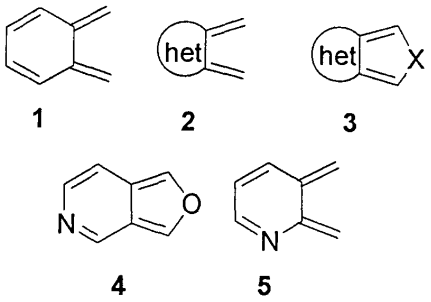
Abstract

Since Cava's pioneering work on the generation of the very reactive species *o*-quinodimethane **1**, studies have continued unabated on the modes of preparation, physical properties, and synthetic applications of **1** and its derivatives. Several review articles published during the past few decades amply bear this out. On the other hand, the heteroaromatic analogues **2** have received much less attention, although this situation is rapidly changing in recent years. In the background of this development, it is surprising that not much systematic work has been done on functional analogues of **2**, e.g. **3** (X = O), which are good candidates for both inter- and intramolecular Diels-Alder reactions leading to an array of heterocyclic ring systems related to natural and non-natural products of biological significance.



The present research has essentially addressed this issue involving both **4** and **5**, details of which are described in this thesis entitled "**Generation and Trapping of Pyridine *o*-Quinodimethanes and Their Functional Analogues: Synthesis of Heterolignans and Conformationally Restricted Analogues of Nicotine**."

The thesis is divided into two chapters, Chapter 1 and Chapter 2.

Chapter 1

This chapter demonstrates that sequential Pummerer-Diels-Alder reaction is suited to efficient synthesis of a variety of heterocyclic ring systems including the potentially bioactive heterolignans. Thus, the Pummerer reaction of an *o*-benzoyl-substituted pyridylmethyl sulfoxide generates an α-thiocarbocation the interception of which by a neighboring keto functionality produces an α-thiosubstituted furo[3,4-*c*]pyridine as transient intermediate; the latter undergoes a Diels-Alder cycloaddition with an added dienophile. Base-induced ring opening of the cycloadduct followed by aromatization gives an isoquinoline derivative that may be looked upon as a heterocyclic analogue of 1-arylnaphthalene lignans. The facility of the sequential Pummerer-Diels-Alder reaction hinges on the experimental conditions, the best results being obtained with heptafluorobutyric anhydride as the triggering agent in toluene containing a catalytic amount of *p*-toluenesulfonic acid. In the absence of a dienophile it is possible to isolate and characterize a rather unstable furo[3,4-*c*]pyridine derivative. An intramolecular variant of this protocol is also feasible with use of unactivated alkenyl tethers of variable length. The usefulness of the sequential Pummerer-Diels-Alder reaction is further demonstrated through the synthesis of a heterolignan with a built-in lactone ring via oxidation of the initial [4+2]-cycloadduct followed by extrusion of phenyl sulfinate and elaboration of the resulting hydoxylated isoquinoline derivative.

Chapter 2

This chapter deals with the trapping of pyridine *o*-quinodimethanes generated by a formal imine-tautomerisation route. Thus, reactions of appropriately substituted

pyridine-derived imines having an *ortho* methyl/phenylsulfanylmethyl group with methyl chloroformate in the presence of Hünig's base generates transient pyridine *o*-quinodimethane intermediates which undergo intramolecular Diels-Alder reaction leading to conformationally restricted analogues of nicotine. That the success of this reaction hinges on the presence of a phenylsulfanyl group in the pyridine sidearm has been demonstrated as in the earlier investigation reported from this laboratory. Recently, conformationally constrained nicotines of the type described in this chapter have become targets of intensive investigation in view of their potential use for the treatment of various central nervous system (CNS) disorders including Alzheimer's disease, Parkinson's disease and depression.