3$), 4.00 (2H, d, C*H*$_2$), 4.05 (3H, s, CO_2CH_3), 5.58 (1H, s, *OH*), 6.65 (1H, s, H-5), 7.66 (1H, s, H-2), 9.76 (1H, s, CHO); EI-MS m/z (%) 224.0 (M^+, 30), 196.0 (100); IR (KBr) 3400–3100, 2945, 2845, 1710, 1618, 1585, 1518, cm^{-1}. Anal. calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.23; H, 5.30.

Thalifoline (1a)

A solution of methylamine in dry EtOH (4 M, 0.27 ml, 1.07 mmol) was added dropwise to a stirred and cooled (0°C) solution of **5** (0.20 g, 0.89 mmol) in CH_2Cl_2 (15 ml) under nitrogen. The reaction mixture was stirred for 30 min. The cooling bath was removed, and $NaBH(OAc)_3$ (Alfa Aesar, 95%, 0.40 g, 1.78 mmol) was added. Stirring was continued under nitrogen at room temperature for 8 h. The reaction mixture was filtered, and the solid was washed with CH_2Cl_2. The filtrate was evaporated under vacuum. Flash chromatograph of the residue, using $CHCl_3$–MeOH (30:1), gave **1a** (102 mg, 55.3%) as a colorless solid. Recrystallization of the solid in chloroform gave colorless crystals. Mp 209.5–210.5 (lit.[3]: 210–212°C); ^{1}H NMR (300 MHz, $CHCl_3$) δ 2.91 (2H, t, $J = 6.39$ Hz, Ar−C*H*$_2$), 3.13 (3H, s, N−C*H*$_3$), 3.53 (2H, t, $J = 6.47$ Hz, N−C*H*$_2$), 3.92 (3H, s, O−C*H*$_3$), 6.61 (1H, s, *H*-5), 7.68 (1H, s, *H*-8); EI-MS m/z (%) 207.0 (M^+, 70), 164.0 (75), 136.1 (100); IR (KBr) 3400–3100, 2955, 2839, 1646, 1613, 1574, 1498, 1293 cm^{-1}.

2-Cyclohexyl-7-hydroxy-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (1b)

Aldehyde **5** (100 mg, 0.45 mmol) was dissolved in 10 mL of freshly distilled CH_2Cl_2 in a 50-mL round-bottomed flask under a nitrogen atmosphere cooled by an ice-water bath, and cyclohexylamine (0.061 mL, 0.53 mmol) diluted by CH_2Cl_2 (2 mL) was added. After stirring for 30 min, $NaBH(OAc)_3$ (95%, 0.20 g, 0.89 mmol) was added. The mixture was stirred for another 8 h at room temperature and filtered. The solvent was removed under reduced pressure. Flash chromatography of the

residue, using $CHCl_3$–MeOH (50:1), gave **1b** (80 mg, 65.1%) as a colorless solid. Recrystallization of the solid in petroleum ether–ethyl acetate gave colorless crystals. Mp 221.5–222.5°C. ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.42–1.52 (4H, m, $2 \times CH_2$), 1.67–1.80 (6H, m, $3 \times CH_2$), 2.83 (2H, t, $J = 6.12$ Hz, Ar$-CH_2$), 3.42 (2H, t, $J = 6.14$ Hz, N$-CH_2$), 3.92 (3H, s, O$-CH_3$), 4.64 (1H, m, N$-CH$), 6.61 (1H, s, *H*-5), 7.67 (1H, s, *H*-8); EI-MS m/z (%) 275.1 (M^+, 70), 192.1 (25), 164.1 (100), 136.1 (80); IR (KBr) 3400–3100, 2950, 1650, 1610 cm^{-1}. Anal. calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.07; H, 7.35; N, 4.96.

2-(2-Methylbenzyl)-7-hydroxy-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (1c)

Procedure for the preparation of compound **1c** was the same as that of compound **1b** with a yield of 67.9%. Mp 200.5–202.0°C. ^{1}H NMR (300 MHz, $CHCl_3$) δ 2.33 (3H, s, Ar$-CH_3$), 2.84 (2H, t, $J = 6.32$ Hz, Ar$-CH_2$), 3.40 (2H, t, $J = 6.17$ Hz, N$-CH_2$), 3.93 (3H, s, O$-CH_3$), 4.79 (2H, s, Ar$-CH_2-$N), 6.61 (1H, s, *H*-5), 7.19–7.26 (4H, m, Ar$-H$), 7.70 (1H, s, *H*-8); EI-MS m/z (%) 297.0 (M^+, 100), 282.1 (20), 192.0 (70), 164.0 (70), 136.1 (45); IR (KBr): 3400–3100, 2956, 1647, 1612 cm^{-1}. Anal. calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.60; H, 6.16; N, 4.62.

2-(2-Chlorobenzyl)-7-hydroxy-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (1d)

Procedure for the preparation of compound **1d** was the same as that of compound **1b** with a yield of 80.2%. Mp 191.5–193.0°C. ^{1}H NMR (300 MHz, $CHCl_3$) δ 2.90 (2H, t, $J = 6.27$ Hz, Ar$-CH_2$), 3.52 (2H, t, $J = 6.27$ Hz, N$-CH_2$), 3.93 (3H, s, O$-CH_3$), 4.90 (2H, s, Ar$-CH_2-$N), 5.80 (1H, s, $-$O*H*), 6.62 (1H, s, *H*-5), 7.21–7.37 (4H, m, Ar$-H$), 7.73 (1H, s, *H*-8); EI-MS m/z (%) 317.0 (M^+, 10), 282.1 (100), 192.1 (15), 164.0 (75); IR (KBr): 3400–3100, 2960, 2840, 1651, 1608, 1580 cm^{-1}. Anal. calcd. for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.08; N, 4.41. Found: C, 64.07; H, 4.90; N, 4.20.

2-(2-Fluorobenzyl)-7-hydroxy-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (1e)

Procedure for the preparation of compound **1e** was the same as that of compound **1b** with a yield of 74.4%. Mp 191.5–192.5°C. ^{1}H NMR

(300 MHz, $CHCl_3$) δ 2.88 (2H, t, $J = 6.30$ Hz, Ar-CH_2), 3.53 (2H, t, $J = 6.32$ Hz, N$-$CH_2), 3.92 (3H, s, O$-$CH_3), 4.82 (2H, s, Ar$-$CH_2-N), 5.72 (1H, s, $-$O*H*), 6.61 (1H, s, *H*-5), 7.02–7.46 (4H, m, Ar$-$*H*), 7.70 (1H, s, *H*-8); EI-MS m/z (%) 301.1 (M^+, 100), 192.1 (15), 164.0 (75), 136.1 (55); IR (KBr): 3400–3100, 2958, 2837, 1646, 1606, 1578 cm^{-1}. Anal. calcd. for $C_{17}H_{16}FNO_3$: C, 67.76; H, 5.35; N, 4.65. Found: C, 67.75; H, 5.13; N, 4.49.

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