

Short Communication

Synthesis of trans-3,4-dibenzyl-2-oxo-tetrahydrofuran

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Trans-3,4-dibenzyl-2-oxo-tetrahydrofuran (6) a substituted tetrahydrofuranoid lignan was synthesized in 70% yield via the Stobbe condensation between (1) benzaldehyde and (2) diethyl succinate. The structure was confirmed by the spectral data such as infra-red, proton magnetic resonance and mass spectrum. It has two similar but non equivalent aromatic groups which appeared at δ : 6.48 - 6.76 and 7.06 - 7.25 as multiplets.

Key words: Lignans, tetrahydrofuranoid, Stobbe.

INTRODUCTION

Lignans belonging to the substituted tetrahydrofuran class represent a unique group not only owing to their distribution pattern (Rao, 1978) but also due to their utility as synthons in the synthesis of 2,4-diaryl substituted furofurans (Jack and Fekarurhobo, 2003). Although, most lignans occur in plants (Jack et al., 2003), a few have been isolated from the urine of humans and animals such as baboons, vevet monkeys and rats (Cooley et al., 1981; Set-Chell et al., 1980).

The physiological importance of these lignans as synergists, anti-hypertensive agents and germination inhibitors cannot be overemphasized (Chakraverty et al., 1979; Sih et al., 1976). Isolation and synthesis of some lignans belonging to this class have been previously reported (Jack and Fekarurhobo, 2003; Jack et al. 2003) using a diaryl dioxo diester.

In this paper, an alternative approach leading to the formation of a lignan belonging to the substituted tetrahydrofuranoid class is described and discussed. The advantage of this method over the other is that the reactions are smoother with fewer mixture of products caused by isomerisation and the overall yield of the butyrolactone is better.

MATERIALS AND METHODS

Infra-red spectra were recorded on Pye-Unicam SP1050 Spectrometer. Proton magnetic resonance was run on a Varian HA

100 instrument using tetramethylsilane (TMS) as an internal standard in CDCl_3 with chemical shift value given in δ (ppm). Mass spectra were obtained on an Airborne Electronic Terrain Map System (AETMS) 9 double focusing spectrometer at 250°C and 70 eV.

Thin layer chromatography (TLC) was performed on silica gel GF 254 plates using ethyl acetate: cyclohexane (1:1) as solvent system. All reagents and solvents were purified before use by refluxing over calcium hydride and redistillation.

Compound (3)

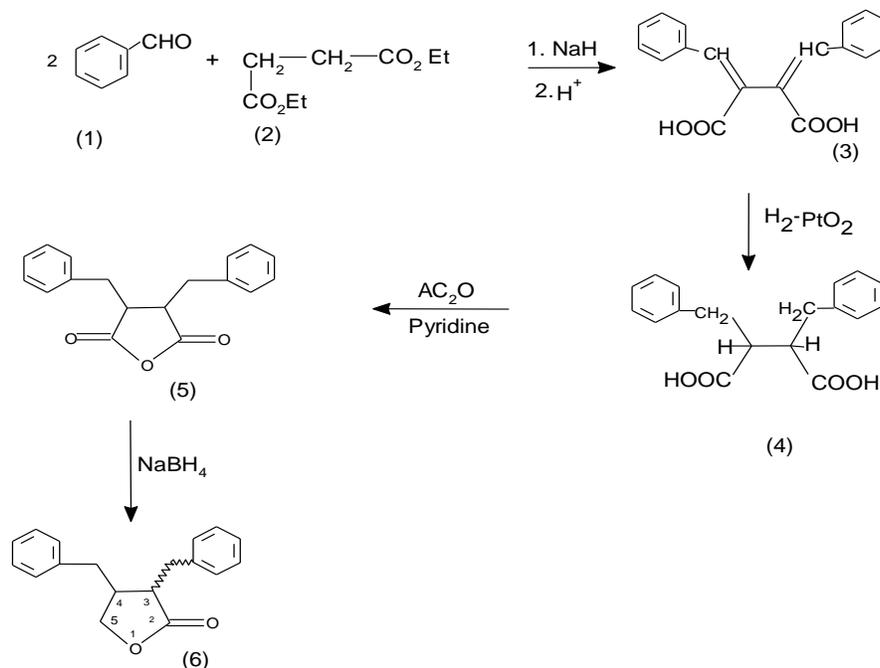
1.92 g (0.08 moles) NaH suspension was put into 1 litre three neck flask and washed with dry pentanes (70 ml x 3). The flask and its content were dried on the pump for a few minutes to remove the pentane. 100 ml dry diethyl ether was added into the flask which was flushed with nitrogen for twenty minutes. To this ethereal suspension of NaH was added dropwise, 6.96 g (0.04 moles) diethyl succinate in 40 ml dry diethyl ether and stirring (with the flask surrounded by cold water) for about two hours until the sodium salt was formed as a sludge. An ethereal solution of 8.48 g [(0.08 moles) benzaldehyde in 80 ml diethyl] ether was added into the flask dropwise while the mixture was stirred continuously for about 4 h. The mixture was acidified with 3 M HCl to pH 1 and then extracted with diethyl ether (80 ml x 3). The ether extract was washed with water (100 ml x 2) and dried over anhydrous Na_2SO_4 . Evaporation of the solvent gave an oil which could not crystallize when treated with ethanol, acetone and acetone ethyl acetate mixture separately.

Yield: 9.2 g (78 %) IR (film) (CH) 3012-2900, (COOH) 2945-2700, (arom.) 1608 cm^{-1} ; ^1H n.m.r (CDCl_3) (COOH) 12.00 s, (ArH) 7.00-6.94 m, (CH) 6.62-6.50 m; mass spectrum M^+ 295.

2,3-bis-benzyl succinic acid (4)

Into a 250 ml two neck round bottom flask containing 100 mg of

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Scheme 1. Refluxation of dibenzyl succinic acid (4) with acetic anhydride and pyridine to yield the anhydride (5) which was partially reduced with sodium borohydride in isopropanol to give the lignan

platinum oxide catalyst was put 5.2 g (0.02 moles) of compound (3) in 100 ml absolute ethanol and hydrogen gas was passed into the flask at room temperature over 7 h, stirring by using a stirrer. TLC of the mixture after 7 h showed that all the starting material had reacted.

The mixture was filtered to remove the platinum and the filtrate evaporated to give an oil which was carried forward to the next reaction.

Yield: 4.6 g (88 %) IR (film) (CH) 3100-2890, (COOH) 2700-2500, (arom.) 1605 cm^{-1} ; ^1H n.m.r. (CDCl_3) (COOH) 12.04 s, (ArH) 7.10-6.90 m, (CH) 5.80-5.54 m, (CH_2) 4.70-4.50 d; mass spectrum M^+ 299.

The anhydride (5)

3 g of compound (4) in 20 ml dry pyridine was refluxed with 80 ml acetic anhydride in a 200 ml round bottom flask for 5 h. The flask was allowed to cool to room temperature and the content poured into 200 ml of ice-cold water in a beaker. After allowing to stand for 30 min the mixture was extracted with ethyl ethanoate (50 ml x 3), washed with 1M HCl (25 ml x 3) and finally with water (30 ml x 2). After drying over anhydrous Na_2SO_4 , the solvent was evaporated to give an oil which failed to crystallize on standing in the fridge over night and also after treatment with n-hexane.

Yield: 2.22 g (78.6 %) IR (film) (CH) 3050-2910, (anhydride) 1866, (arom.) 1610 cm^{-1} ; ^1H n.m.r. (CDCl_3 , ArH) 7.40-6.80 m, (CH) 5.10-4.80, (CH_2) 3.10-2.90; mass spectrum M^+ 281.

Trans-3,4-dibenzyl-2-oxo tetrahydrofuran (6)

1.5 g (5.4 mmoles) of (5) was suspended in 40 ml isopropanol in a 200 ml flask and 100 mg (2.7 mmoles) NaBH_4 was slowly added,

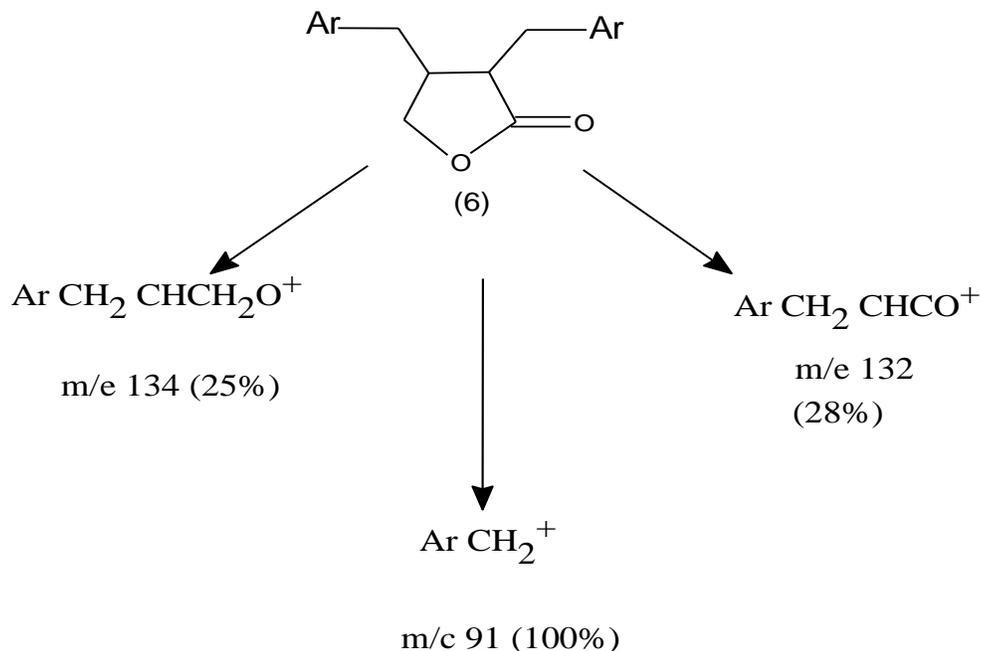
and was stirred for 36 h. 50 ml of aqueous ether was added and the pH of the medium was brought to 6 with dilute HCl with vigorous stirring.

The organic layer was removed, washed with water (25 ml x 3), dried over anhydrous Na_2SO_4 , filtered and evaporated to give a gum which defied many attempts to crystallize it.

Yield: 980 mg (70 %) IR (film) (CH) 3090-2900, (γ -lactone) 1770, (arom.) 1608 cm^{-1} ; ^1H n.m.r. (CDCl_3) (ArH, 5H) 7.06-7.25 m, (ArH, 5H) 6.48-6.76 m, (ArCH₂, 4H) 2.52 m, H-3 (1H) 2.92 m, H-4 (1H) 2.96 m, H-5 (2H) 3.87, 4.13 dd; mass spectrum M^+ 267.

RESULTS AND DISCUSSION

The reaction involved the classic Stobbe condensation using an ethereal solution of two moles of benzaldehyde (1) with one mole of diethyl succinate (2) in the presence of sodium hydride. Acid hydrolysis gave the unsaturated substituted succinic acid 3 which could not crystallize in attempt to purify it. Catalytic hydrogenation of (3) over platinum oxide in absolute ethanol at room temperature gave 2,3-bis-benzyl succinic acid (4) in over 80% yield. When the dibenzyl succinic acid (4) was refluxed with acetic anhydride and pyridine, it afforded the anhydride (5) which was partially reduced with sodium borohydride in isopropanol to give the lignan (6) as a gum having R_f 0.58 using silica gel GF254 in a system ethyl ethanoate: cyclohexane (1:1) v/v (Scheme 1). There was also another minor spot overlapping the major spot having R_f 0.58. This may presumably account for the difficulty encountered in crystallizing the lignan (6) which may be



Scheme 2. Establishment of the molecular formula $\text{C}_{18}\text{H}_{18}\text{O}_2$ for the lignan (6) from the mass spectrum giving the parent peak at m/e 266 with other attendant prominent peaks at m/e 134 and 132 corresponding to the fragment ions $\text{ArCH}_2\text{CHCH}_2\text{O}^+$ and $\text{ArCH}_2\text{CHCO}^+$ respectively. The base peak is the benzyl cation ArCH_2^+ at m/e 91.

considered as a mixture.

In the infra-red spectrum of the lignan (6), the presence of an aromatic and a five member γ -lactonic groups at ν_{max} 1608 and 1770 cm^{-1} respectively were evident. This can be distinguished from the anhydride (5) which has an R_f 0.46 in the same solvent system above and gave a band at ν_{max} 1866 cm^{-1} (Jack and Orubite, 2009). The anhydride (5) also gave a molecular ion peak M^+ at m/e 280.

The molecular formula $\text{C}_{18}\text{H}_{18}\text{O}_2$ was established for the lignan (6) from the mass spectrum which gave the parent peak at m/e 266 with other attendant prominent peaks at m/e 134 and 132 corresponding to the fragment ions $\text{ArCH}_2\text{CHCH}_2\text{O}^+$ and $\text{ArCH}_2\text{CHCO}^+$ respectively (Scheme 2). The base peak is the benzyl cation ArCH_2^+ at m/e 91.

The proton magnetic resonance spectrum of the lignan (6) revealed signals characteristic of two similar but non equivalent aromatic groups which centred at δ 6.48-6.76 and 7.06-7.25 as multiplets with each group integrating for five protons. In addition, the AB- parts of two ABX-systems which centred at δ 4.13 ($J_{\text{AB}} = 9$, $J_{\text{AX}} = J_{\text{BX}} = 7$) and δ 2.96 ($J_{\text{AB}} = 14$, $J_{\text{AX}} = 5$, $J_{\text{AB}} = 6$) could be detected arising from the partial structures of $\text{OCH}_2\text{-CH-CH-}$ and $\text{ArCH}_2\text{CH-}$ with the methylene protons next to the oxygen appearing as double doublet at δ 3.87 and 4.13. Consequent on these facts, the structure of this lignan is given as (6) in Scheme 1.

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