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A DIRECT METHOD FOR THE CONSTRUCTION OF BENZENE RINGS, AND ITS USE IN THE TOTAL SYNTHESIS OF ISMINE

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Practical methods for the direct annellation of benzene rings to olefinic bonds are rare. We wish to report a novel method of accomplishing this which provides, inter alia, a useful one-step synthesis of unsymmetrical biphenyls.

The addition of trans, trans-1,4-diacetoxybutadiene (I) to dienophiles (II) furnishes adducts of type (III) which might be expected to aromatize easily; indeed, in several cases the thermal elimination of acetic acid has been reported.[2,3] We have observed that heating various dienophiles with I at 100-110° leads directly to aromatized products (IV).

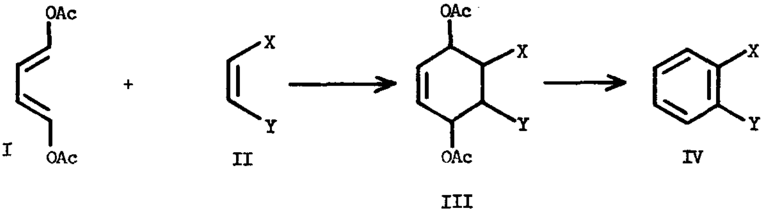


Table I lists representative examples. Quinones react readily, as previously noted for juglone.[2] The use of nitrostyrenes as dienophiles provides a series of 2-nitrobiphenyls, useful intermediates in the synthesis of unsymmetrical carbazoles.[4]

TABLE I

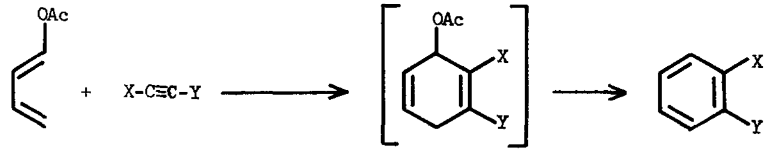
AROMATIC PRODUCTS FROM THE REACTION OF 1,4-DIACETOXYBUTADIENE WITH DIENOPHILES

Dienophile	Product	Yield (°/o)
p-Benzoquinone	1,4-Naphthoquinone 9,10-Anthraquinone	73 8
1,4-Naphthoquinone	9,10-Anthraquinone	45
β-Nitrostyrene	2-Nitrobiphenyl	20
3,4-Dimethoxy-β-nitrostyrene	3,4-Dimethoxy-2'-nitrobiphenyl	26
3,4-Methylenedioxy-β-nitrostyrene	3,4-Methylenedioxy-2'-nitrobiphenyl (V)	45
Dimethyl acetylene-dicarboxylate	Dimethyl-3-acetoxy-phthalate	49
Phenylpropiolic acid	2-Phenyl-3-acetoxy-benzoic acid	28

Notes for Table I: Additions to quinones were done in refluxing benzene solution; all others were carried out without solvent at 100-110°. Satisfactory analyses were obtained for all new compounds. Known compounds were identified by comparison with authentic samples.

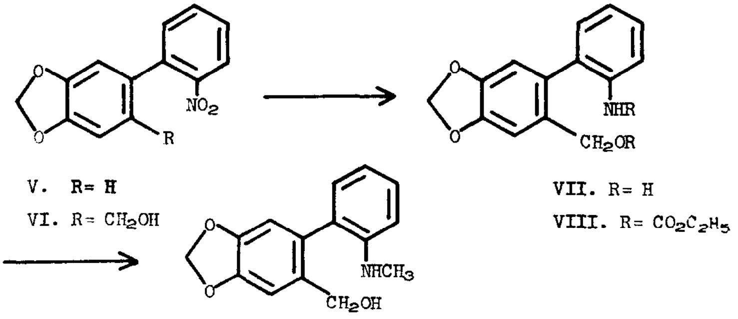
Acetylenic acid derivatives afford products which retain one of the acetoxy groups; in the adduct from phenylpropiolic acid, the acetoxy group lost is that expected on the basis of an ionic elimination mechanism. The product in this case, 2-phenyl-3-acetoxybenzoic acid, was readily cyclized by sulfuric acid to 4-hydroxyfluorenone.

Aromatic products should also be available from the reaction of acetylenic dienophiles with 1-acetoxybutadiene. We have found that this reaction, illustrated below, leads directly to benzene derivatives without isolation of the intermediate Diels-Alder adducts.



Acetylenes tested were dimethyl acetylenedicarboxylate, methyl phenylpropiolate, and "benzyne"[5], which yielded, respectively, dimethyl phthalate (43 ^{o}/o), 2-carbomethoxybiphenyl (6 ^{o}/o), and naphthalene (11 ^{o}/o).

A striking example of the utility of this new method of construction of benzene rings, especially for unsymmetrical biphenyls difficultly obtainable by the Ullmann or other methods, is its use in the synthesis of ismine (IX), an alkaloid isolated from various Amaryllidaceae species by Highet.[6] 3,4-Methylenedioxy-2'-nitrobiphenyl (V), prepared as shown in Table I, served as the starting material. Treatment with formaldehyde and hydrogen



V. R= H

VI. R= CH_2OH

VII. R= H

VIII. R= $CO_2C_2H_5$

IX.

chloride in acetic acid, followed by hydrolysis with bicarbonate, gave the hydroxymethyl derivative (VI). Catalytic hydrogenation yielded the amine (VII), converted by treatment with ethyl chlorocarbonate in pyridine to (VIII). Lithium aluminum hydride reduction gave ismine, m.p. 97-98°, identical by mixed m.p. comparison and infrared spectra with the natural base.

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