PROBLEM 9

[SUPPL Problem 9 # 1]

Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

Compound **4** (TAPSOC - cribrostatin) is a dark blue natural quinone with powerful antibiotic properties, first isolated from a marine sponge (*Cribrochalina sp.*) [1]. No one knows yet the chemo-ecological service of cribrostatin to its mother organism but antibiosis against sea bacteria and other microorganisms sounds logical considering the metabolic effort involved in the biosynthesis.

An interesting aspect of **5** from the human standpoint is its strong activity against antibiotic-resistant strains of the lung scourge *Streptococcus neumoniae*, a worrisome bacterium causing millions of deaths a year. Also, **4** is an antineoplastic material which destroys cancerous cells by fueling the oxidative cycle of natural reactive oxidative species (ROS), a particularly effective cell destroying weapon of leucocytes (white cells).

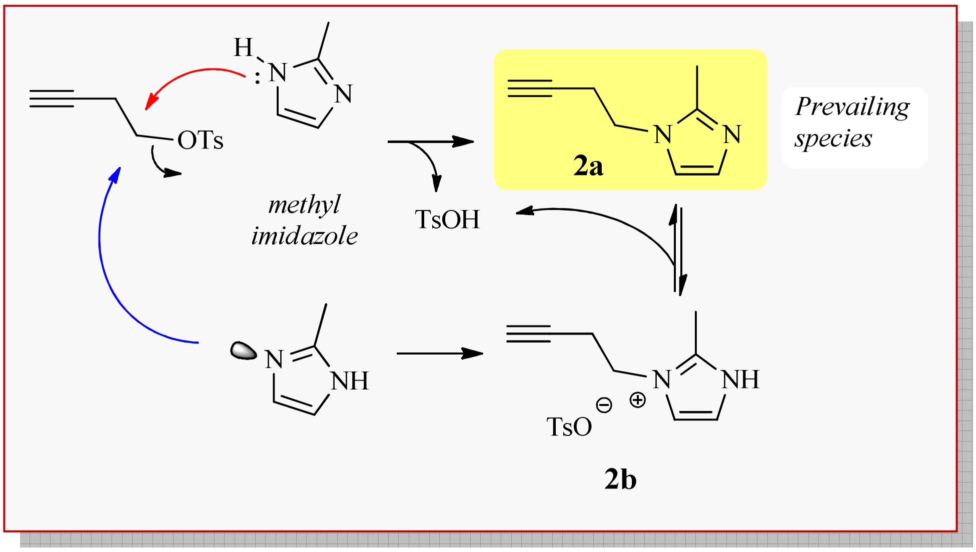
This activity is centered in the quinone moiety of cribrostatin, which involves an interesting electron transfer mechanism (not shown here). Several other benzoquinones from terrestrial organisms seem to protect them from herbivory, fungal and bacterial attack as a result of the oxidative stress induced inside the attackers.

Professor Stephen Martin, at the University of Texas in Austin, embarked on an expedite synthesis of **4** using an approach already reviewed in this book. The particular chapter will not be revealed for you to work out the problem first.

A word about Imidazole

Also worth commenting is the preparation of the imidazole derivative **2**. It does not come in a commercial bottle but is created in situ by the reaction of 2-methyl imidazole and butynyl tosylate in acetonitrile at 70 ºC.

A small side problem is the structure of the active substitution product that finds **1** in the mixture. As a result of imidazole having two different N atoms, the nucleophilic attack on the tosyl substrate may occur on account of either one. Which one? Additionally, both substitution products may be in equilibrium. Which is the dominant structure for the next step? Scheme SP9.1.1 gives the answer [3].



SCHEME SP9.1.1

REFERENCES AND NOTES

[1] Pettit GR, Collins JC, Knight JC, Herald DL, Nieman RA, Williams MD, Pettit RK. J. Nat. Prod. 2003;66:544-547.

[2] Several other blue compounds occur in marine organisms. Among the best well known is 'something' in shoe crab blood, hemolymph really. These fossil-like creatures are captured and partly bled to obtain this hemolymph for medicinal testing. Then, they are released back to the ocean (about 80-90% of them survive). The blue color does not have anything to do with quinone derivatives but with the protein in charge of oxygen capture and transport in their bodies. This is hemocyanin. At its core there are two copper atoms in redox Cu(I) ⇆ Cu(II) equilibrium mediated by O_2, very much in the same manner of Fe(II) ⇆ Fe(III) in hemoglobin. The Cu(II) hemocyanin is the deep blue chemical species.

[3] Joules JA, Mills K Heterocyclic Chemistry. Wiley-Blackwell, New York, Oxford. 2012, p 462.