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Cyclobutanone photoadducts of HCN and malononitrile: useful intermediates for the synthesis of *C*-nucleosides

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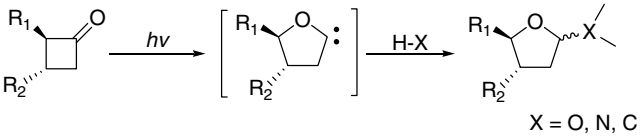
Abstract—Photochemistry of cyclobutanones in the presence of HCN or malononitrile give photoadducts derived from oxacarbene insertion into C–H. These intermediates are useful for the preparation of *C*-nucleosides by structural elaboration of the CN groups.

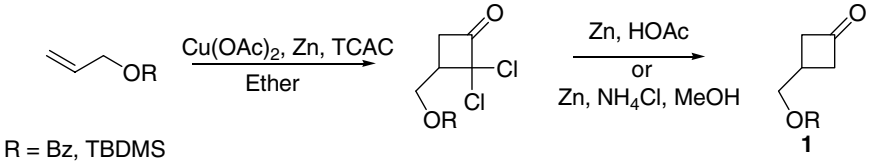
1. Introduction

Structurally modified nucleosides in which a methylene carbon replaces the oxygen of furanose (carbocyclic nucleosides) have been widely investigated for their medicinal properties[1] and we have previously reported on the one-carbon homologation of cyclobutanones protocol as an entry to such systems.[2] As a consequence of this structural modification the glycosidic bond becomes more resistant to nucleoside phosphorylase and hydrolase degradations. Similarly, the bonding of the furanose ring directly to a carbon of the aromatic base (*C*-nucleosides) renders greater stability to the nucleoside.[3] A third class of carbon nucleosides involves bonding of the base with furanose via a methylene bridge (homonucleosides), and has only recently come to the fore as potential antiviral and antitumour drug candidates.[4] Many existing synthetic methods, like those used in other nucleoside syntheses, involve classical methods of carbohydrate chemistry which are specific to the particular sugar unit, and often suffer from unwanted side reactions. We have used the photochemical isomerization of cyclobutanones to the corresponding oxacarbene as a synthetic route to nucleosides.[5] The basis of this approach is the photochemical ring-expansion of cyclobutanones and trapping of a transient oxacarbene with weakly acidic X–H functional groups (Scheme 1). The ring-expansion takes place regioselectively with retention of the ring-substituent stereochemistry.



Scheme 1. Photochemical ring-expansion of cyclobutanones.

Although other non-photochemical methods exist for ring-expansion of cyclobutanes and subsequent structural elaboration to nucleosides and oligosaccharides, such processes often involve reaction conditions (Lewis acid or base) which render substituents to become labile



Scheme 2. Cyclobutanone synthesis.

Keywords: Photochemistry; Cyclobutanone; Oxacarbene; *C*-Nucleosides.
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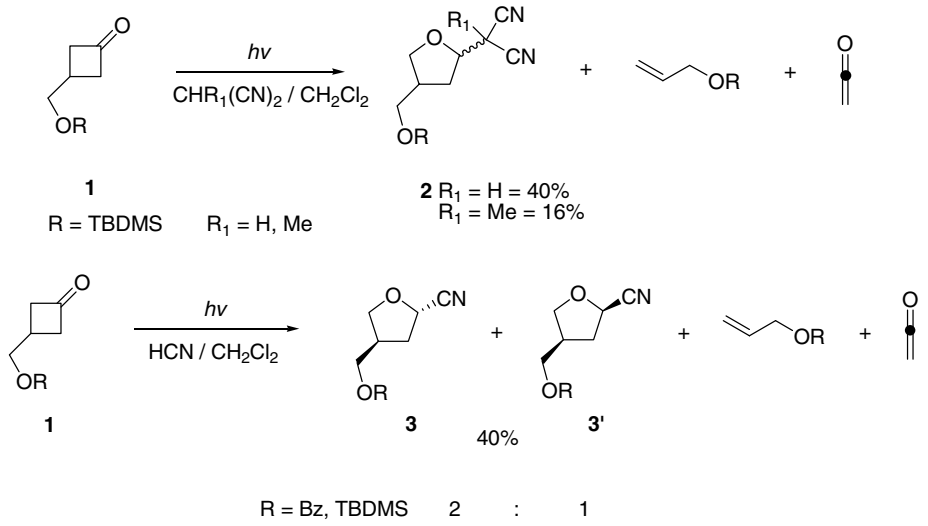
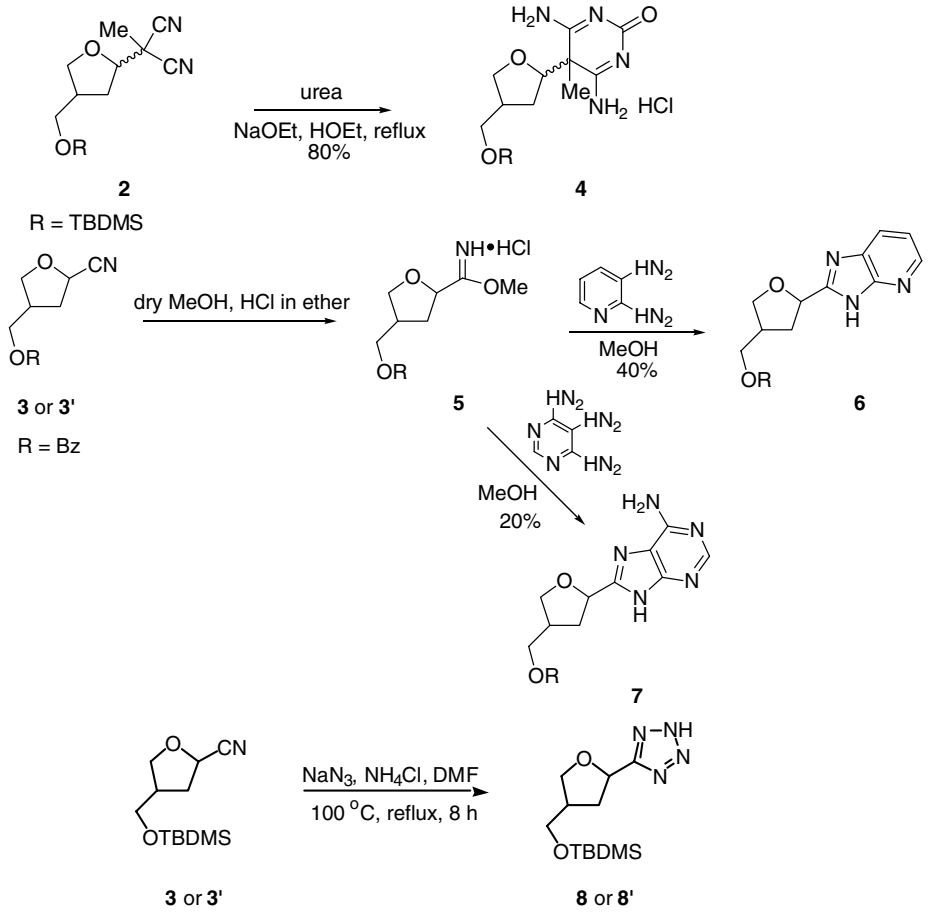


Scheme 3. Malononitrile and HCN photoadducts of ketone **1**.

and/or undergo stereochemical equilibration. Furthermore, the current glycosylation method eliminates an additional step in that both ring-expansion and coupling steps can be accomplished in a single reaction. In the current study we report the photochemical ring-expansion of cyclobutanones to form HCN and malononitrile photoadducts. To our knowledge, this is the first example of the insertion of a cyclobutanone derived oxacarbene into a C–H function.[6] Both photoadducts are useful starting materials for structural elaboration to heterocycles, specifically, carbon nucleoside analogues.



Scheme 4. Heterocyclic compounds from malononitrile and HCN photoadducts.

2. Results

Cyclobutanones **1** were prepared by [2+2] cycloaddition of the corresponding alkene with dichloroketene, followed by dechlorination in 50–70% yield (Scheme 2).

Irradiation of CH_2Cl_2 solutions of ketones **1** (R = Bz, TBDMS) (5×10^{-3} M) with malononitrile, methylmalononitrile or HCN (5 equiv) led to the formation of adducts **2** and **3**, respectively, in about 40% yields and 16% for methylmalononitrile (Scheme 3).[7] The remaining products are derived from cycloelimination. The stereoisomers of **3** could be separated and the stereochemistry assigned based on NOESY analysis. The trans-isomer was formed in a slightly higher yield compared to the cis-isomer. The cis-isomer of **3** has the more shielded anomeric hydrogen (δ 4.68 ppm for R = TBDMS and δ 4.76 ppm for R = Bz) relative to the trans-isomer (δ 4.75 ppm for R = TBDMS and δ 4.86 ppm for R = Bz) in their ^{1}H NMR spectra. The stereoisomers of **2** could not be separated.

Condensation of **2** (R = H) with guanidine hydrogen chloride salt, urea or thiourea according to the method of Bio et al.[8] did not give any heterocycle formation. However, methylmalononitrile adduct **2** (R = Me) reacted with urea under the same conditions to give **4** in 80% yield (Scheme 4).

The HCN photoadducts **3** (*trans*) and **3′** (*cis*) reacted with 2,3-diaminopyridine and 4,5,6-triaminopyrimidine to give the corresponding 1*H*-Imidazo[4,5-*b*]pyridines, **6** (*trans*) and **6′** (*cis*), and purines **7** (*trans*) and **7′** (*cis*), respectively via imidate salt **5** (Scheme 4).[9] Other *C*-nucleoside analogues prepared in this study are the tetrazole derivatives (Scheme 4). Reaction of the cyano photoadduct **3** or **3′**, sodium azide and ammonium chloride in DMF gave tetrazole furanoside **8** or **8′** (75%).[10]

3. Summary

The photochemical ring-expansion of cyclobutanones with malononitrile and hydrogen cyanide give photoadducts by direct insertion into the acidic C–H function. These adducts can be condensed with appropriate reagents to give heterocyclic *C*-furanosides, which are analogues of *C*-nucleosides. Since cyclobutanones with stereochemically defined ring-substituents are commonly available by classical synthetic methods, many of which involve enantioselective reactions,[11] these *C*-nucleoside analogues can also be prepared in optically enriched forms.

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