Asian Journal of Chemistry Vol. 16, No. 2 (2004), 978–982

Synthesis of Rofecoxib and Study of Lactone Ring Stability

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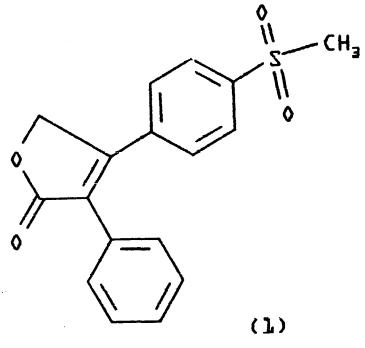
The synthesis of Rofecoxib [4-(4′-Methyl Sulfonyl Phenyl)-3-Phenyl- 2-(5H) Furanone] was carried out and various combination of solvents were tried to study the stability of the lactone ring during one pot cyclization of the lactone ring. It was found that removal of water from the reaction mixture during the reaction prevents the lactone ring from decomposing and thereby avoiding any by-products formation. Also the product was isolated from the reaction mixture by an improved method thereby facilitating the recovery of the organic base salt and hence providing a good commercial manufacturing process for Rofecoxib.

Key Words: Synthesis, Rofecoxib, Ring stability.

INTRODUCTION

Rofecoxib (Vioxx^R, MK 966) an approved product in several countries is used in humans as an anti-inflammatory drug to relieve the signs and symptoms of osteoarthritis and for the treatment of primary dismenorrhea. It is a member of a class of compounds called COX-2 inhibitors, due to their ability to selectively inhibit the action of the cyclooxygenase (COX-2) enzymes, which is implicated in pain and inflammation[1].

Non-steroidal anti-inflammatory drugs exert most of their anti-inflammatory, analgesic and antipyretic activity and inhibit hormone induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase also known as cyclooxygenase[2].



(1)

Traditional non-steroidal anti-inflammatory drugs (NSAID) act by blocking the action of both COX-2 and COX-1 enzymes[3] where the COX-1 enzyme is responsible for maintaining normal G1 function. Being a selective inhibitor of the COX-2, Rofecoxib[4] is effective against pain and inflammation

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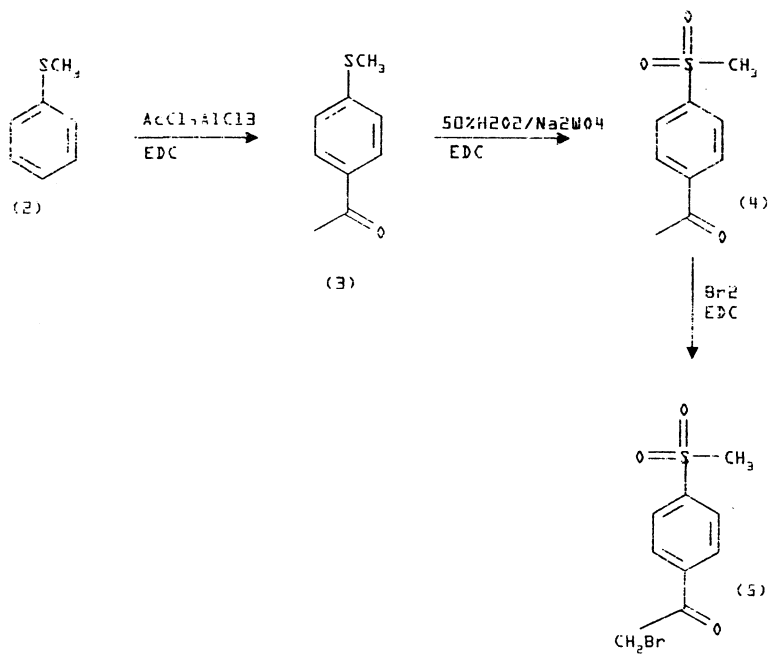
with significantly reduced risk of severe G1 toxicity associated with nonselective NSAIDs[5].

Rofecoxib(1) [4-(4′-methyl sulfonyl phenyl)-3-phenyl-2-(5H)-furanone] is a tricyclic bi-aryl lactone compound with a central butenolide moiety. Various synthesis methods have been reported in the past[1, 2, 6–8, 10]. These methods disclosed a multi-step synthesis method for making bi-aryl furans *via* bi-aryl lactones utilizing a ketoester internal cyclization to the lactones. A different method utilizing magnesium mediated carbometallation of propargyl alcohol was also published for preparing Rofecoxib.[9]

We have found out that in the methods for preparing Rofecoxib *via* cyclization of keto ester with phenyl acetic acid in DMF in presence of organic bases like DBU* or DIPA* as has been mentioned in the synthesis methods available the lactone ring breaks thereby leading to byproducts formation during the reaction process which was confirmed by us. In this paper, we describe an improved method of synthesizing Rofecoxib using a mixture of solvents and azeotropically removing water generated during the reaction, thereby stabilizing the lactone ring.

EXPERIMENTAL

Bromoketone [2-Bromo-l-(4-(methyl sulfonyl) phenyl) ethanone], an important intermediate for the synthesis, was prepared according to **Scheme-1** illustrated below.



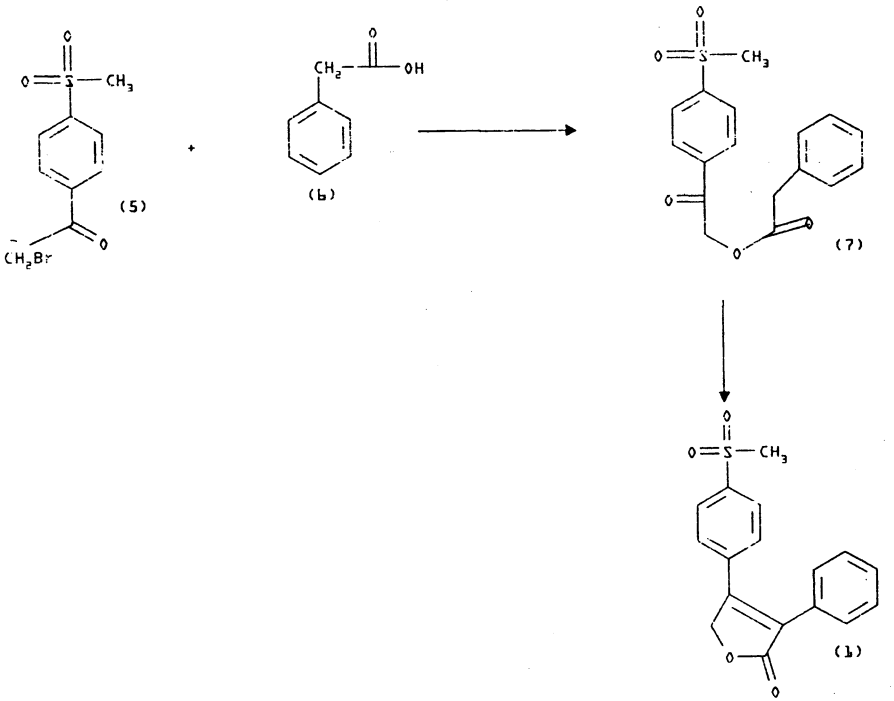
Scheme-1

As a change to the existing process for making bromoketone we have utilized a single solvent EDC (ethylene dichloride) throughout the reaction and proceeded all the three stages without isolating any of the individual stages.

Thus, thioanisole **(2)** was converted to 4-(methylthio)acetophenone **(3)** by Friedel and Crafts reaction of acetyl chloride in presence of a Lewis acid catalyst in EDC as a solvent[11]. The product was not isolated and proceeded after quenching and neutralization for oxidation with 50% hydrogen peroxide and sodiumtungstate/sulphuric acid catalyst thereby producing 4-(methylsulfonyl) acetophenone **(4)**.

The EDC layer containing **(4)** was washed and neutralized and then brominated after activating with HBr, thereby producing 2-bromo-1-[4-(methylsulfonyl) phenyl] ethanone **(5)** in 74% yield from thioanisole.

The bromoketone thus produced was condensed with phenylacetic acid **(6)** in presence of triethylamine as depicted in **Scheme-2** and the Triethylamine. HBr so produced was filtered to recover back triethylamine. The ester **(7)** so formed was cyclized in a mixture of DMF : benzene or toluene (1 : 3) in presence of strong organic bases DBU/DIPA* and with heating to azeotropically remove water formed in the reaction by Dean and Stark method to form the final product Rofecoxib **(1)**.



Scheme-2

4-(Methylthio)acetophenone [3][11]: Acetyl chloride (308 mL; 4.33 mol) was added to a cold (0–5°C) solution of anhydrous $AlCl_3$ (600 g; 4.5 mol) in ethylene

dichloride (2.0 L). Thioanisole **(2)** (378 mL; 3.22 mol) was then added with cooling to maintain the temperature of the reaction mixture below 5°C. The completion of the reaction was checked on TLC [benzene : ethylacetate = 7 : 3]. The reaction mixture was then quenched in Ice + HCl mixture and the organic layer was separated and then washed with water and saturated solution of sodium bicarbonate. Finally, 2.4 L of EDC layer containing the product **(3)** was obtained. A sample obtained by evaporating EDC gave a product having a melting point of 80.5–81.5°C[1].

4-(Methyl sulfonyl)acetophenone (4): To the solution of EDC, containing **(3)** was added 1.2 L of D.M. water and sodium tungstate (5.2 g; 0.158 mol) and sulphuric acid (5.2 mL; 0.97 mol). The reaction mixture was then heated to 40–45°C and 50% hydrogen peroxide (430 mL; 6.32 mol) was then added dropwise maintaining a temperature of 50°C. The mixture was then aged for another 3 h at 50°C and then the organic layer was separated and washed with saturated sodium bicarbonate solution (2.0 L) and then with brine (1.0 L). The organic layer measuring around 2.25 L and containing **(4)** was then taken for bromination. A sample obtained by evaporating EDC gave a product having a melting point of 128–129.5°C (lit. m.p. = 129–130°C)[1].

2-Bromo-1-(4-(methylsulfonyl) phenyl) ethanone (5): To a solution of **(4)** in EDC was added after initiation with 48% HBr (6.0 mL) bromine (526 g; 3.29 mol) during 26–30 h maintaining a temperature of 25 ± 3°C.

After ageing the mixture for 2–3 h, the organic layer was washed with water and then neutralized with a saturated solution of sodium bicarbonate and brine.

The organic layer was then distilled to recover back EDC and the final traces of EDC were removed azeotropically with water. The solid obtained as slurry in water was filtered and dried to obtain 660 g (2.38 mol) of crude product (m.p. 127–128°C) (lit. m.p. 128.5–129°C).

4-(4′-Methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone (1): To a 1.0 L three-necked round-bottom flask equipped with a mechanical stirrer and temperature probe was charged phenylacetic acid **(6)** (49.0 g; 0.36 mol), bromoketone **(5)** (100.0 g; 0.36 mol) and DMF (150 mL). Triethylamine (50 mL; 0.36 mol) was then added dropwise over a period of 1 h. After complete addition, the reaction was stirred for another 30 min and then the triethylamine·HBr formed was filtered out. The DMF filtrate containing compound **(7)** was then charged to a 1.0 L three-necked RBF equipped with a stirrer and Dean & Stark assembly on one neck. Benzene (300 mL) and DIPA* (93.26 mL; 0.71 mol) were added to the flask and the reaction was heated to reflux. Water generated during the reaction was separated over a period of 6–7 h (6.5–7.0 mL). The progress of the reaction was monitored on TLC.

Later the reaction was cooled to 10°C and conc. H_2SO_4 (38.0 mL; 0.71 mol) was added dropwise through a dropping funnel maintaining a temperature of 5–10°C. During the addition compound **(1)** along with sulphate salt of DIPA* precipitate out of the reaction mixture. After complete addition the solids were filtered. DIPA* sulphate was recovered by slurrying the solids in water. Compound **(1)** so obtained was washed with acetone and then dried for 12 h under vacuum at 25°C to finally yield pure yellow solid of compound **(1)** in 60% yield.

m.p. 204.7°C; ^{1}H NMR (acetone-d_6): δ = 7.96 (δ, 2H, J = 8.4 Hz), 7.68 (d, 2H, J = 8.4 Hz), 7.42 (s, 5H), 5.37 (s, 2H), 3.15 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 172.4, 156.0, 142.0, 135.8, 129.8, 129.1, 128.9, 128.7, 127.4, 126.9, 70.9, 43.1; MS (Pos ESI): $[M + H]^+$ = 315.1.

RESULTS AND DISCUSSIONS

We conclude from the above performed experiments that it is the generation of water molecule during the cyclization of the lactone ring that reacts and decomposes the lactone ring during the reaction, thereby generating impurities and thus decreasing the yields. Thus with the above experiments we produced Rofecoxib in above 99% purity confirmed by HPLC and characterized by ^{1}H NMR and ^{13}C NMR. Rofecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor and is used as an anti-inflammatory drug.

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(*Received*: 21 August 2003; *Accepted:* 20 December 2003) AJC-3302