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Dipolar Cycloaddition of Cyclic Rhodium Carbenoids to Digonal Carbon. Synthesis of Isoeuparin

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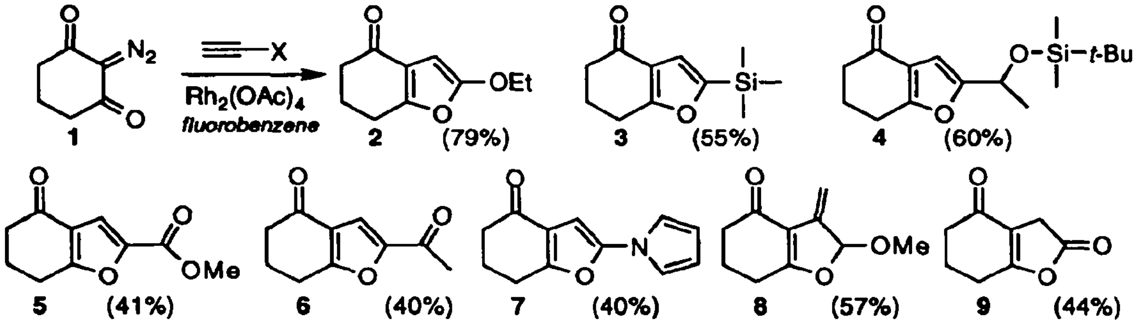
Abstract: *Diazocyclohexanediones undergo dipolar cycloadditions with substituted acetylenes to provide 2-substituted tetrahydrobenzofuran-4-ones and with allenes to provide 2(H)-3-methylenedihydrofuranones.*

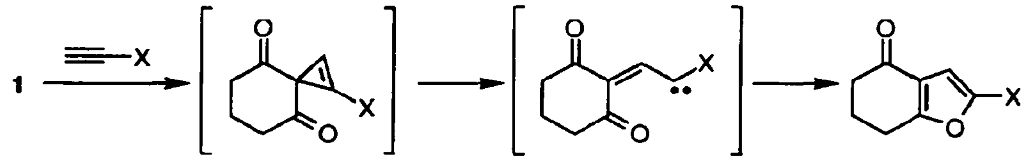
We have recently reported that the rhodium-mediated dipolar cycloaddition of cyclic diazodiketones to aromatic heterocycles is a rapid synthetic entry into complex polyheterocyclic systems.[1] While cycloadditions of such diazoketones to other unsaturated functionalities such as nitriles[2] and acetylenes[3] are known, the utility of these reactions for synthetic purposes has not been exploited. Consequently, we have examined the reactions of diazocyclohexane-1,3-dione (1) with both cumulenes and electron-deficient and electron-rich acetylenes.



The reactions are conducted in fluorobenzene at room temperature for 20h in the presence of 3 equiv of acetylene and 1-2 mol % of $Rh_2(OAc)_4$. As summarized above, tetrahydrobenzofuran cycloaddition products are readily obtained from both types of polar acetylenes. While the yields are somewhat better with electron-rich substrates, as would be expected for the reaction of an electron-deficient carbenoid, effective reactions still occur with electron-poor acetylenes. Only one regioisomer was seen in each case. The structures of the acetylene adducts were assigned on the basis of the chemical shift of the β-furan proton and by the conversion of 4 -> 6 (TBAF, 86%; PDC, 92%). N-Ethynylpyrrole[4] provides only 7, with no evidence of C-H insertion or cycloaddition to the endocyclic alkene as we have observed previously.[1] No adducts were produced from reactions of 1 with disubstituted acetylenes such as 4-octyne, *bis*-trimethylsilylacetylene, or dimethyl acetylenedicarboxylate. The dipolar cycloaddition to cumulenes is of more limited scope than that to acetylenes. While methoxyallene is converted to adduct 8 in 57% yield, 1,1-dimethylallene and *tert*-

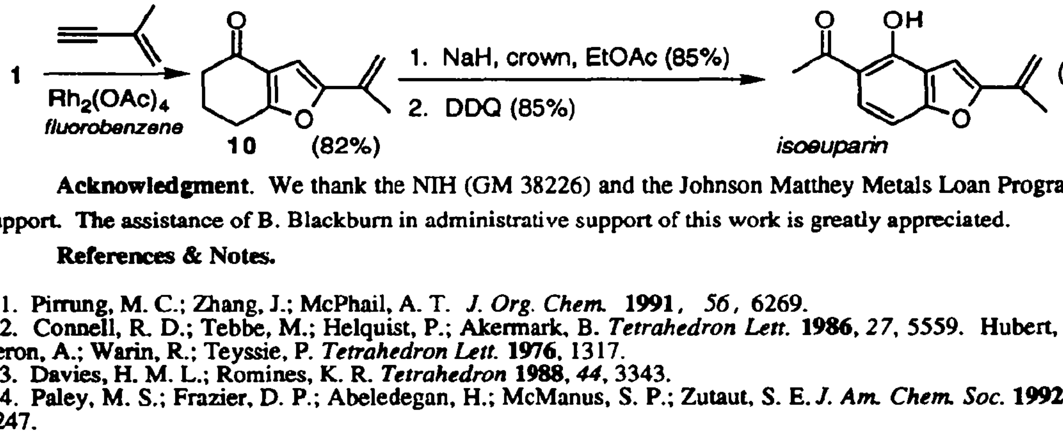
butoxyallene provide mixtures of adducts in low yield. This reaction thus seems sensitive to steric effects. Trimethylsilylketene gives **9**, presumably the product of desilylation during chromatography.

While direct evidence regarding the mechanism of such cycloaddition reactions is meager, it has been shown that cyclopropenation of acetylenes by rhodium carbenoids can occur and that the cyclopropene adducts can be rearranged to furans under metal catalysis.[5] Were that process to occur *via* electrocyclic ring-opening to a carbene (or metal carbenoid) that may be stabilized either by electron-donating or electron-withdrawing substituents, the exclusive formation of 2-substituted furan products could be explained (eq 1). Precedent for a process in which rhodium carbenoid addition to an acetylene generates a second carbenoid comes from the work of Padwa[6] and Hoye.[7] In fact, with an acyclic diazo-β-ketoester, Hoye has also seen dipolar cycloaddition products in intramolecular reactions. Padwa has also recently reported that the isomerization of cyclopropenes to furans can be mediated via rhodium complexes.[8]



(1)

This reaction has been utilized in a straightforward synthesis of isoeuparin, a natural product of mixed polyketide/isoprenoid biogenesis (eq 2).[9] This cycloaddition to isopropenylacetylene (4 eq) occurs in excellent yield to generate the isopropenyl furan substructure found in a wide range of terpenoids. The preparation of isoeuparin is completed by acetylation of the ketone enolate and aromatization with DDQ. The product so obtained (60% from **1**) possesses spectroscopic properties (NMR, IR) identical to those reported.



(2)

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