Regiospecificity of Organometallic Azide Attack on Citraconic Anhydride

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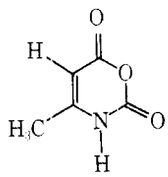
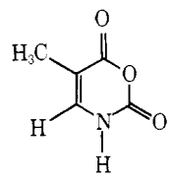
Previous work from this laboratory has shown the generality of the reaction of substituted maleic anhydrides with trimethylsilyl azide to produce the biologically important oxazinedione isostere of pyrimidinediones.[1] Obviously, the synthetic utility of this reaction relative to other routes[2] to substituted oxazinediones depends on which regioisomer, 4-X or 5-X, is obtained. Since both 4-substituted, e.g., oxaorotate,[2a] and 5-substituted, e.g., oxathymine,[2b,c] oxazinediones are of interest, our investigation centered on methods for driving the reaction toward either 4-X or 5-X. Our initial report[1b] reported exclusive production of 4-CH_3 in the reaction of citraconic anhydride with trimethylsilyl azide in chloroform. The subsequent report by Skoda[2b] of a mixture of 4-CH_3 and 5-CH_3 oxazinediones in this reaction caused a reexamination of our procedure.



4-CH_3

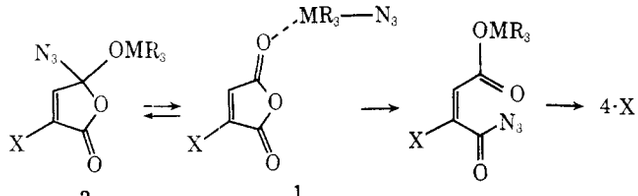


5-CH_3

Since the olefinic ^1H NMR resonances of 4-CH_3 (δ 5.41) and 5-CH_3 (δ 7.35) are well separated, the reaction may be easily monitored by NMR spectroscopy. The crude oxazinedione fraction obtained by ethanolysis of the reaction mixture contains a 7:3 ratio of 4-CH_3 and 5-CH_3 products. In our previously used[1b] recrystallization solvent ethyl acetate, 5-CH_3 remains in the mother liquors. Not surprisingly, a zealously recrystallized analytical sample was pure 4-CH_3. When chloroform is used as recrystallization solvent, 5-CH_3 is less soluble and can be selectively crystallized.

In attempts to selectively produce either regioisomer, we varied solvent and organometallic azide. Rather discouragingly, where there is any measurable yield, a 2:1 mixture of 4- and 5-CH_3 is produced. Me_3SiN_3 in dioxane (80 °C, 2.5 h) or the bulkier triethylsilyl azide (neat, 70 °C, 4.5 h) gave the same isomer distribution, but only 10–17% yield. Triethylsilyl azide in benzene, or triphenylsilyl azide either neat or in chloroform, totally failed to react. Sodium azide in dioxane, HMPT, DMF–benzene, or even dioxane with 10 mol % of trimethylsilyl azide as catalyst also failed to react.

For all substituted maleic anhydrides[1b,c] the 4-X oxazinedione, *the product of attack at the more hindered carbonyl,* is the major regioisomer, regardless of the electronic nature of X (halogen, aryl, or alkyl). This observation is best rationalized by assuming that the reaction is initiated by complexation of azide at the less hindered carbonyl of 1,[8] followed by preferential attack of N_3 on the other carbonyl, leading irreversibly to oxazinedione. Addition generating **2** is reversible while that leading to acyl azide **3**[1b] is not.



2 **1** **3**

The reaction of simple carbonyls with Me_3SiN_3 is slow.[3] The reduced yield with Et_3SiN_3 and the nonreactivity of Ph_3SiN_3 and NaN_3 are in agreement with their lessened ability, relative to Me_3SiN_3, to complex with carbonyls. Triphenylsilyl azide, for example, is unreactive with acyl halides under conditions where trimethylsilyl azide reacts smoothly.[4]

Tri-*n*-butylstannyl azide, a recently proposed[5] alternative to trimethylsilyl azide, afford somewhat better yields of oxazinedione (up to 47%), but with hardly any regiospecificity. The facility with which tin expands its coordination sphere[6] and the demonstration that 1,8-bis(trimethylstannyl)-naphthalene is less crowded than its silicon analogue[7] imply that an organotin can complex readily with citraconic anhydride.

In conclusion, although none of the organometallic azides studied produces a single regioisomer from citraconic anhydride, for maximum yield and ease of workup tri-*n*-butylstannyl azide is the reagent of choice for conversion of maleic anhydride to oxazinediones. For synthesis of regioisomeric oxazinediones, the β-keto ester route[2a] is preferred.

Experimental Section

General Comments. ^1H NMR spectra were determined on Varian XL-100-15 and Perkin-Elmer R-32 spectrometers using internal Me_4Si as a standard. Silyl azides were purchased from Petrarch Systems, Inc., Levittown, Pa. Column chromatography (silica gel Woelm Activity I) and thin-layer chromatography (silica gel GF) were performed with ethyl acetate as eluent. Solvents were dried over Linde 4A molecular sieves. Ratios of 4- and 5-methyloxazinedione product were determined by careful NMR integration of the olefinic hydrogen resonance.

Citraconic Anhydride with Trimethylsilyl Azide in Chloroform. The previously reported procedure[1b] was modified to maximize the isolated yield of 5-CH_3. By refluxing a mixture of 1 mol each of citraconic anhydride and trimethylsilyl azide in 150 mL of chloroform for 19 h and subsequent ethanolysis, 45 g (35%) of a mixture of methyloxazinediones was obtained, mp 103–120 °C. The ratio of 5-CH_3 (δ 1.80 and 7.35) to 4-CH_3 (δ 2.11 and 5.41) was 30:70. Two fractional crystallizations from $CHCl_3$ afforded pure 5-methyloxazinedione in variable yield, mp 138 °C dec (lit. 130[2b] and 134–135 °C[2d]). Recrystallization of the crude mixture from EtOAc[1b] afforded pure 4-methyloxazinedione.

Citraconic Anhydride with Tri-*n*-butylstannyl Azide. A mixture of 44 mmol of citraconic anhydride and 50 mmol of tri-*n*-butylstannyl azide[5a] in 50 mL of chloroform was heated at reflux for 3.5 h and then hydrolyzed with 0.9 mL of water. Extraction into ethyl acetate and column chromatography gave 2.61 g (47%) of methyloxazinediones; the 4-CH_3/5-CH_3 ratio was 60:40. The yield with benzene solvent was 33%; in a neat reaction the yield was 10%.

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Registry No.—4-CH_3 oxazinedione, 51440-82-5; 5-CH_3 oxazinedione, 51255-10-8; citraconic anhydride, 616-02-4; trimethylsilyl azide, 4648-54-8; tributylstannyl azide, 17846-68-3.

References and Notes

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(8) We are indebted to Professor P. Grieco for suggesting this explanation.

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