CHM 202 – Problem of the week

Rofecoxib (Vioxx®) is a cyclooxygenase-2 inhibitor (COX-2 is the enzyme which mediates the body’s response to arthritis and other inflammatory conditions). Unfortunately, recent studies have indicated that Vioxx® can cause dramatic increases in blood pressure and is linked to a variety of heart malfunctions. *The molecule is also unusually acidic.* Loss of a proton, as shown below, affords a conjugate base (A) that immediately and irreversibly reacts with a number of biological methylating agents (CH₃-X, see reaction scheme below).

a) Explain why Rofecoxib is so much more acidic than typical hydrocarbons. Upon deprotonation, the conjugate base is resonance stabilized and aromatic (as shown in B).

b) Draw arrows to show the flow of electrons in the reaction of A to B. See below.

c) Why do you think the alkylation (think of an S_N2 reaction) occurs only on the oxygen and not at the site of proton removal (on the carbon)? With O-alkylation, a methoxyfuran can form which again is aromatic. Methylating at carbon will give the unsaturated lactone which is non-aromatic.

d) Draw the *exo* adduct that occurs when furan B reacts with propenal (you may replace the phenyl rings with “Ar”). Diels-Alder adduct will have the OCH₃ and CHO groups on adjacent carbons.