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THE REACTIONS OF BENZYNE WITH α,β-UNSATURATED CARBONYL COMPOUNDS

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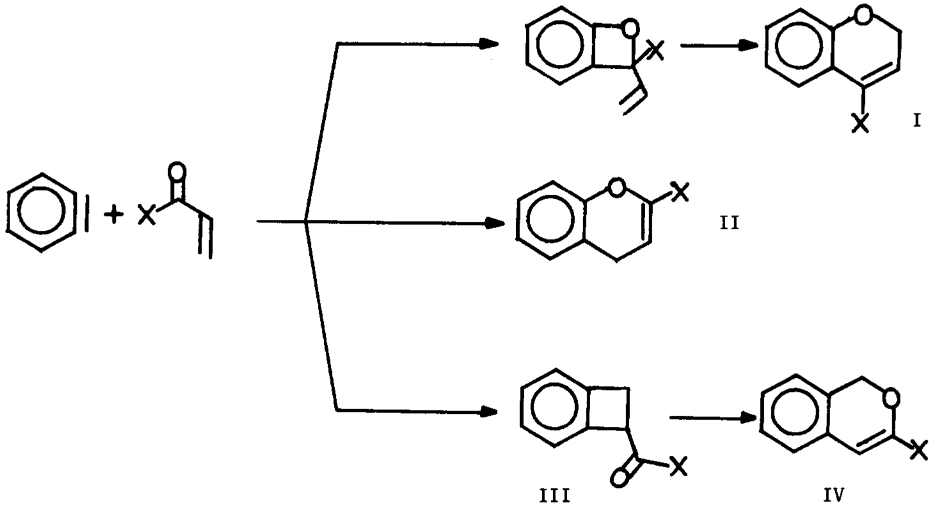
The cycloaddition of benzyne to conjugatively unsaturated esters[1] and aldehydes[2] has already been reported in the literature. In the former case, only cycloaddition to the carbon-carbon double bond to produce III-a was reported. In the latter example, only Type I products derived from initial carbonyl cycloaddition were detected.

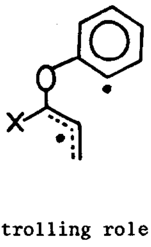


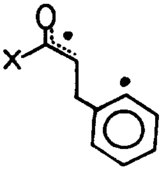
a : X=OEt, b : X=H, c : X=CH_3, d : X=C_2H_5, e : X=C_6H_5, f : X=SCH_3

In order to elucidate the factors responsible for this selectivity, we have investigated the reactions of benzyne[3] with a variety of α,β-unsaturated carbonyl compounds. Generation of benzyne in the presence of a large excess of methyl vinyl ketone produced the carbon-carbon double bond cycloadduct, 1-acetylbenzocyclobutene[5] (III-c), and the Diels-Alder product, 2-methyl-4H-chromene (II-c) [nmr (100 MHz, CCl_4) 7.16-6.60 δ (m, 4.5 H), 4.59 δ (br t, J=3.0 Hz, 0.9 H), 3.33 δ (br d, J=3.0 Hz, 1.8 H), 1.86 δ (br s, 2.7 H); precise mass measurement: calcd for $C_{10}H_{10}O$; 146.0732, found 146.0722], in a 7:1 ratio. The total absolute yield was ca. 48% as determined by vpc analysis with an internal standard. Depending upon the vpc conditions, an additional product, 3-methylisochromene (IV-c), could be produced at the expense of its valence isomer III-c.[5] However, 4-methyl-2H-chromene (I-c), the product from carbonyl cycloaddition was shown to be absent by synthesis of an authentic sample[6] and vpc comparison. Similar results were obtained with ethyl vinyl ketone, except that now the ratio of carbon-carbon double bond to Diels-Alder cycloadduct had decreased to ca. 4.7 to 1; such a change is in accord with known steric substituent effects in 2-substituted butadienes.[7] When benzyne was allowed to react with an excess of phenyl vinyl ketone, only IV-e, the rearranged carbon-carbon double bond cycloadduct, was obtained. Authentic III-e also rearranged entirely to IV-e under our vpc conditions.[5] Generation of benzyne in the presence of methyl thiolacrylate produced thioester III-f [nmr (100 MHz, CCl_4) 7.28-6.86 δ (m, 4.2 H), 4.40 δ (t, J=4.0 Hz, 0.9 H), 3.48 δ (d, J=4.0 Hz, 2.0 H), 2.30 δ (s, 2.9 H); precise mass measurement: calcd for $C_{10}H_{10}OS$: 178.0452, found: 178.0456; ir (neat) ν_{CO} 1679 cm^{-1}] in approximately 45% yield.

Had the stabilities of the presumed biradical allyl (V) and oxallyl (VI) intermediates played a controlling role in directing the mode of cycloaddition, we would have expected to observe an increase in the amount of the Type I carbon-oxygen cycloadduct as the substituent X became more electron withdrawing. The observed results are, however, inconsistent with such a scheme, but are in accord with a mechanism

V

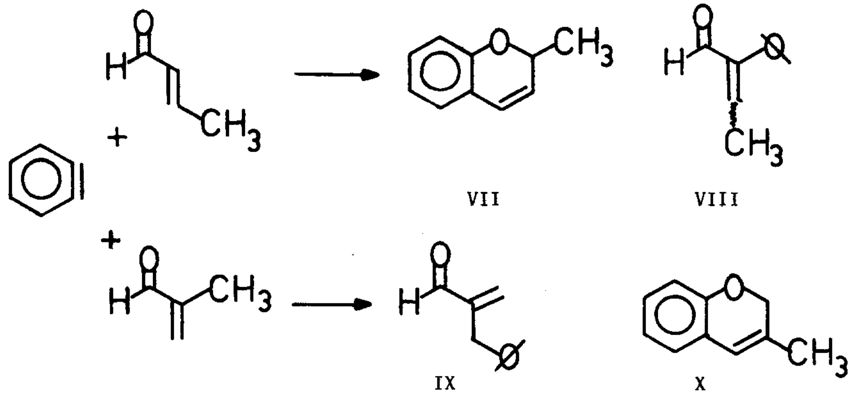




VI

whereby the reactivity of the initial carbonyl (i.e., aldehyde > ketone ~ thioester[8] ~ ester) is the determining factor.

In seeming agreement with this explanation, we have found that Type I products from aldehydes can be supressed by the introduction of α-substituents. For example, crotonaldehyde reacts with benzyne to produce two compounds in a 19:1 ratio. The major product has already been identified as 2-methyl-2H-chromene (VII),[2a,9] the rearranged carbonyl cycloadduct. The minor component is exceedingly difficult to isolate and, on the basis of its nmr spectrum, we have tentatively identified it as a mixture of (E)- and (Z)-α-phenylcrotonaldehyde [E- and (Z)-VIII],[10] a substance presumably arising by isomerization of the β,γ-unsaturated ene product. Benzyne also reacts with methacrolein to produce two products in a 19:1 ratio with an overall yield of 55%. In contrast to the above reaction, however, the major compound was now derived



via the ene reaction pathway and was found to be α-methylene-hydrocinnamaldehyde (IX).[12] The minor product has been identified as 3-methyl-2H-chromene (X) [nmr (100 MHz, CCl_4) 6.80-6.50 δ (m, 3.8 H), 6.07 δ (br s, 1.0 H), 4.60 δ (br s, 2.2 H), 1.80 δ (br s, 3.0 H); precise mass measurement: calcd for $C_{10}H_{10}O$: 146.0732, found: 146.0725], the product derived from initial carbonyl cycloaddition. In order to determine if the carbonyl addition had, in fact, been retarded or the ene reaction accelerated, or if both changes were occurring, we performed a competition experiment involving benzyne and an excess of both crotonaldehyde and methacrolein. The relative rate data is presented in the following table. These results indicate a substantial decrease in the rate of carbonyl cycloaddition upon α-substitution. Such an effect, perhaps steric

	K_{rel}^{co}	K_{rel}^{ene}
crotonaldehyde	19.0	1.0
methacrolein	1.7	31.7

in origin, is consistent with our explanations. It is also interesting to note that the ene reaction rate is also very sensitive to the substitution pattern. The source of this latter effect is currently under investigation.

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10. Enough sample was obtained to secure a PFT-NMR spectrum. As our acquisition time was much shorter than the expected T_1 relaxation times for these protons, integral values were not recorded. The 100 MHz nmr spectrum of (E)- and (Z)-VIII in CCl_4 was as follows: 9.52 δ (s), 9.18 δ (s), 7.34-6.92 δ (m), 6.90-6.62 δ (m), 1.98 δ (d, J=6.9 Hz), 1.41 δ (d, J = 6.5 Hz). Compare these values to those for (Z)-α-phenylcrotononitrile.[11] It should also be noted that even if our structural assignment is incorrect, it still serves to set an upper limit on the relative rate of the ene reaction.
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