SYNTHESIS AND CHARACTERIZATION OF NEW TETRALONES AS INTERMEDIATES FOR PODOPHYLLOTOXIN ANALOGUES.

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Abstract

Podophyllotoxin is a naturally occurring lignan. It exhibits mainly antimitotic activity. Podophyllotoxin and its derivatives and analogues (a), (b) showed good antimitotic activity. The new tetralone intermediates 4-(3', 4'-dimethoxy phenyl) 6, 7 dioxymethylene -1-tetralone and 4-(3', 4', 5'-triimethoxy phenyl) 6, 7 dioxymethylene-4-1-tetralone intermediates of Podophyllotoxin were synthesized in good yields by Chalcone route. They are required for analogues of Podophyllotoxin.

Key Words

Synthesis, Chalcones, Cyclopropyl ketone, Tetralones, Podophyllotoxin.

1. Introduction

Podophyllotoxin1 is a strong antimitotic agent which has been extracted from two important medicinal plants named Podophyllum Emodi an Indian species and Podophyllum Peltatum a North American species. It also occurs in many other plants of Podophyllum species. Podophyllotoxin and several of its derivatives and analogues showed good antimitotic activity. It was decided to synthesize new tetralone intermediates 6 and 7 for analogues of Podophyllotoxin by Chalcone route (scheme-1).

2. EXPERIMENTAL

2.1 Material and methods.

All the reagents and chemicals were purchased and used without further purification. Melting points were taken in open capillary tubes and are uncorrected. The precoated silica gel TLC plates were used to monitor the progress and completion of the reaction. The products were purified by recrystallisation from methanol or from column chromatography. IR spectra in KBr were recorded on Perkin-Elmer model 683 or 1310 Spectrometers. H1 NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded using tetramethyl silane (TMS) as an internal reference are recorded on Bruker spectrometer. Elemental analyses were performed on a Perkin elmer 2400. The Mass spectra were obtained on CEC-21-100B.
Podophyllotoxin 1

(a)

(b)


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a. $R_1^1 = H$, $R_2^1 = R_3^1 = OCH_3$,
b. $R_1^2 = R_2^2 = R_3^2 = OCH_3$. 

I

II

III

IV

$R_1^3$, $R_2^3$, $R_3^3$
Reagents and conditions

(I) Ac₂O, fused ZnCl₂, stirred at rt(29⁰C) for 4 hours.

(II) NaOH, H₂O, C₂H₅OH stirred at rt(29⁰C) for 4 hours.

(III) NaH, dry Benzene, Trimethyl sulphonium Iodide, stirred at rt(29⁰C) for 10 hours and further for 50-60⁰C for 1 hour.

(IV) Anhyd SnCl₄, Ac₂O, dry CH₂Cl₂ stirred at 29⁰C for 5 hours.

SCHEME 1

2.2 SYNTHESIS

2.2.1 General procedure for the synthesis of chalcones 4(a-b).

1-Acetyl-3, 4-benzodioxole (5g) and substituted benzaldehydes (4.5grams) were stirred in water (25ml) and ethanol(15ml) mixture in the presence of Sodiumhydroxide (2grams) at room temperature (29-30⁰C) for 6 hours. Then the reaction mixture was kept overnight in an ice bath. The precipitated products were filtered and recrystallized from methanol.

1] 1-(benzo[d][1,3]dioxol-6-yl)-3-(3,4-dimethoxy phenyl) prop-2-en-1-one:

Color: Light yellow solid. Yield: 80%. M.P: 68-70⁰C. IR (KBr): 1664cm⁻¹ (C=O), 1573(C=C).

¹H NMR(CDCl₃): δ 5.99(s,2H,-O-CH₂-O), 7.56(d,J=3Hz,1H,αC-H), 7.69(d, J=3Hz,2H,βC-H), 6.814-7.65(m,6H,Ar-H).

¹³C NMR Spectra:


2] 1-(benzo[d][1,3]dioxol-6-yl)-3-(3,4,5-tri methoxy phenyl) prop-2-en-1-one:

Color: Light yellow solid. Yield: 80%. M.P: 75⁰C. IR (KBr): 1655cm⁻¹ (C=O), 1579(C=C).

¹H NMR(CDCl₃): δ 6.05(n,d,J=3Hz,1H,αC-H), 7.62(d,J=3Hz,2H,βC-H), 6.84-7.43(m,5H,Ar-H).

¹³C NMR Spectra:

2.2.2 General procedure for the synthesis of cyclopropyl ketone.

Sodium hydride (0.9g) was added in portions to the stirred suspensions of trimethyl sulfoxonium iodide (7g) in dry Benzene (20 ml). The reaction mixture was stirred for 20 minutes at 30°C. Chalcones (8g) in dry Benzene (15ml) is added drop wise during 30 minutes to the above solution. The reaction mass was stirred at 28-29°C for 4 hours and raised the temperature to 50-60°C for 1 hour. The completion of the reaction was confirmed by thin layer chromatography and the reaction mixture was poured into 5% hydrochloric acid solution (20ml). The precipitated gummy residue was extracted into chloroform. The combined organic layer was washed with water, dried over anhyd.Na₂SO₄ and concentrated under reduced pressure. They were recrystallized from methanol.

1] (benzo[d][1,3] dioxol-6-yl) (2-(3,4-dimethoxy phenyl) cyclopropyl) methanone:

Color: Light yellow solid. Yield: 70%. Melting Point: 121-123°C. IR(KBr): 1650 cm⁻¹ (C=O), 1604 (C-C of cyclopropyl), 1592 (ArC=C). ¹H NMR (CDCl₃): 5.96-5.98 (s, 2H, -O-CH₂-O-), 1.98 (m, 1H, C₁-H-), 0.75-0.80 (t, 2H, J=4 Hz, -C₂-H), 2.28 (m, 1H, C₃-H), 5.98-7.69 (m, 6H, Ar-H). Mass Spectrum: 327(M+1). Anal.calcd.for: C₂₀H₂₀O₆, C=76.68, H=5.30, O=18.02. Found C=76.69, H=5.26, O=18.04.

2] benzo[d][1,3] dioxol-6-yl) (2-(3,4,5-trimethoxy phenyl) cyclopropyl) methanone:

Color: Light yellow solid. Yield: 70 %. M P.: 133-135°C. IR (KBr): 1655 cm⁻¹ (C=O), 1603 (C-C of cyclopropyl), 1596 (ArC=C). ¹H NMR (CDCl₃): 5.997 (s, 2H, -O-CH₂-O-), 2.59 (m, 1H, C₁-H), 1.248-1.45 (t, 2H, J=4 Hz, C₂-H), 2.69 (m, 1H, C₃-H), 6.77-7.63 (m, 5H, Ar-H). Mass Spectrum: 357(M+1). Anal.calcd.for: C₁₉H₁₈O₅, C=69.93, H=5.56. Found C=69.88, H=5.57.

2.2.3 General procedure for the synthesis of key intermediate tetralones.

Cyclopropyl ketones (3g) were dissolved in dry dichloromethane (25ml). Acetic anhydride (0.94 ml) and anhydrous stannic chloride (1ml) were added. The resultant reaction mixture was stirred at 27-29°C for 3 hrs. The completion of reaction was known by TLC. The reaction mixture was poured into 5% HCl solution (20 ml), the product was extracted into Chloroform. The organic layer was washed with 5% HCl followed by water, dried over anhyd. Na₂SO₄ and concentrated under vacuum using a rotary evaporator to give brown residue.
product was purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent. The benzene solution was concentrated to a small volume (20ml) and hexane (100ml) was added drop wise to give products in good yields. They were recrystallized from methanol.

1] 7, 8 dihydro-8-(3, 4-dimethoxy phenyl) naphtho[2,3-d][1,3]dioxol-5(6H)-one.
Color: Dark brown solid. Yield of the product: 68.35%. Melting Point: 102-104°C. IR (KBr): 2915 cm\(^{-1}\) (C-H), 1602 (C=C), 1661 (C=O).\(^1\)HNMR (CDCl\(_3\)): 5.96-5.98 (s, 2H, O-CH\(_2\)-O), 2.57 (tt, 2H, C\(_2\)-H), 2.577 (m, 2H, C\(_3\)-H), 4.027 (t, 1H, C\(_4\)-H), 7.047-7.757 (m, 5H, Ar-H). Mass Spectrum (ESI, m/z): 327 (M+1). Anal. calcd. for C\(_{19}\)H\(_{18}\)O\(_5\): C=69.93, H=5.56, O=24.51 Found C=69.91, H=5.45, O=24.4.

2] 7, 8-dihydro-8-(3,4,5-trimethoxy phenyl) naphtho [2,3-d][1,3]dioxol-5(6H)-one.

3. Results and discussion

1, 3-methylenedioxy acetophenone 2 was prepared in excellent yield by acylation reaction of 1, 3-benzodioxole with acetic anhydride in presence of fused zinc chloride. The chalcones 4(a-b) were prepared in good yields by the claisen-schmidt condensation of compound 2 with substituted benzaldehydes separately in the presence of sodium hydroxide in ethanol-water mixture. The cyclopropyl ketones 5a-b were prepared in good yields by the reaction of chalcones 4(a-b) with trimethyl sulphonium iodide in presence of sodium hydride in benzene. The tetralone 6&7 were prepared in good yields by the intramolecular cyclization of cyclopropyl ketones 5 a-b in presence of anhydrous stannic chloride and acetic anhydride in dry dichloromethane. The structure of all the synthesized compounds were confirmed by IR, \(^1\)H NMR, Mass spectra and elemental analysis. The \(^1\)H NMR spectrum of 6 showed distinct singlets at \(\delta 6.58\) and 7.53 assignable to aromatic C\(_5\)-H and C\(_8\)-H respectively and broad multiplet
between δ2.62-3.16 for C₂, C₃ and C₄ protons. IR spectrum showed the carbonyl group stretching frequency at 1677cm⁻¹. Tetralone 7 showed similar spectra.

4. Conclusioin

In this summary, a convenient synthesis of tetralones as intermediates for podophyllotoxin analogues has been developed. The chalcone method gave good yields of tetralones. We have used environmental friendly chemicals and conditions. They are very useful for the synthesis of analogues of podophyllotoxin.

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