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Synthesis of novel isoxazole-benzoquinone hybrids via 1,3-dipolar cycloaddition reaction as key step

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ABSTRACT

An efficient method for the preparation of novel 2-(5-arylisoxazol-3-yl)cyclohexa-2,5-diene-1,4-dione hybrids via 1,3-dipolar cycloaddition followed by an oxidation reaction using ceric ammonium nitrate (CAN) has been described. Using this method, various aryl as well as alkyl substituted isoxazole-benzoquinone hybrids were synthesized in high yields.

The search for new antitumor agents having less toxicity and more cytotoxicity potency is the major interest in the present day research.[1] The quinone containing compounds have been widely used for their antitumor and anticancer activities.[2] But the problems associated with these compounds such as toxicity and drug resistance have stimulated an intense demand for the discovery of new and novel antitumour agents.[3] In the last few decades significant progress has been made in the screening of quinone containing compounds for antitumour activity.[4]

Among a number of cytotoxic antibiotics, a few are clinically tolerable as antitumor agents.[5] While antibiotics display an enormous diversity in chemical structures, quinone antibiotics such as adriamycin, mitomycin C, and streptonigrin[6] deserve special attention (Fig. 1). Although they share a common trait of interference with the synthesis of DNA as well as RNA investigations on their mode of action have revealed an intrinsic characteristic feature of each compound, that is intercalation between stacked base pairs for quinone antibiotics, covalent binding to DNA after the intracellular reduction and superoxide formation through the oxido-reduction cycle.[7] In this context, search of new class of molecules containing quinone moiety has always fascinated the organic as well as medicinal chemist.

Compounds containing the quinone group present an important class of biologically active molecules that are wide spread in nature.[8] Isoxazole derivatives show hypoglemic, analgesic, anti-inflammatory, antifungal, anti-bacterial and HIV-inhibitory activities.[9] Synthesis of hybrid natural products has gained momentum in recent years.[10] It is expected that combining features of more than one biologically active natural segment in a single molecule may result in pronounced pharmacological activity while retaining high diversity and biological relevance.[11] There are a few reports describing the preparation of quinone-hybrid with other natural products. For example, quinone-amino acids,[12] sugar-oxasteroid-quinone,[13] quinone-annonaceous acetogenins,[14] conduritol-carba-sugar[15] hybrids have been described using different synthetic protocol. Quinone–isoxazole hybrid shows significant antifungal activity as well as agricultural application.[16] Arylated quinones possess unique visual and electronic properties that make them useful in photosynthesis and appealing structures to the dye industry.[17]

Depending on the substitution pattern, arylated quinones were prepared by a few general methods.[18] Meerwin reactions with aryldiazonium salts and oxidation of the corresponding aromatics are among the most popular. But the disadvantage of this method is that aryldiazonium salts are difficult to prepare, are unstable and have been shown to be explosives. Other methods such as the Pummerer arylation and direct arylation protocols have also been used for the installation of electron rich aryl or hetero aromatics. When these reactions are carried out on mono-substituted 1,4-benzoquinones, an issue of regioselectivity arises, as the arylation can lead to a 2,5 or to a 2,6-disubstituted 1,4-benzoquinone. Most

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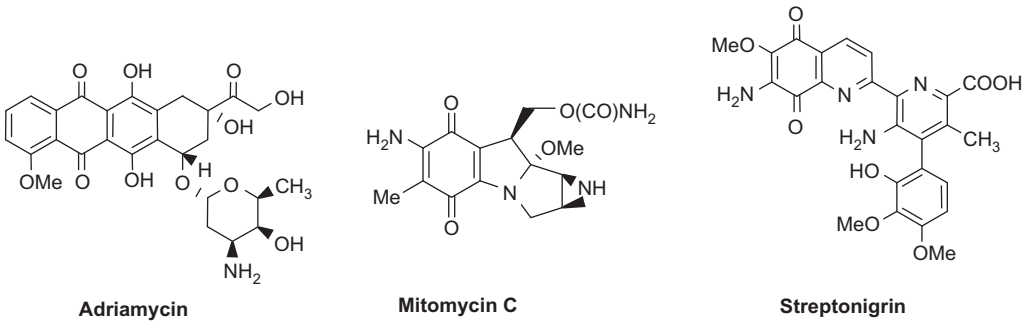
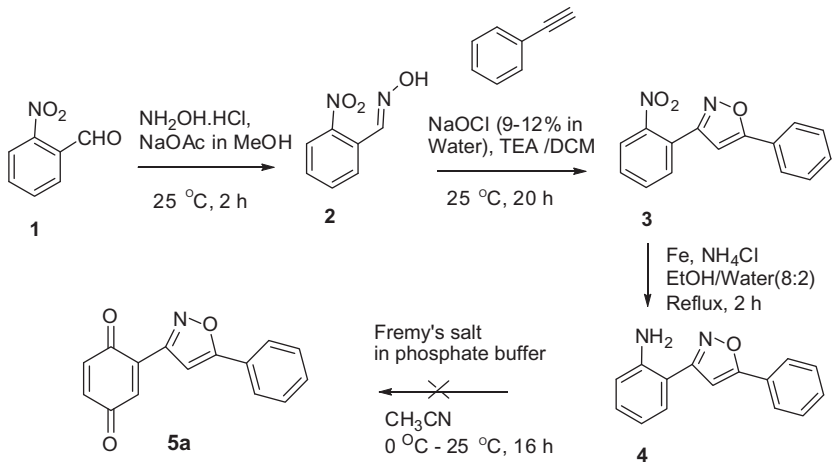
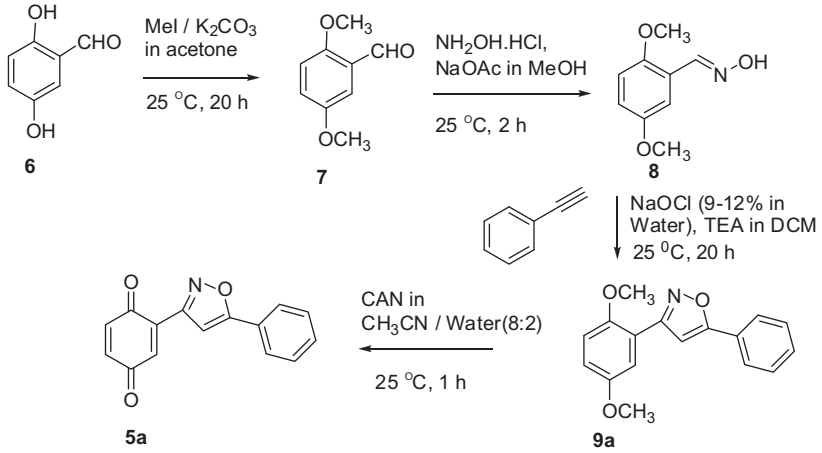


Figure 1. Quinone antibiotics.



Scheme 1. Attempted 1,3-dipolar cycloaddition and oxidation reactions using 2-nitrobenzaldehyde as starting material.



Scheme 2. 1,3-Dipolar cycloaddition and oxidation reactions using 2,5-dihydroxybenzaldehyde as starting material.

of these procedures take place with low regioselectivities and give poor yields with electron-deficient aryl groups. In this respect, transition metal mediated cross-couplings are wider in scope than the other procedures.[19] However, their application requires the previous selective functionalization of the starting quinones with a halogen or triflate group suitable for coupling. Also, the ability of quinones to act as ligands and oxidants to transition metals, such as palladium, poses additional challenge to cross-coupling approaches.[20] Alternate strategy employing protected halo-dihydroquinones followed by deprotection[21] has proven both lengthy and inefficient, as have Diels–Alder/functionalization/retro Diels–Alder sequence.[22] For this reason, a more general method for the functionalization of quinones is in demand. There are some reports of fused benzoquinones such as pyrrolobenzimidazoles (PBI) and indolobenzoquinones by Skibo et al.[23] Recently, Baran's group has developed a practical C–H functionalization of quinones with boronic acids.[24] In a similar approach Csaky and co-workers have reported a mild method for the direct arylation of 2-aryl-1,4-ben-