

CHM 202

Problem of the week –
due Monday, Jan 30, 2006

1.(16) 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 ($\text{CH}_3\text{-X}$, see reaction scheme below).

- Explain why Rofecoxib is so much more acidic than typical hydrocarbons.
- Draw arrows to show the flow of electrons in the reaction of **A** to **B**.
- Why do you think the alkylation (think of an $\text{S}_{\text{N}}2$ reaction) occurs only on the oxygen and not at the site of proton removal (on the carbon)?
- Draw the *exo* adduct that occurs when furan **B** reacts with propenal (you may replace the phenyl rings with "Ar").

