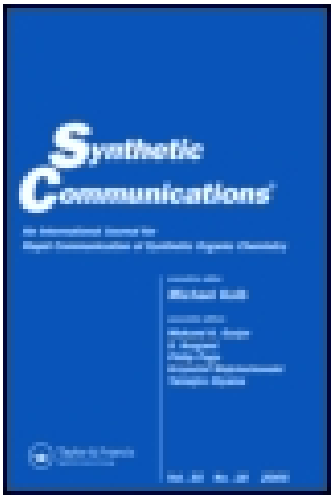

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SHORT SYNTHESIS OF COX-2 INHIBITOR INOTILONE

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An efficient three-step synthesis of COX-2 inhibitor inotilone from acetaldoxime is described. The structure of inotilone was elucidated via an aldol reaction between 5-methyl-3(2H)-furanone and 3,4-dihydroxybenzaldehyde. This approach describes a convenient pathway to 5-alkyl-3-furanones through isoxazole chemistry.

Keywords: COX-2 inhibitor; 3(2*H*)-furanone; inotilone; isoxazol ring

In 2006, Wangun and coworkers[1] reported the isolation and structure elucidation of an unusual 5-methyl-3(2*H*)-furanone derivative, inotilone **1**, along with several phenylpropanoid-derived polyketides from the fruiting body of the mushroom *Inonotus* sp. (Fig. 1).[1]

When evaluated for its inhibitory activities in COX (cyclooxygenase) assays, inotilone **1** showed a potent COX-2 inhibitory activity with IC_{50} value of 0.03 μM.[1] The selective inhibition of COX-2 showed by inotilone **1** is comparable to those of the already marketed selective inhibitors meloxicam and nimesulide.[2] Therefore, the selective inhibitory potency of inotilone along with its unique structure inspired us to design a simple synthetic route to prepare inotilone and possibly its analogs. Inotilone can be synthesized via aldol reaction between 5-methyl-3(2*H*)-furanone **2** and 3,4-dihydroxybenzaldehyde **3** (Scheme 1).

In 2007, Shamshina and Snowden[3] first reported the synthesis of inotilone in six steps, starting from 2,4-pentanedione, by applying the Mukaiyama aldol reaction between trimethylsilyloxyfuran and 3,4-dihydroxybenzaldehyde in the last step. One of the main goals of our current research is to exploit the isoxazole ring in the total synthesis of natural products that contain the 3(2*H*)-furanone ring. Studies showed that catalytic hydrogenation of isoxazole ring under mild conditions broke the N−O bond, thus providing β-iminoenol, which can be converted in situ to 3(2*H*)-furanone by acidic treatment followed by basic treatment (Scheme 2).[4]

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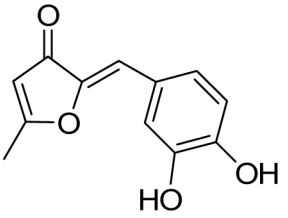
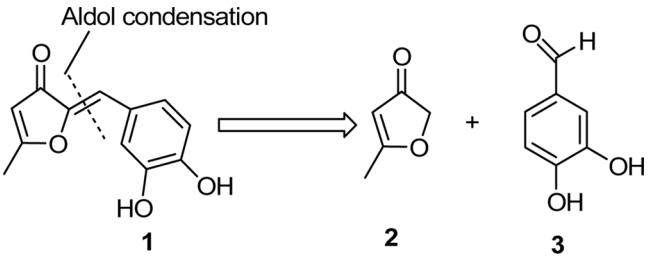
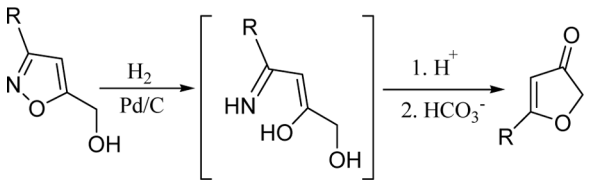


Figure 1. Inotilone **1**.



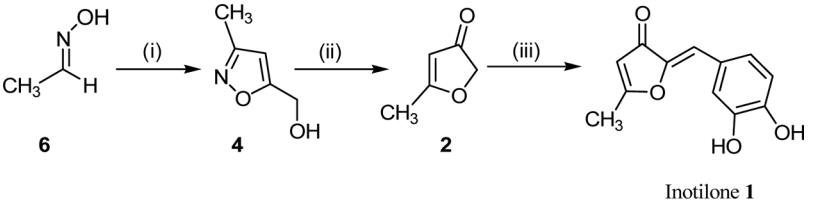
Scheme 1. Retrosynthetic strategy.



Scheme 2. Conversion of isoxazole ring to 3(2*H*)-furanone.

RESULTS AND DISCUSSION

The synthesis of inotilone (Scheme 3) started with the preparation of 3-methyl-5-(isoxazolyl) methanol **4** from acetaldoxime **6**, according to the method of Chimichi and coworkers.[5] Therefore, acetaldoxime was treated with sodium hypochlorite and triethylamine to form nitrile oxide, which reacted insitu with propargyl alcohol in a [3 + 2] cycloaddition reaction to form compound **4** in 64% yield. Catalytic hydrogenation of compound **4** in the presence of 10% palladium on charcoal in MeOH occurred smoothly, giving a white solid, which was subsequently subjected to acidic hydrolysis with hydrochloric acid (1 M, pH < 1) followed by treatment with saturated bicarbonate solution to afford 5-methyl-3(2*H*)-furanone **2** in 80% yield. Compound **2** was converted to the enol form after standing, as confirmed by ^{1}H NMR ($CDCl_3$). As depicted in the retrosynthetic analysis outlined in Scheme 1, we envisioned inotilone through an aldol reaction between



Scheme 3. Synthesis of inotilone. Reagents and conditions: (i) Propargyl alcohol, Et_3N, NaOCl, $CHCl_3$, 0 °C; (ii) (a) H_2/Pd-C, MeOH, room temperature; (b) HCl (1 *M*), then sat. $NaHCO_3$; (iii) 3,4-dihydroxybenzaldehyde, K_2CO_3, THF, room temperature.

3(2*H*)-furanone **2** and 3,4-dihydroxybenzaldehyde **3**. In this context, the reaction of freshly prepared sample of compound **2** with 3,4-dihydroxybenzaldehyde in tetrahydrofuran (THF) in the presence of aqueous potassium carbonate afforded inotilone **1** in 70.9% yield.

In conclusion, we have described a quick synthesis of COX-2 inhibitor inotilone **1** in only three steps with 36.4% overall yield starting from commercially available acetaldoxime. This work highlights the utility of the isoxazole ring as a precursor for the 3(2*H*)-furanone ring.

EXPERIMENTAL

General

The reagents and solvents were obtained from Aldrich and used without further purification. Infrared (IR) spectra were obtained with a Nicolet Magna 560 spectrometer. NMR spectra were recorded on a Bruker Avance 400 (^{1}H: 400 MHz; ^{13}C: 100.6 MHz). The internal standard used was tetramethylsilane (TMS). Data are reported as chemical shift (multiplicity, number of protons, coupling constant). Mass spectra were measured using a Quatro Ultima PT (Waters Corp., MA, USA) instrument.

3-Methyl-5-(isoxazolyl)methanol 4

Propargyl alcohol (5.72 g, 0.102 mol), triethylamine (0.69 g, 0.0068 mol), and sodium hypochlorite (5%, 40.0 mL) were mixed in 200 mL of chloroform. Acetaldoxime **5** (1.0 g, 0.0169 mol) was added dropwise to the cooled reaction mixture. The reaction mixture was further stirred in the ice bath for 45 min. The heterogeneous mixture was separated, and the aqueous layer was extracted with chloroform (2×10 mL). The organic layer was dried, filtered, and concentrated under vacuum. The resulting yellow oil was purified by column chromatography on silica gel using EtOAc/hexanes for elution to give compound **4**. Yield 64%: IR (KBr) ν_{max} in cm^{-1}: 3369 (O−H), 1610 (C=C), 1560 (C=N aromatic); ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 2.29 (s, 3H), 3.47 (s, 1H), 4.72 (s, 2H), 6.09 (s, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ in ppm: 11.26, 56.30, 102.43, 159.78, 171.08. HPLC-MS m/z calcd. for $C_5H_8NO_2$, 114.11; found 114.11 (MH+).

5-Methyl-3(2*H*)-furanone 2

A mixture of 3-methyl-5-(isoxazolyl)methanol **4** (2.59 g, 0.023 mol) and Pd/C 10% (1.14 g) in methanol (40.7 ml) was hydrogenated for 6 h. The reaction mixture was filtered and washed with methanol, and the solvent was removed under vacuum to yield a white solid. The white solid was dissolved in HCl (1 M), and the mixture was stirred for 4 h, then neutralized with saturated $NaHCO_3$. The product was extracted with diethyl ether (3×10 mL), dried, filtered, and concentrated to give compound **2.** Yield 80%: IR (KBr) ν_{max} in cm^{-1}: 1694 (C=O), 1600 (C=C), 1289 (C−O); ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 2.25 (s, 3H), 4.50 (s, 2H), 5.49 (s, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ in ppm: 17.16, 75.87, 105.31, 191.97, 203.26. HPLC-MS m/z calcd. for $C_5H_7O_2$, 99.04; found 99.05 (MH+).

Inotilone 1

A solution of K_2CO_3 (2.2 g) in water (10 mL) was added to a solution of 5-methyl-3(2*H*)-furanone **2** (0.77 g, 7.9 mmol) and 3,4-dimethoxybenzyladehyde **3** (1.30 g, 7.8 mmol) in THF (10 mL). The reaction mixture was stirred under reflux for 3 h, and the product was extracted with dichloromethane (3×10 mL). The organic layer was separated, dried, filtered, and concentrated under vacuum, and the residue was purified by column chromatography on silica gel using EtOAc/hexane for elution to give compound **1** as orange solid. Yield 1.22 g, 70.9%; mp: 177.4°C. ν_{max}(KBr)/cm^{-1} 3340 (O−H), 1678 (C=O), 1606 (C=C), 1256 (C−O); ^1H NMR (400 MHz, DMSO-d6) 2.40 (s, 3H), 5.58 (s, 1H), 6.53 (s, 1H), 6.82 (d, 1H, *J* 8.3 Hz), 7.19 (dd, 1H, *J* 1.9 Hz and 8.3 Hz), 7.38 (d, 1H, *J* 1.9 Hz); ^{13}C NMR (100.4 MHz, DMSO-d_6) δ in ppm: 16.61, 106.39, 112.87, 116.83, 118.87, 123.86, 125.67, 145.27, 146.41, 149.09, 181.42, 187.59. HPLC-MS m/z calcd. for $C_{12}H_{10}O_4$, 218.06; found 218.0 (M^+). These data compare favorably with the published data.[1,3]

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