Towards the Synthesis of Asymmetric Water Soluble Curcumin Analogues: Synthesis of (E)-ethyl 3-(4-hydroxy-3-methoxyphenyl)acrylate

Brenda S. Casillas, Jason Giles, Katherine Pierce, Sameh Helmy
California State University Channel Islands, Camarillo, CA

Background
Curcumin, the main curcuminoid that gives turmeric its color, has been the subject of many studies which demonstrate its potential as a treatment for a wide range of ailments.1-6 A common obstacle of these studies is curcumin's poor bioavailability, due to its highly lipophilic structure. Several groups have designed syntheses to produce hydrophilic analogues; however, these strategies involve highly toxic reagents, complex purifications, and large quantities of hazardous waste.7-9 Our group is working toward a mild, novel synthesis based on a BF3 mediated coupling of (E)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one (vanillylidene acetone) with (E)-ethyl 3-(4-hydroxy-3-methoxyphenyl)acrylate ((E)-ethyl ferulate) as shown in Scheme 1.

Scheme 1:

In previous work we have developed a mild, high yielding synthesis of vanillin-dicarbonyl. In this work we explore the conditions necessary for the synthesis of (E)-ethyl ferulate.

Aldol Condensation
Initial efforts focused on attempting to synthesize the compound via an Aldol condensation. It was found in the literature that vanillin could be reacted directly with ethyl acetate and a promoting base. Two bases were examined, disopropyl amine (DIA) and aqueous sodium hydroxide. These conditions were found to be ineffective. On addition of DIA the reaction mixture developed an orange color under constant stirring and heat. The reaction was monitored by TLC and was halted when no further change in vanillin concentration was detected. After evaporation of excess ethyl acetate the mixture solidified into orange crystals, a result of the large quantity of vanillin present at the end of the reaction. 1H NMR showed that less than one percent of ethyl ferulate was synthesized. A second attempt at the mixed Aldol condensation using similar conditions was performed substituting aqueous NaOH for the DIA. It was found that these conditions hydrolyzed the ethyl ester producing ethanoic acid and ethanol.

References:

Wittig Reaction
With the Aldol condensation determined to be ineffective, a Wittig reaction was proposed to form the carbon-carbon double bond. In an initial attempt (carboethoxymethyl)triphenylphosphonium bromide was reacted with vanillin in the presence of lithium hydroxide (Scheme 2). These conditions were investigated using two solvents: THF and chloroform. In both attempts it was found that the reaction produced the desired product, however, both solvents gave a 50:50 E,Z ratio. In the second attempt the Horner-Wadsworth-Emmons modification of the Wittig reaction was conducted reacting triethylphosphonoacetate with vanillin in the presence of sodium ethoxide (Scheme 3). This reaction was found to give a 93:7 E,Z ratio. In addition, the by-product of this reaction is water simplifying purification. When using vanillin, the excess sodium hydride deprotonated the phenolic group generating the sodium salt of vanillin which is insoluble in organic solvents. This heterogeneous reaction resulted in only 5% conversion of the vanillin to ethyl ferulate. When morpholino substituted vanillin was used there was no risk of deprotonation, and the reaction was homogeneous (Scheme 4). These conditions resulted in 75% conversion of the starting aldehyde to the desired ester in 4 hours (Figure 1).

References:

Determination of E/Z Selectivity
On finding that the Wittig reaction was an attractive route, the focus switched to determining conditions that would selectively favor the E isomer of ethyl ferulate. 1H NMR was utilized to determine the E/Z ratio of the product mixtures from the Wittig reactions. The Karplus equation indicates that the coupling constant for the Z isomer of ethyl ferulate ranges from 8-12 Hz, whereas the coupling constant for the E isomer ranges from 16-20 Hz. With this information, the 1H NMR spectra were examined and the peaks corresponding to each of the isomers determined. The actual coupling constants were found to be JZ=16.2 Hz for the E isomer and JZ=12.7 Hz for the Z isomer. Integration of the peaks corresponding to H3 and H2 allowed for the determination of the mole ratio of the two isomers in the product mixture. Figure 1 shows that the E,Z ratio resulting from the Wittig reaction was 50:50 indicating that the reaction is not selective for either isomer. Figure 2 shows that the E,Z ratio from the Horner-Wadsworth-Emmons modification of the reaction was 93:7 indicating that these conditions are more selective for the E isomer. The final reaction using the morpholino vanillin resulted in a 96:4 E,Z selectivity.

References:

Conclusions
It was found that the Horner-Wadsworth-Emmons modification of the Wittig reaction gave high E,Z selectivity under mild conditions. The use of carboethoxymethyl triphenylphosphonium bromide in a traditional Wittig reaction gave a 50:50 E,Z ratio, whereas triethylphosphonoacetate gave 93:7 E,Z ratio as determined by 1H NMR spectroscopy. It is believed that the difference in selectivity is a direct result of the difference in steric hindrance of the two reagents. Further, the use of O-alkylated benzaldehydes resulted in improved yields over phenolic benzaldehydes.

Figure 1: 1H NMR showing 75% conversion of starting aldehyde to ferulic ester

Figure 2: 1H NMR showing 96:4 E,Z ratio of isolated ferulic ester product