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Microwave Synthesis of Ortho-Bromo-Vioxix

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ABSTRACT

The synthesis of a radioactively-labeled organic compound, 3-(2-[^{123}I] iodo phenyl)-4-(methanesulfonyl phenyl)-5H-furan-2-one was attempted in a seven-step research project. This compound is a derivative of VIOXX, a COX-2 inhibitor, and will be the third isomer in a project to use these compounds as potential agents for Single Photon Emission Computed Tomography (SPECT), a biomedical imaging technique. Completion of the first four steps has been achieved with good success, as well as a subproject involving similar reactions that utilize microwave chemistry, a technique that is necessary for the fourth reaction.

SUMMARY

Reaction I was a textbook Friedel-Crafts Acylation, converting thioanisole to 1-(4-methylsulfanyl phenyl)-ethanone. Aluminum chloride, or more specifically, the acylium ion, was used as the electrophilic reagent. A solution of aluminum chloride in chloroform was stirred in an ice bath to maintain a temperature below 10°C during the addition of aluminum chloride. Thioanisole was then added to the solution after about ten minutes. This was the rate-determining step of the reaction and so had to be kept cold to insure that it went as slowly as possible. The ice bath was then removed and the mixture allowed to come to room temperature. During this step the color changed from clear to a yellow-green to a deep blue-green. Stirring was maintained for 1.5 hours. Thin-layer chromatography (TLC) was used to test for the presence of starting material in the reaction mixture. If none was present, the mixture was again placed in an ice bath and was washed with ice cold water to separate the organic and aqueous layers. The color again changed to give a white aqueous top layer and a yellow-brown bottom organic layer. The solution was then washed in a separatory funnel three times with ice-cold water. This was done to extract any highly polar materials such as inorganic salts, acids, or bases into the aqueous layer, which was removed each time. The organic solution was then washed with brine, a saturated sodium chloride solution, to remove any residual acids/bases and water. The remaining organic solution was then dried over magnesium sulfate to remove any water. The solvent was then evaporated to give a yellowish crystalline solid with a melting point of 74-80°C in a 99% yield. This solid

was then recrystallized with a 80:20 hexane: ethyl acetate solution to give a white crystalline solid with a purer melting point of 80-81°C. Nuclear magnetic resonance (NMR) was used to insure the product was pure.

Reaction II oxidized 1-(4-methylsulfanyl phenyl)-ethanone to 1-(4-methanesulfonyl phenyl)-ethanone using 1.5 equivalents of magnesium monoperoxyphthalate (MMPP) as the oxidizing agent. A solvent of 3:1 methanol: dichloromethane (DCM) was used as the MMPP was added over a period of ten minutes. The reaction ran at room temperature for 2.5 hours. It was then filtered by gravity filtration and the filtrate was washed with copious amounts of DCM to insure that all of the product was filtered through. A mixture of water and sodium carbonate was then added to the organic layer; if no bubbling occurred in this step, then the reaction was complete. The organic layer was then washed with saturated sodium bicarbonate solution four times in a separatory funnel. This converted any acidic impurities (due to the MMPP byproducts) to their anionic salts which would be highly polar and soluble in the aqueous layer which would be removed. The solution was then washed with deionized water one time to remove all basic impurities and any highly polar or polar, low molecular weight substances. This was followed with an extraction with brine to remove any residual acids or bases and water. The solution was dried over magnesium sulfate for about fifteen minutes and then the solvent evaporated to give white crystalline solid in 88% yield at a melting point of 126-128°C. NMR showed the product was pure.

Reaction III was the bromination of 1-(4-methanesulfonyl phenyl)-ethanone to 2-Bromo-1-(4-Methanesulfonyl phenyl)-ethanone. The oxidation product from the previous reaction was dissolved in chloroform, cooled to 0°C, and then catalyzed with a pinch of aluminum chloride to undergo a textbook acid-catalyzed halogenation of the α-carbon of a ketone with bromine. A solution of bromine in chloroform was added dropwise to the cold reaction mixture over a period of ten minutes. The solution turned from white to a dark brown as the enol reacted with the electrophilic bromine. The solution then returned back to a light orange or sometimes white color as the reaction came to completion. The reaction usually took one hour to complete. The ice bath was then removed and water was added to quench the reaction and return the product back to a ketone; the mixture was stirred for twenty minutes to ensure the reaction was

completely quenched. The color was white or clear at this stage. The mixture was washed with water two times to remove any polar impurities and brine two times to remove any residual acids, bases, or water. The solution was then dried over magnesium sulfate for 15-20 minutes and concentrated under pressure to give a white crystalline solid with a 95% yield and a melting point of 127-129°C. NMR was used to show that the product was pure and free of solvent.

Reaction IV proved to be much more difficult. This step attempted to couple 2-Bromo-1-(4-Methanesulfonyl phenyl)-ethanone and ortho-Iodophenyl-acetic acid in a ring-closing metasthesis (RCM) reaction. The desired product was 3-(2-Iodo phenyl)-4-(methanesulfonyl phenyl)-5H-furan-2-one. Many problems arose during this reaction. Originally, 3-(2-Bromo phenyl)-4-(methanesulfonyl phenyl) 5H-furan-2-one was used in this step. Equal parts of the two compounds were dissolved in acetonitrile and stirred while 1.1 equivalents of the base triethylamine were added slowly. The solution stirred at room temperature for thirty minutes, after which time it was cooled to 0°C with an ice bath. Two equivalents of the strong base 1,8-Diazobicyclo[5.4.0]-undec-7-ene (DBU) were then added dropwise and the mixture stirred for another thirty minutes at 0°C. The basic mixture was then acidified with 1 N hydrochloric acid until a color change from dark brown to yellow was observed. Ice and cold water were then added to quench the reaction, and the mixture stirred until all was dissolved. The sticky orange precipitate was filtered and rinsed with water. The product remained in the filter paper in a crude wet state. It was dissolved in DCM, dried over magnesium sulfate, and then filtered. The product was concentrated on silica gel and placed on a silica packed glass column. Column chromatography and TLC were used in an attempt to isolate the product, using a solution of hexane and ethyl acetate in increasing polarities (30%-80%) to elute the pure compound. The solution was then washed with water and DCM and concentrated.

However, the reaction never went to completion and pure product was never recovered, probably due to the strong steric hindrance between the bromine of the ortho-bromophenylacetic acid and the carbonyl oxygen of the neighboring ring in the structure of the desired product. Many variations were done in an attempt to make this reaction work. Smaller columns were used. The columns were wet-packed instead of dry-packed. Reagents were added over longer periods of time. The column was run over a longer

period of time. The chromatography isolation was performed on the same day as the reaction to insure that the product was not degrading from the acidic silica gel. TLC was taken at much shorter intervals during the column isolation. The reaction was performed using only triethylamine base to ensure the ring was closing. Ortho-chlorophenylacetic acid was used because the chlorine atom is much smaller than the bromine atom and so might not be as sterically hindered. Ortho-iodophenylacetic acid was used because although the iodine atom is much bigger, it is also more reactive than bromine. Sometimes a yellow or white powder would come off the column, but usually the final product was a resin instead of the desired solid. NMR analysis always showed a mixture of compounds and the elemental analysis was never in the correct range to show the product was the desired compound.

At this point the decision was made to change courses with the direction of the project. Research was done on a fairly new technique in chemistry, microwave chemistry. Microwave chemistry has changed how many modern chemical reactions are performed. With the increased power and heat of a microwave, a reaction that would be run using traditional thermal conditions over the course of days or longer can now be completed in a matter of minutes. Other benefits are that this method is "greener" since it uses less solvent and that there is much more time made available to explore different options and conditions. One drawback in our research, however, is the smaller amounts of product obtained. During research into this area, a procedure was developed to attempt the fourth reaction one more time using the microwave method. 2-Bromo-1-(4-Methanesulfonyl phenyl)-ethanone and ortho-Iodophenyl-acetic acid in 1 millimole amounts were combined in a test tube with acetonitrile as solvent and three equivalents of triethylamine as base. The reaction was run in a microwave at 100°C for twenty minutes to give a dark green-black mixture. TLC showed that the reaction was complete. The basic solution was then neutralized with hydrochloric acid, turning it from a dark blue to yellow. Washing with saturated sodium bicarbonate and saturated sodium chloride returned the solution to a dark blue color. The organic layer was concentrated onto silica gel and then run through a short dry silica column with a 60:40 ethyl acetate:hexane mixture. Pure product soon eluted, as shown by the NMR analysis and the elemental analysis.

At this point, similar reactions were done using microwave methods in an attempt to facilitate these processes. Interestingly, none of the other compounds reacted resulted in a pure product, even though similar sulfone derivatives were used. Many reactions were performed to change conditions in an attempt to affect an easy procedure, but to no avail.

This project will be completed after three more steps. The fifth step of the project will be a Suzuki coupling reaction using the catalyst 1,1'-Bis(diphenylphosphino) ferrocene-palladium(II)dichloride dichloromethane complex. This should lead to 4-(4-Methanesulfonyl phenyl-3-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaiodolan-2yl)-phenyl]-5Hfuran-2-one. This compound will then be reacted with potassium trifluoroborate in the sixth step of the project. The trifluoroborate salt will then be radioiodinated to give the final product, 3-(2-[^{123}I]iodo phenyl)-4-(methanesulfonyl phenyl)5H-furan-2-one.