Facile Synthesis of 9,10-Dihydro-4H-Benzo [4,5] Cyclohepta [1,2-b] Thiophene-4-One: A Crucial Drug Intermediate-Application of Wittig-Horner Reaction

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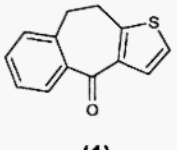
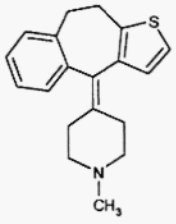
Abstract: Synthesis of 9,10-dihydro-4H-benzo [4,5] cyclohepta[1,2-b] thiophene-4-one, a key pharmaceutical intermediate was described by two different routes. The formation of Cannizzaro reaction products was observed in first route. Wittig-Horner reaction conditions were utilized in the second route to obtain the title compound in good yield.

Introduction

Condensed tricyclic systems exhibit psychopharmacological and antihistamine properties. Many tricyclic compounds having two aromatic rings grouped around a central seven membered ring display various types of biological actions like analgesic[1], antiinflammatory[2], antiasthmatic[3] and antidipressants[4]. Different derivatives of these ring systems have been introduced as drugs in therapy. In this line, the leading pharmaceutical products are the antimigraine agent pizotifen[5, 7] **(2),** the antiasthmatic agent ketotifen[6, 8,9] **(3),** non ulcerogenic antiinflammatory and antiarthritic agents[10,11]. The present work was now continued to synthesize the interesting tricyclic skeleton of 9,10-dihydro-4H-benzo [4,5] cyclohepta [1,2-b]thiophene-4-one[5,6], a tricyclic ketone **(1)**. The main task of our investigation was the synthesis of tricyclic ketone.



(1)



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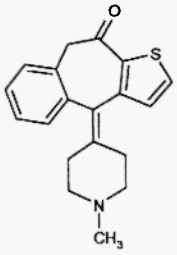
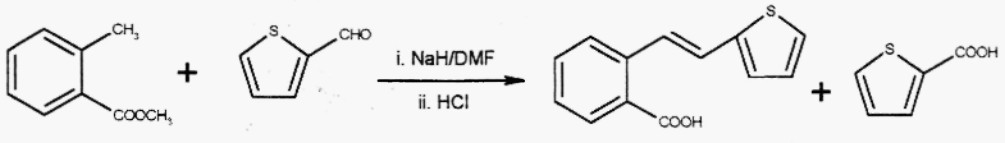


(3)

Several researchers have worked on the synthesis of tricyclic ketone and many reports were reported[5, 11-15]. In all the above methods, the starting materials are costly, reaction conditions are drastic and involves more steps. In continuation of our work on the synthesis of tricyclic derivatives of pharmacological importance, the synthesis of tricyclic ketone was undertaken.

Results and Discussion

To prepare the tricyclic ketone, 2-[2-(2-thienyl) vinyl] benzoic acid **6** is the key compound and was prepared by the reaction of thiophene-2-carboxaldehyde **5** and methyl-o-toluate **4**. Thiophene-2-carboxaldehyde was prepared by the reaction of thiophene with dimethylformamide[16.17]. The reaction of thiophene-2-carboxaldehyde with methyl-o-toluate in presence of sodium methoxide was reported in a Swiss patent[14]. In our present work, to obtain better yield the reaction was carried out using sodium hydride in dry DMF. Cannizzaro reaction of thiophene-2-carboxaldehyde also took place in the reaction that was confirmed by the formation of thiophene-2-carboxylic acid **7** (18% yield) and thienyl-2-methanol. However, the major product is vinyl carboxylic acid **6**. The thienyl vinyl benzoic acid, thiophene carboxylic acid and the unreacted o-toluic acid were isolated as pure products by careful extraction of the organic layer with 5% sodium hydroxide (Scheme 1). The reduction of olefinic acid was achieved by hydrogenation[14] using Pd-C and was cyclized with polyphosphoric acid[5] to obtain the tricyclic ketone **(1).**



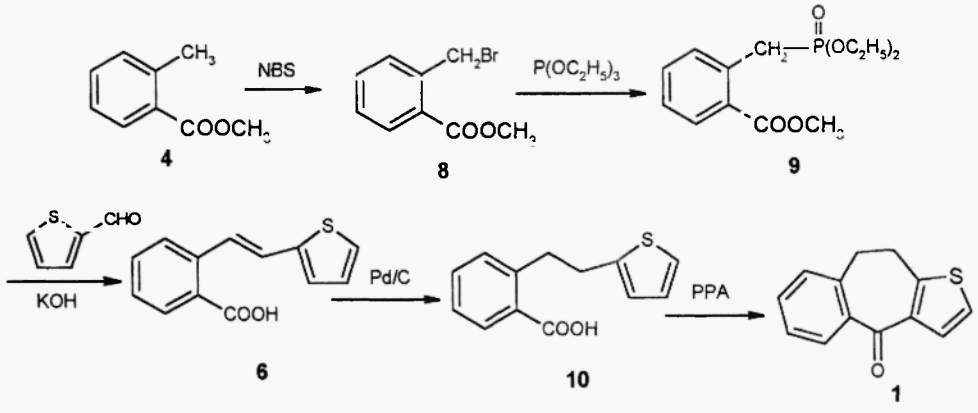
4 **5** **6** **7**

Scheme-1

In the above scheme though the vinyl carboxylic acid is formed in a single step, the reaction work-up is tedious, side products and polymerized products have

reduced the yield. To improve the yield of the acid, the application of 'Wordsworth-Emmons'[18] reaction conditions were utilized as shown in Scheme (2).

Methyl-o-toluate was brominated with N-bromosuccinimide to obtain methyl (2-bromomethyl) benzoate **8.** Then, phosphonate **9** was obtained by heating bromo compound with triethyl phosphite. The thienyl vinyl benzoic acid **6** was prepared by Wittig-Horner reaction of phosphonate and thiophene-2-carboxaldehyde in 80% yield. The reduction of olefinic acid was achieved by palladium carbon hydrogenation[14] to obtain **10** and was cyclized with polyphosphoric acid[5] to obtain tricyclic ketone (1). The purity of the compound was determined by GLC on Hewlett Packard 5840A instrument using 3ft.×1/4" glass column packed with 3% OV-1 under the conditions: Oven temperature programmed from 150 °C - 275 °C at the rate of 10.0 per minute, injection port and flame ionization temperatures was maintained at 275 °C and 300 °C respectively. Flow rate (pressure) of the carrier gas (Nitrogen) was 35 ml/min. The purity of the product was 97.47% against the standard sample purity of 99.72%.



Scheme-2

In conclusion, thienyl vinyl benzoic acid **6** was prepared by using sodium hydride and the formation of side products of Cannizzaro reaction were observed and isolated. Further more, the tricyclic ketone was more conveniently prepared by using commercially available cheap raw materials employing Wittig-Horner reaction conditions, thus simplifying the reaction work-up and the yield was considerably improved.

Experimental

Melting points were determined on a Buchi capillary melting point apparatus. The ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on a VG micromass 70-70H mass spectrometer and IR spectra were recorded on Nicolet FT IR-740.

2-[2-(Thienyl) vinyl] benzoic acid **6** (from Scheme1):

To a well-stirred mixture of sodium hydride (7.2g., 0.24 mole) (80%) in 160 ml dry DMF was added a solution of freshly distilled thiophene-2-carboxaldehyde (22.4g., 0.2 mole) and methyl-o-toluate (30g., 0.2 mole) at 0 ^{0}C by dropwise over a period of 45 minutes. The reaction was continued at R.T. for 12 hr. DMF was removed under vacuum, 60ml toluene and 150ml water were added to the residue and the aqueous phase was adjusted to pH 2 by the addition of 6N hydrochloric acid. The organic phase was separated; the aqueous phase was extracted twice with toluene and washed with water. The combined organic layer was extracted with 2% NaOH (2x50mL) as first fraction followed by 1x50mL (second fraction). The remaining organic layer was further extracted with 2% NaOH (4x50mL) as third fraction. Compound **6** was obtained by acidification of the above third alkali fraction with 6N HCl. The solid obtained was filtered washed with water and dried (21gm. 45% yield), m.p. 122-124 °C (reported[5] 126-128 °C). ^{1}H-NMR ($CDCl_3$, 200mHz): 6.9-7.3 (4H, m, Ar-H), 7.3 (1H, d, J = 12Hz), 7.5 (1H, dd, J = 6.5Hz, Ar-H), 7.6 (1H, d, J = 6.5Hz, Ar-H), 7.8 (1H, d, J – 12Hz), 8.0 (1H, dd, J = 6.5Hz, Ar-H); M^+: m/z = 230.

Thiophene-2-carboxylic acid **7:**

Thiophene-2-carboxylic acid was obtained from the above first alkali fraction by acidification with 6N hydrochloric acid. The solid obtained was filtered and dried. Melting point and spectral data confirmed the structure of the thiophene-2-carboxylic acid. Yield 18%.

2-[2-(Thienyl) vinyl] benzoic acid **6** (from Scheme 2)**:**

Methyl-o-toluate (15g., 0.01 mole) was dissolved in carbontetrachloride (100 ml). To this solution N-bromosuccinimide (17.8g., 0.01 mole) and benzoylperoxide (100mg) were added under stirring. The reaction mixture was refluxed for 2h. The succinimide was filtered and the solvent was removed. The residue was distilled under reduced pressure to obtain the methyl (2-bromomethyl) benzoate **8** in 82% yield and its structure was confirmed by spectral data. Equimolar quantities of

monobromocompound (10g., 0.043 moles) and triethyl phosphite (7.25g., 0.043 moles) were heated at 150 °C for 5h. The reaction mixture was distilled under reduced pressure to obtain Diethyl (o-carboxymethylbenzyl) phosphonate **9** in 80% yield. To a solution of diethyl phosphonate **9** (0.858gm, 0.003 moles) in dry THF (30 ml), containing powdered potassium hydroxide (0.336g., 0.006 moles) was added thiophene-2-carboxaldehyde (0.336gm, in THF, 10ml). The reaction mixture was stirred for 15 minutes at room temperature and filtered. The filtrate was cooled and acidified with 3N HCl to give the thienyl vinyl benzoic acid **6** in 80% yield.

2-[2-(Thienyl) ethyl] benzoic acid **10:**

A solution of thienyl vinyl benzoic acid **6** (21g. 0.09 moles) in 2% sodium hydroxide (200 ml) was hydrogenated with palladium carbon (4.45g., 5%) at 100 °C and at 20-atmosphere pressure for 12 h. After cooling the reaction mixture, catalyst was removed by filtration and filtrate was acidified with 6N hydrochloric acid, to yield thienyl ethyl benzoic acid **10** (16.9gm, 80% yield), m.p. 108-109 °C (reported[5] 110-111 °C). IR (KBr): 3350-3400 cm^{-1} (OH) and 1680 cm^{-1}(C=O). ^{1}H-NMR($CDCl_3$, 200 MHz) : 3.1-3.3 (m, 2H), 3.4-3.6 (m, 2H), 6.8-7.5 (6H, m,), 8.1 (1H, d, J = 6.5Hz) 9.3(br.1H), M^+: m/z = 232.

9,10-Dihydro-4H-benzo [4,5] cyclohepta [1,2-b] thiophene-4-one **1:**

To a well stirred solution of polyphosphoric acid (45g., prepared from 16g. orthophosphoric acid and 29g. phosphorus pentoxide) in xylene (60ml) was added thienyl ethyl benzoic acid **10** (10.7g., 0.046 mole) and the reaction mixture was heated at 120-130 °C for 2h. under vigorous stirring. After cooling, water and toluene were added to the reaction mixture. The organic layer was separated, aqueous layer was extracted thrice with toluene and the combined organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the tricyclic ketone was obtained as dark brown oil (5.9gm. 60% yield). IR (neat): 1620 cm^{-1}(C=O). ^{1}H-NMR($CDCl_3$, 200MHz): δ, 3.2(4H, s, 9,10-H); 6.9 (1H, d, J = 5.7, 3-H); 7.2-7.4 (3H, m, 6,7,8-H); 7.7(1H, d, J = 5.7Hz, 2-H); 7.9 (1H, dd, J = 6.5Hz, 5-H), M^+:m/z = 214.

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