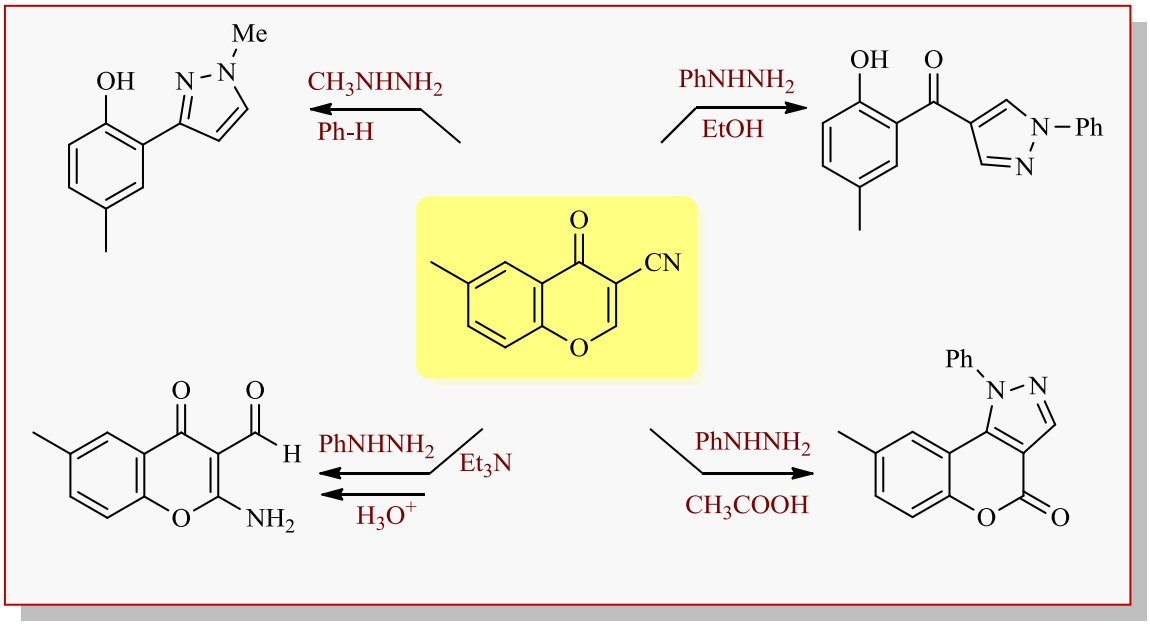
PROBLEM 50

[SUPPL Problem 50 # 1]

Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

The chemistry of the benzopyrone nucleus, typical of vary many natural products including the extended flavonoid collection, is well known and predictable. Nonetheless, the introduction of an EW group on C^3, like CN or HC=O, modifies substantially its chemical behavior [1-3]. Some of these reactions are summarized in Scheme SP50.1.1, which by themselves constitute an attractive mechanistic problem set you may wish to pounce on as a warm up.



SCHEME SP50.1.1.

The reaction of TAPSOC Scheme 50.1, reported by professors Julia Stephanidou-Stephanatou and Constantinos Tsoleridis at the Aristotle University of Thessaloniki in Greece and their collaborators, expands this territory significantly by inserting this novel chemistry into the fast growing province of multicomponent reactions (MCR). Remarkable molecular complexity, including important alteration of the original scaffold in relatively high yielding products and short reaction times, emerges from this procedure. In this particular case though, compound **4** was not the anticipated product, but a welcome addition all the same owing to its unique structural virtues. Your own should serve you well in designing the entailed mechanism and configure the foreseen target as well.

Be reminded that many new reactions are discovered in the course of studies with a more practical end in mind. In this case, researchers were attracted by the synthetic approaches to the substituted chromone nucleus (reds in Figure SP59.1.1), an essential part (a pharmacophore) of several natural products and derivatives with potent biological activities with potential therapeutic applications.

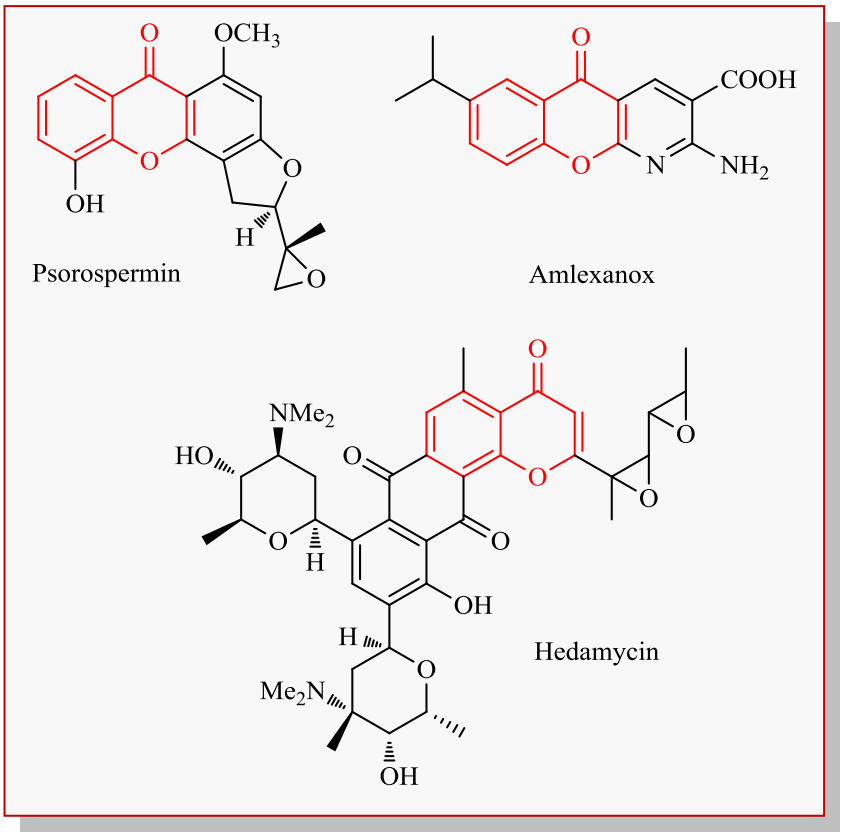
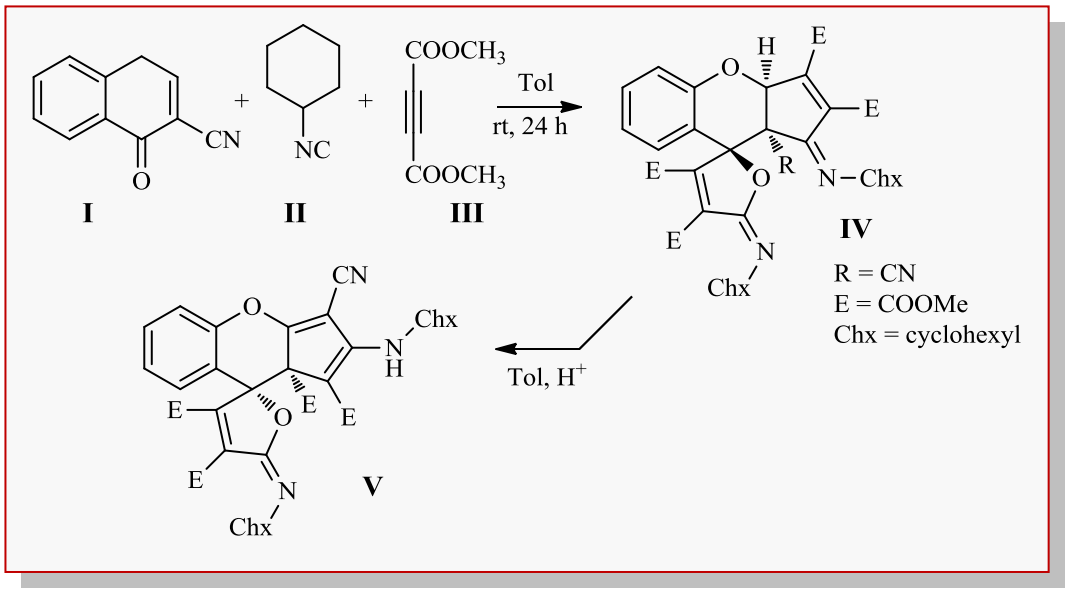


FIGURE SP50.1.1.

You may wonder what do TAPSOC Scheme 50.1 and the underlying research have to do with any synthetic strategy for these sophisticated compounds. The clear-cut answer is that recognizing new chemistry of complex nuclei is highly valuable for understanding the physiological behavior, frequently a complicated affair, of such compounds in the body and in pathological entities, on the one hand.

As well, this information helps in establishing the limits of bench chemistry in this class of materials and prepares scientists for avoiding unwanted (or sought after) reactions to get to more potent derivatives and larger, richer compound libraries. Besides, these reactions make wonderful problems for people like you to work out.

To show you this, let me suggest that, once you find a solution to problem 50, you embark (and your discussion group if you have one) in solving the mechanism of Scheme SP50.1.2 shown below, also developed by the same research group [4]. Obviously, the toluene/H+ step is the more challenging and fun part.



SCHEME SP50.1.2.

By the way, let me add that, while the reaction went smoothly at rt with cyclohexyl isocyanide (**II**), and product **IV** underwent rearrangement to **V** when a catalytic amount of pTosH was added, a parallel reaction with *t*-butyl isocyanide required heating and its homolog of product **IV** DID NOT undergo rearrangement to the

homolog of **V**. In addition, the benzyl carbon undergoes inversion of configuration. Please explain both facts.

REFERENCES

[1] Rashid MA, Rasool N, Appel B, Adeel M, Karapetyan B, Mkrtchyan S, Reinke H, Fischer C, Langer P. Tetrahedron 2008;64:;5416-5425.

[2] Ibrahim MA. Synth. Commun. 2009;39:3527-3545.

[3] Sosnovskikh VY, Moshkin VS, Kodess MI. Tetrahedron Lett. 2009;50:6515-6518; Sosnovskikh VY, Moshkin VS, Kodess MI. J. Heterocyclic Chem. 2010;47:629-633.

[4] Tertzidis MA, Zarganes Tzitzikas T, Tsimenidis C, Stephanidou-Stephanatou J, Tsoleridis CA, Kostakis CF. J. Org. Chem. 2012;77:9018-9028.