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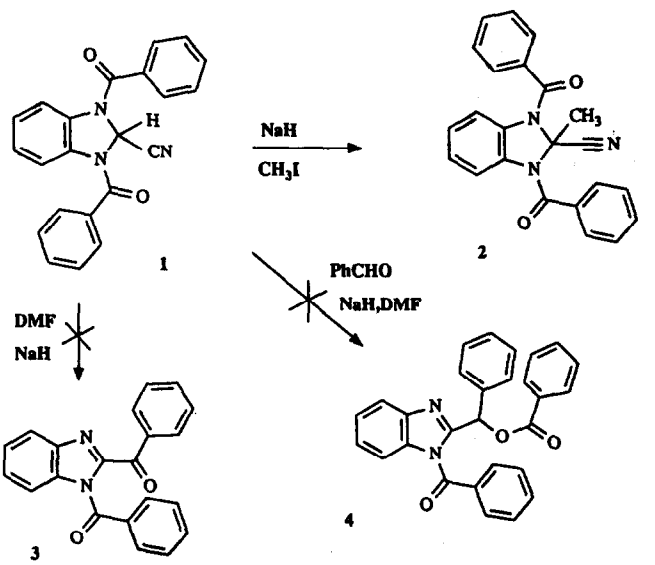
X - RAY CRYSTAL STRUCTURE AND REACTIONS OF 2-CYANO-1,3-DIBENZOYL-2,3-DIHYDROBENZIMIDAZOLE, A NOVEL REISSERT COMPOUND.

Yajnanarayana H. R. Jois, Michael A. G. Berg, Joseph S. Merola and Harry W. Gibson*,
Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061.

ABSTRACT: The X-ray crystal structural analysis and energetically favoured conformation calculated by the MM2 method for the new, novel benzimidazole Reissert compound **1** are reported. A highly delocalized and very stable carbanion is interpreted by resonance structures. Interesting reactions of compound **1** are discussed.

The relative ease of preparation and more importantly the low cost make benzimidazoles attractive as potential pharmaceutical agents[1] as well as monomers for high performance polymers[1,2]. The positions 1,2,3 are the reactive centers of the molecule which dictate the chemistry of benzimidazoles. However, 1,2-dihydrobenzimidazoles with substitution at 1,2 and 3 positions are not easily accessible with the routes available in the literature. We have approached this problem by examining a Reissert reaction on benzimidazole[3]. The Reissert compound, 2-cyano-1,3-dibenzoyl-2,3-dihydrobenzimidazole (**1**), is unique in

Scheme 1



this respect. For example, one can vary 1,3-substituents depending on the acid chlorides chosen; because N-1 is acylated prior to Reissert compound formation, two different acyl groups can be introduced. Position 2 has a reactive cyano group; and most importantly, the hydrogen at C-2 is highly acidic. Thus, in principle we have

the ability to vary substituents on N-1, C-2 and N-3 positions of the benzimidazole molecule and, consequently, to produce varied benzimidazole derivatives of interest.

Due to steric and electronic considerations the X-ray crystal structure of Reissert compound **1** is of particular interest to us; three possible amide conformers are possible (syn / syn, syn / anti, anti / anti). Further, about the same time we published our earlier results[3] relating to the synthesis of Reissert compound **1**, Uff *et al.*[4] also noted the synthesis of compound **1**, but with a mp 60 °C lower. Thus, the X-ray crystal structural analysis of **1** was carried out to unequivocally prove its structure; the ball and stick plot for compound **1** is shown in Figure-1[5].

The energetically favoured conformation calculated by the MM2 method (Figure-2) is similar to the structure obtained by X-ray diffraction methods. The two phenyl rings are out of plane and are orthogonal to, whereas the carbonyl groups are coplanar with, the benzimidazole ring. The cyano group is pseudo axial to the benzimidazole ring. The amide moieties are in the same configuration with the carbonyl oxygens cis to the 2-position. However, the X-ray data indicates that the carbonyl groups are coplanar with the benzimidazole ring.

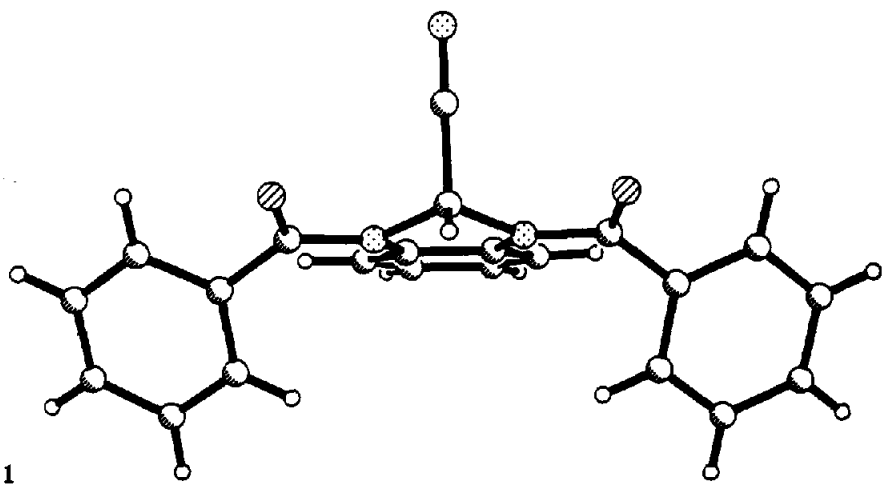


Figure 1

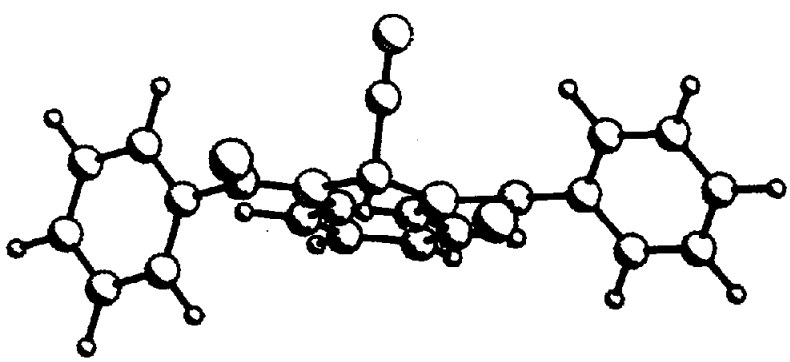
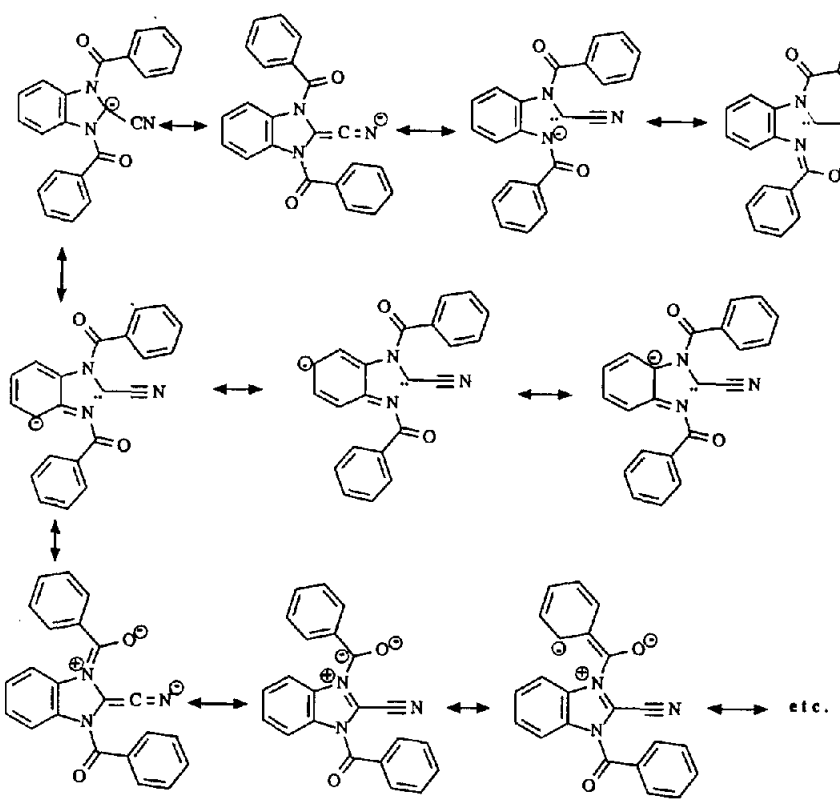


Figure 2

Based upon the well documented chemistry of Reissert compounds[6]; we expected Reissert compound **1** upon (a) methylation to give **2**, (b) treatment with NaH / DMF to form rearranged product **3**, and (c) benzaldehyde condensation to yield **4** (Scheme-1). Normally, Reissert compounds in the presence of MeI / NaH in DMF yield methylated product in 2-3h at rt quite easily[6]. However, alkylation of Reissert compound **1** in the presence of an equivalent of NaH in DMF with excess alkyl halide (3-5 equivalents) turned out to be a very slow process. In fact, stirring the reaction mixture 24h at rt yielded less than 5% methylated compound **2**. Heating the reaction mixture to 65 °C for 24h led to a 10% yield of **2**. A maximum ratio of product to substrate (30:70) by proton NMR was observed when the anion was generated at -20 °C prior to the addition of methyl iodide. Similar reactions with benzyl chloride as well as n-bromobutane were also unsuccessful. Surprisingly, there was no rearranged product (**3**) noticed in any of the above alkylation reactions. However, the presence of a highly delocalized and highly stable anion was indicated by the deep blue color formation after the addition of NaH. The possible resonance structures are shown in Scheme - 2.

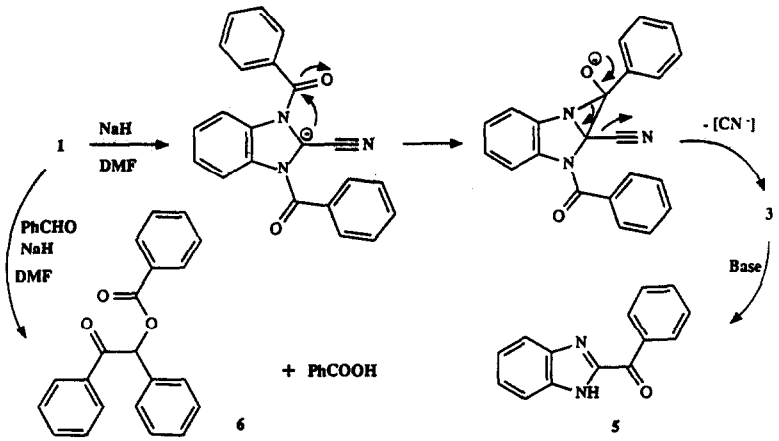
Scheme 2



Interestingly, when the Reissert compound **1** was subjected to the NaH (one equivalent) in DMF reaction conditions, 2-benzoylbenzimidazole[7] [**5**, 81%, mp 210-11°C (lit.[8] mp 209-10°C)] was obtained, instead of the expected 1,2-dibenzoylbenzimidazole (**3**). Reissert anions undergo rearrangement through the aziridine intermediate[9]. Thus, **1** via the Reissert anion (Scheme-3) in an intramolecular process produces **3**, which apparently hydrolyzes under basic reaction conditions to **5**.

The benzaldehyde condensation reaction of 1 in the presence of NaH (one equivalent) in DMF yielded benzoin benzoate[7] [6, mp 124-5°C (lit.[10,11] mp 124-5°C)] and benzoic acid (Scheme-3) instead of the expected ester 4. Even after careful repeated experiments, our attempts to isolate the heterocyclic product of this reaction failed. The formation of the benzoin benzoate might be following the same course of reactions as in case of purine Reissert compounds[10].

Scheme 3



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