

CHEMISTRY OF BENZYNE

S.M. ABDUL HAI and A. WADOOD QURESHI

PCSIR Laboratories, Karachi 39

(Received November 22, 1974; revised March 11, 1974)

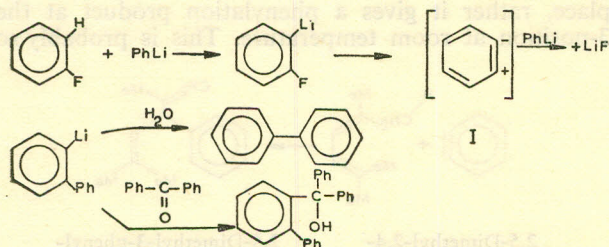
Abstract. Benzyne, also referred to as dehydrobenzene and cyclohexadienyn, is a short-lived intermediate; member of a class of organic reactive intermediates, which have evaded isolation. This class of intermediates has been the subject of intensive investigation, because it serves as a useful source for the syntheses of various compounds of academic and commercial importance which otherwise are obtainable only via long and cumbersome routes. Its electronic structure and reaction mechanism involved in its reaction have been the focus of attention. It is known to enter into reaction with *pi* and *sigma* bonds of suitable substrates. Its various reactions and their mechanism alongwith its electronic structure are discussed.

Introduction

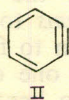
Benzyne, also referred to as dehydrobenzene and cyclohexadienyn, is a short-lived intermediate; member of a class of aromatic reactive intermediates, which have evaded isolation or physical detection so far.

Its discovery led to a very vast activity to probe the possibility of its being utilized in the syntheses of complex molecules. A door was opened to an entirely new field and it offered a challenge to those chemists who like to probe the pathways of molecules enroute to the formation of various novel adducts. This class of organic intermediates has been the subject of investigation in recent years from the point of view of the formation of various compounds of academic and commercial importance, and also from the point of view of studying bonding in them and the reaction mechanism involved in their reactions.

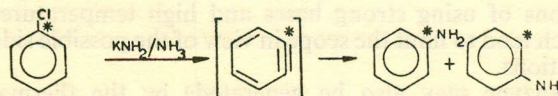
As early as 1902 such species was proposed to be involved in reactions of various compounds. It again drew scientists' attention in 1942, when its involvement² was experimentally shown as an intermediate in the reaction of PhLi with C₆H₅F. The final product depended upon subsequent treatment of the reaction mixture.



In the early days benzyne was supposed to exist in the dipolar form I, but later symmetrical structure II was proposed for it.



But so far the hypothesis of its existence was not generally accepted. Considerable time elapsed before in 1953 the theory of benzyne intermediate was put³ on a firm footing by C¹⁴ labelling experiments. It was observed that chlorobenzene-1-C¹⁴ on treatment with potassium amide gives equal amounts of aniline-1-C¹⁴ and aniline-2-C¹⁴. The results were explained by the following mechanism:



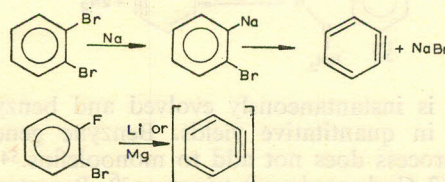
This work was followed by reports from Huisgen⁴ which in general proved the existence of benzyne intermediate. Reports from other quarters also pointed to its existence and supported the symmetrical structure II for it. Subsequent work, including labelling experiments confirmed its existence.

Modes of Generation

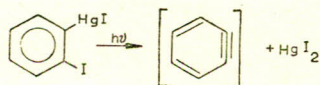
Benzyne is prepared in a variety of ways. Being an extremely reactive intermediate it combines readily with electron donors.

Chlorobenzene is just one of the many aryl halides to react with potassium amide. Both fluoro- and bromobenzenes yield benzyne when treated with amide ion, and good evidence is available that a two-step E₁cB type elimination reaction is involved.

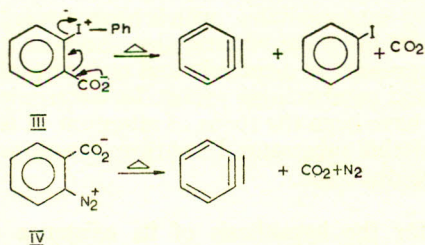
Apart from being formed from the reaction of a halo-benzene with strong bases the reaction of *o*-dihalo-benzenes with metals such as Na, Li, Mg yields benzyne.^{19,22}



Photolysis of mercuric salt²⁰ also gives benzyne.

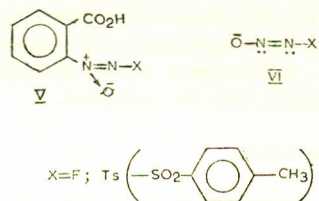


Recent work has evolved several methods for the generation of this intermediate. Now a chemist has at his disposal versatile methods for its generation, which suit his reaction conditions and convenience. Thus it may be generated in a thermal process from diphenyliodonium-2-carboxylate¹⁶ and thermally or photochemically from benzenediazonium-2-carboxylate.^{17,18,28,29,65}



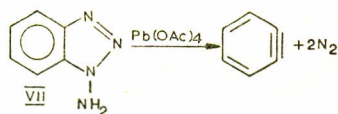
The latter compound serves as a good source and offers lot of convenience, since it is easily prepared by aprotic diazotization of anthranilic acid. It can be stored at low temperatures and gives benzyne on mild heating. These compounds serve very good purpose for the study of the reactions of benzyne, as it can be generated from them without having to encounter the complications of using strong bases and high temperatures which tend to limit the scope in view of the possible side reactions.

Benzyne may also be generated⁹ by the thermal decomposition of compounds of the type azoxytoluenesulphonate and azoxyfluorobenzoid acid.



The nature of the decomposition process remains obscure. Apparently a free radical pathway is operative, giving rise to nitrogen and aryl radicals. However, ionic pathway leading to CO₂, benzyne, and involving a nitrogen precursor⁹ such as diimide VI, can also be envisaged.

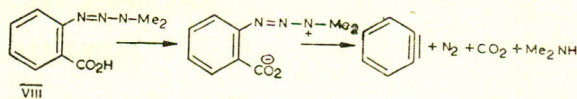
By Oxidative Process. Benzyne may be produced by the lead tetraacetate oxidation¹⁰ of 1-aminobenzotriazole (VII).



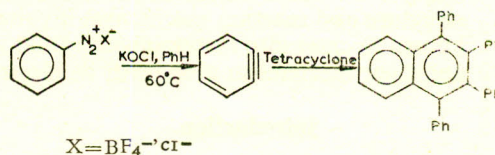
Nitrogen is instantaneously evolved and benzyne is obtained in quantitative yields. Benzyne generated by this process does not add to monoolefins.⁵⁴

Via 1-(2-Carboxyphenyl)-triazenes.²⁶ Benzyne may be formed by thermal decomposition of triazenes.

Thus 1,2,3,4-tetraphenylnaphthalene is formed in 50% yield when VIII is refluxed in PhCl in the presence of 2,3,4,5-tetraphenylcyclopentadiene. The formation of benzyne is facilitated by the addition of equivalent amount of perchloroacetic acid. The reaction is thought to proceed via an inner salt.



From Diazonium compounds.²⁷ Certain diazonium salts on treatment with potassium hypochlorite (KOCl) in benzene solution at 60°C yield benzyne which reacts with tetracyclone to give 1,2,3,4-tetraphenylnaphthalene.²⁹



With anthracene, triptycene is formed in 41% yield.

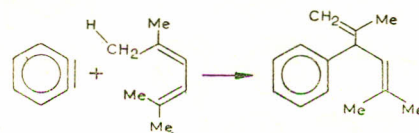
From Peroxides.⁴¹ Photolysis of phthaloyl peroxide through a Pyrex vessel yields benzyne, which exhibits its usual reactions.

Reactions

Benzyne forms adducts with a wide variety of substrates. It is electrophilic and reacts with all nucleophiles in a fast step. The general reactions of benzyne and other arynes are discussed below:

Ene Reaction. The 'ene' reaction is the indirect substituting addition of a compound with a double or triple bond (enophile) to an olefin with an allylic-H (ene). For a long time this reaction has been neglected and was overshadowed by the related Diels-Alder addition. In the case of benzyne the net outcome of this reaction is phenylation accompanied by shift of the olefinic bond in the ene. Because of its electrophilic nature, it acts as one of the most powerful enophiles. A few representative instances are cited below.

Arnett⁶ studied the reaction of benzyne with open chain dienes. It was observed to his surprise that the usual Diels-Alder type of cyclization does not take place, rather it gives a phenylation product at the 3-position at room temperature. This is probably so

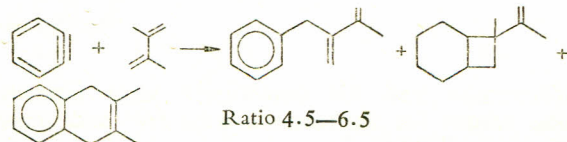


2,5-Dimethyl-2,4-hexadiene

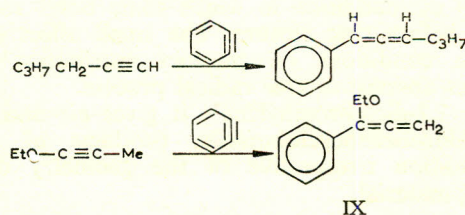
2,5-Dimethyl-3-phenyl-1,4-hexadiene

because the diene cannot be forced into a *cisoid* conformation required for the ring closure. The isobutylene groups are *trans* to each other, and steric hindrance prevents them to fall on the same side of the molecule, whereby one of them is in a proper position for addition to benzyne.

In its reaction with 2,3-dimethyl-1,3-butadiene⁸ the ene reaction predominates to the extent of 4.5–6.7 times the ratio of addition reaction (1,2 and 1,4 combined together).

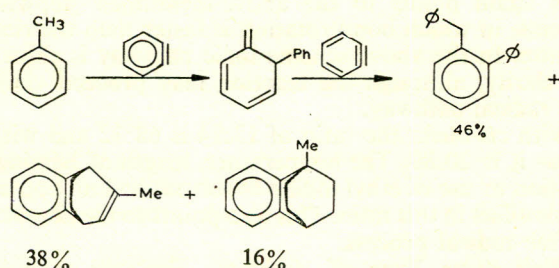


In the ene reaction of benzyne with 1-octene⁷ the *trans* isomer has been reported to be formed as the major product, although other products were not identified. It has been suggested that the bulky and flexible *n*-pentyl chain prefers to be oriented away from the attacking benzyne:



This product (IX) undergoes further 1,2 type of addition with benzyne to give two isomers.

With toluene it gives a combination of products involving various kinds of addition reactions:



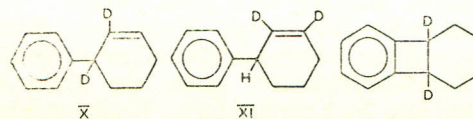
Thus a product of ene reaction and two products of 1,4-addition are observed. It may be noted that the product of 1,4-addition at the electron rich *o* and *p*-positions is formed in greater yield. Ethylbenzene and isopropylbenzene react in a similar fashion, but *t*-butyl benzene which does not contain an allylic-H fails to give any ene product. Tetrafluoro- and tetrachlorobenzynes only give Diels-Alder type adducts with toluene. This may be due to the strong electron withdrawing effects of the halogens in benzyne, which do not permit polarization of charges to enable it to abstract a proton necessary for the ene reaction.

1-Methylnaphthalene undergoes (4+2) cycloaddition exclusively with preferential attack (63%) on the methylated ring. 2-Methylnaphthalene forms the double ene product, 2-benzyl-1-phenylnaphthalene in 38% yield, in addition to the Diels-Alder adduct. This difference is due to simple electronic effects, i.e. enophiles, like electrophiles attack preferentially the more electron rich α -carbon of naphthalenes.

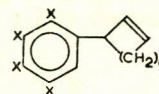
In the case of reactions with *cis*- and *trans*-acetoxy- and methoxypropene²³ the ene product is formed in

about 10% of the total products. With *cis*-olefin the ene product does not exceed 10%, but in cases of *trans*-olefin its yield is substantial. This may be due to the steric inhibitions imposed by the *cis*-olefin.

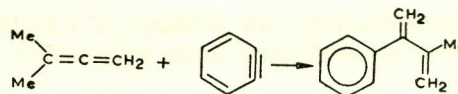
Benzyne reacts with cyclohexene⁷ to give both the ene-adduct, 3-phenylcyclohexene, and the cycloadduct, 1,2-phenylene cyclohexane. In its reaction with 1,2-dideuteriocyclohexene,²⁴ only the true ene-adduct (X) is obtained, presumably via a concerted reaction. None of the isomeric ene-adduct (XI) or cycloadduct is formed.



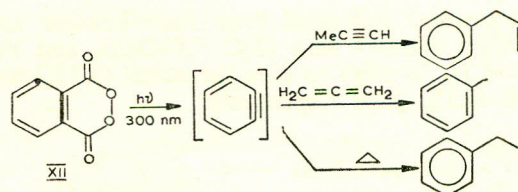
Benzyne and its tetrafluoro isomer reacts²⁵ with cyclohexene and cyclopentene via a concerted 6-membered transition state, in which the position of the double bond in the cycloolefin is shifted. The products were 3-(2,3,4,5-tetrafluorophenyl) and 3-phenylcyclohexene and cyclopentene I (X = F, H; *n* = 3,2 respectively).



The reaction of benzyne with allenes³² proceeds by 2+2 cycloaddition or by ene-like reactions with the formation of 1,3-diene or an acetylene, analogous to monoenes.



Benzyne generated by the photodecomposition of phthaloylperoxide (XII) reacts⁴¹ with methyl acetylene, allene and cyclopropane to give the following products:



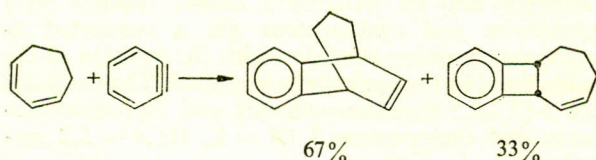
This is in contrast with the work on vinyl cyclopropane.⁸ There the ring is left intact, which is perhaps due to the ready availability of π -electrons from the double bond to electrophilic benzyne.

In the reaction of benzyne with *trans*-ethyl propenyl ether, ethyl 2-phenyl allyl ether²⁵ (product of ene reaction) is formed to the extent of 14% while the same product is formed only in 0.9% yield from the *cis*-olefin. It is so because the ene reaction is concerted and sterically inhibited in the *cis*-olefin by the interaction of bulky substituents with the benzyne ring. Here again the *trans* orientation of the olefin permits a more favourable transition state for H-abstraction compared to the *cis*-olefin.

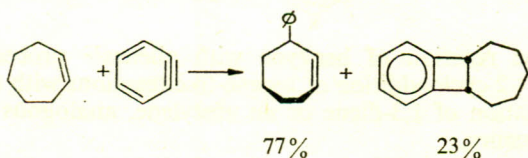
Addition Reactions. Benzyne undergoes simple addition reactions across the double bond. The reaction usually takes place under mild conditions. The driving force seems to be the release of strain, accompanied by aromatization in the aromatic nucleus. The electrophilic properties exhibited by benzyne are mostly due to this fact, and all activated double bonds offer a good source of electrons.

Thus benzyne adds to 1,3-butadiene¹⁸ at 100°C to form 1,4-dihydronaphthalene in 70% yield. Butadiene is obtained from 3-sulpholene and it is presumed that major portion of the diene is in the preferred *cis* conformation, allowing such good yield.⁶⁸

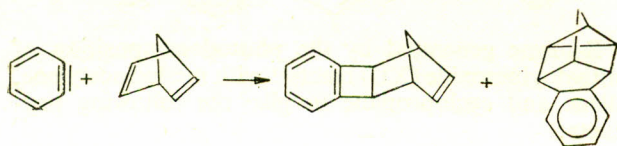
Reaction with Dienes and Mono-enes. Reaction of benzyne (from *o*-benzene diazonium carboxylate) with 1,3-cycloheptadiene⁶² gives the Diels-Alder adduct and also 2+2 cycloadduct. No ene product is found in this reaction.



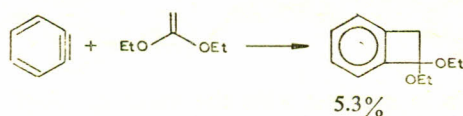
With cycloheptene⁶² it gives 3-phenylcycloheptene (product of ene reaction) and a product of 2+2-cycloaddition.



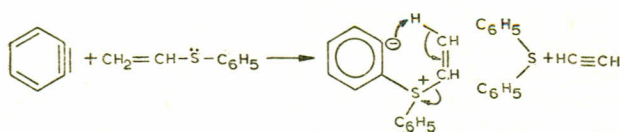
With norbornadiene two products of 1,2-addition and 1,5-addition are formed in the ratio of 7:3.



Thus benzyne generated from fluorobenzene and butyllithium reacts⁴⁸ with $H_2C=C(OEt)_2$ and $Ph-S-CH=CH_2$ in ether to give the acetal (5.3%) and Ph_2S in 44.5% yield respectively.

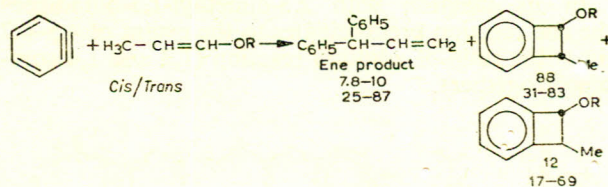


The formation of Ph_2S may be visualized as follows:

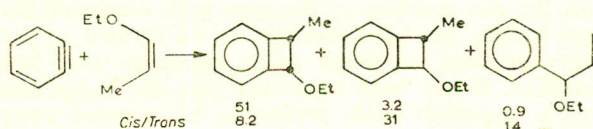


A six-membered transition state may be involved in the formation of the sulphide.

In its reaction with *cis* and *trans*-acetoxy and methoxypropene,²³ the *cis*-olefin under a wide variety of conditions gave the following product distribution:

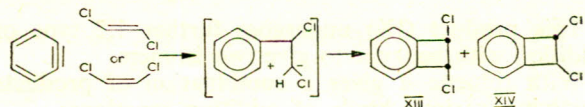


Wasserman and his coworker¹⁵ have reported similar results for the reaction with *cis*- and *trans*-ethyl propenyl ether.



These results are best explained by a non-concerted¹⁴ cycloaddition in which some bond rotation occurs before ring closure. The small affect of the reaction conditions on product distribution^{14,15,23} indicates absence of free radical process.

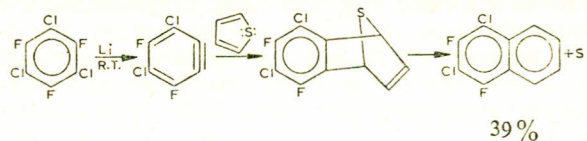
With 1,2-dichloroethylene¹⁴ it gives *cis*- and *trans*-1,2-dichlorobenzocyclobutanes, products of 1,2-cycloaddition irrespective of the geometry of the starting material.



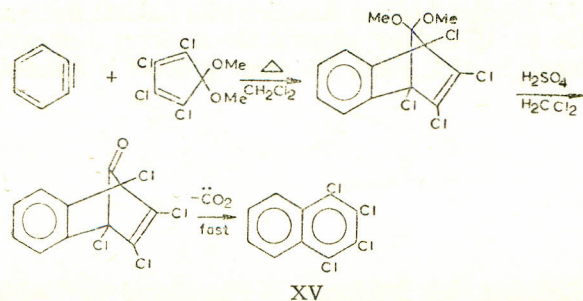
This again points to the above-mentioned stepwise process, in which bond rotation is faster than the ring closure. In the above scheme ionic pathway is shown for clarity, although the reaction may proceed via a free radical pathway.

With *cis*-olefin the ratio of 13:14 is 68:32 and with *trans*- it is 20:80. The temperature, length of heating, dilution or use of ethyl iodide as solvent had no appreciable effect in this ratio. This also points to the absence of free radical process.

Diels-Alder Type of Addition. Benzyne acts as dienophile in the Diels-Alder reaction. Thus perhalogenated benzyne reacts with thiophene⁴⁹ to give 1,3-dichloro-2,4-difluoronaphthalene in 39% yield.

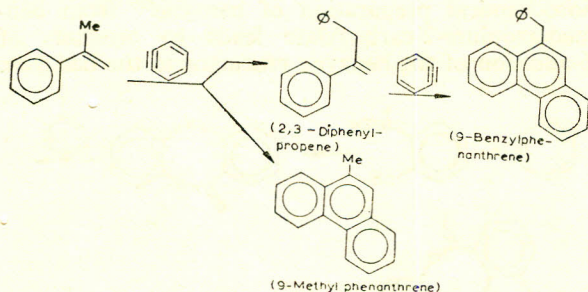


Benzenorbornene derivatives can be obtained by the reaction of benzyne with cyclopentadiene derivatives.⁵⁰ Thus 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene adds benzyne generated from *o*-carboxybenzene diazonium chloride⁴⁸ and propylene oxide to give 1,2,3,4-tetrachloro-7,7-dimethoxybenzenorbornene. The latter compound on hydrolysis (H_2SO_4/CH_2Cl_2) yields the rare 1,2,3,4-tetrachloronaphthalene (XV) in quantitative yield. This method affords a convenient source of XV and surpasses other methods in terms of convenience, ease of handling and yield of the final product.

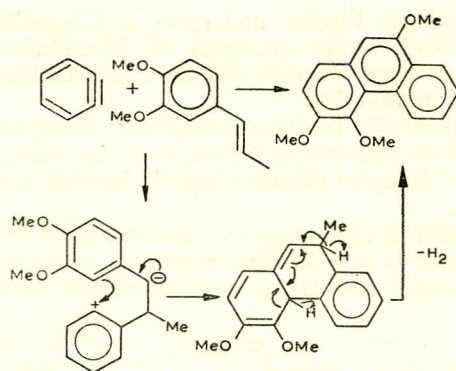


Benzene generated from *o*-bromofluorobenzene adds to cyclopentadiene in Diels-Alder fashion to give 1,4-dihydro-1,4-methanonaphthalene.

α -Methylstyrene offers a very good arrangement for cyclization. Benzene adds to α -methylstyrene followed by cyclization and it also undergoes an 'ene' reaction followed by further addition and cyclization to phenanthrene ring.

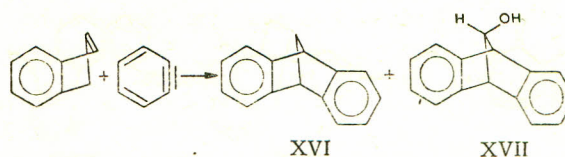


In case of 1,2-dimethoxy-4-(α -methyl)vinyl benzene also, phenanthrene ring formation occurs.⁸

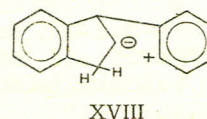


Cyclization of 1-(2-bromo-4,5-dimethoxy benzyl)- and 1-(2-chloro-4,5-methylenedioxybenzyl)-7-benzoyloxy-1,2,3,4-tetrahydro-6-methoxyisoquinoline with sodamide in liquid ammonia afforded the dibenzindolizine derivatives, which on further appropriate treatment affords the above-mentioned heterocycle. The cyclization is proposed to go by benzyne route. In the reaction with vinyl cyclopropane derivatives,⁸ the polarizable cyclopropane ring is unaffected and the reaction occurs only at the double bond.

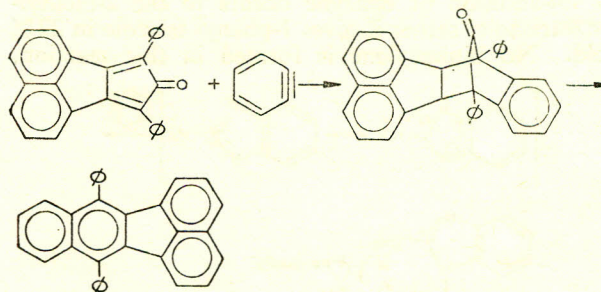
Indene⁵³ is known to give various adducts. Bond formation usually occurs at the 2,3-, 1,3- or at 2,7—a position depending on dienophile. To benzyne it adds at the 1,3-position.



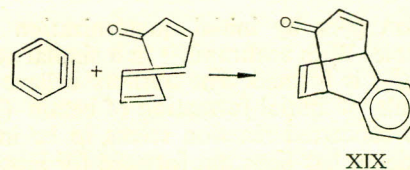
Formation of XVI may be preceded by the formation of a dipolar species XVIII followed by 1,2 shift of proton and ring closure. In the presence of water and oxygen XVII is formed.



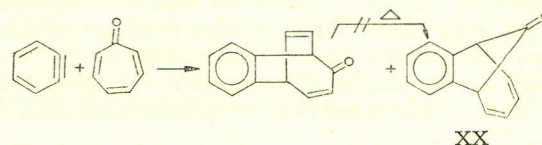
Benzynes generated from 1-aminobenzotriazole by oxidation with $Pb(OAc)_4$ undergoes a Diels-Alder type addition to 1,3-diphenylisobenzofuran.



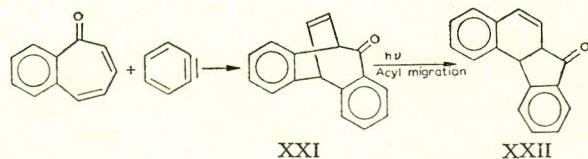
Benzene undergoes addition to planer tropone⁶³ to give novel 6,7-benzobicyclo-(3.2.2)-nona-3,6,8-triene-2-one (XIX). This type of system has recently attracted considerable attention, and this path offers a convenient one step method for its preparation.



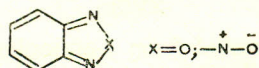
This product is the result of a simple Diels-Alder type of 1,4-addition. Miwa and his coworkers,⁶⁴ however, have also isolated another product formed by 1,6-cycloaddition of tropone to benzyne. This is 7,8-benzo-bicyclo(4.2.1)nona-2,4,7-triene-9-one (XX). It may result by isomerization of I, but is found that XX is formed by a direct 1,6-cycloaddition and not by thermal rearrangement of XIX.



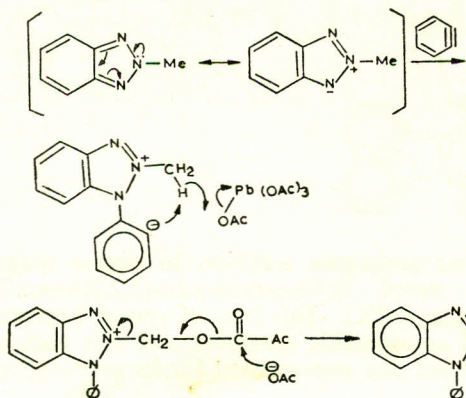
Another example of 1,4-addition of benzyne to the tropone system is the thermal addition of benzyne to 2,3-benzotropone³⁴ to give 3,4:6,7-dibenzo-bicyclo-(3.2.2)-nona-3,6,8-triene-2-one (XXI), which on photolysis gave XXII as a result of acyl migration.



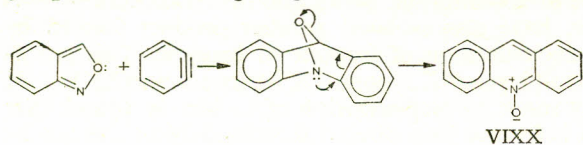
In order to extend this 1,4-addition⁵⁴ of benzyne to hetero 1,3-dienes, benzyne generated by the $\text{Pb}(\text{OAc})_4$ oxidation of 1-amino triazole was reacted with XXIII to see if a Diels-Alder type of reaction would occur. It was found that, a benzyne dimer, biphenylene is the only product in 86 and 48% yield of its reaction with excess benzofurazan and benzofuroxan respectively, and no 1,4-addition takes place. Similarly



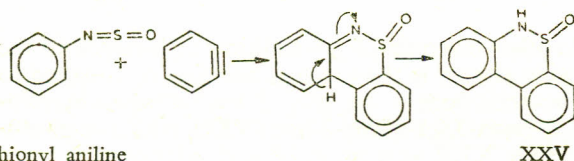
no 1,4-addition of benzyne occurs to the 2-methylbenzotriazole, rather it gives 1-phenyl triazole in 22% yield. No biphenylene is formed in this reaction.



The reaction goes by initial quaternization of N-1 of the triazole. With anthranil,⁵⁴ in a similar reaction, acridine (5%) is formed. The authors believe this to be the result of initial formation of betain (XXIV), and no 1,4-concerted reaction seems to be involved. But no evidence has been put forward for inoperation of a concerted 1,4 Diels-Alder type addition followed by rupture of the bridge to give the N-oxide. The reason

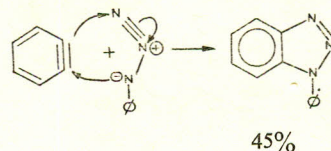


for this, however, seems to be the above-mentioned examples of hetero 1,3-dienes in which 1,4-addition does not take place. With acridine itself no addition of benzyne occurs, rather biphenylene is the only product. In the case of thionylaniline 1,4-addition of benzyne does take place to form sulphinamide (XXV).

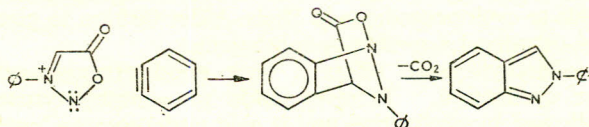


Thionyl aniline

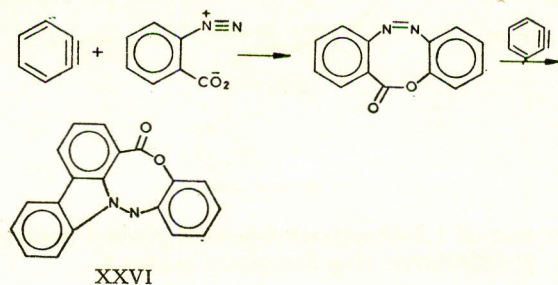
1,3-Dipolar Addition. Reaction with Azides: Benzyne adds to 1,3-dipolar phenylazide to form 1-phenyl-triazole in 45% yield. No other product is isolated.



Reaction with Syndones: *N*-Phenylsyndone⁶⁷ adds to benzyne at 30–40°C to form 2-phenylimidazole.



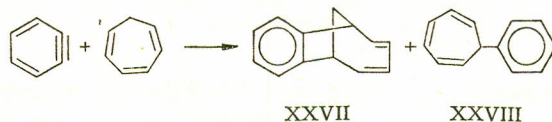
1,6-Addition. Examples of 1,6-addition of substrates to benzyne are also available.^{64,65} Thus a photochemical preparation of benzyne⁶⁵ from benzenediazonium-2-carboxylate leads to products of 1,6-addition of the benzyne precursor to the benzyne.



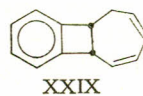
The adduct further undergoes a 1,3-addition to form XXVI. Other examples of 1,6-addition have since then been found,⁶⁴ and are discussed elsewhere in this manuscript.

Reaction with Tetracyanoethylene: Benzyne does not add to tetracyanoethylene,⁵⁴ or its oxide. Only dimer of benzyne (biphenylene) is isolated from the reaction.

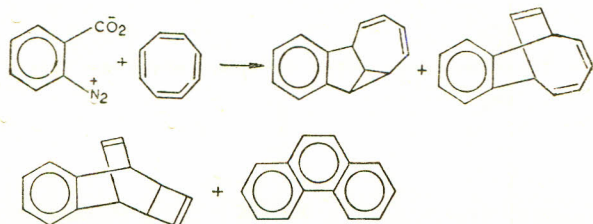
Addition to Cyclotrienes:⁵⁵ Benzyne adds to cycloheptatriene to give XXVII, a product of 2+6 cycloaddition and XXVIII, a product of ene reaction.



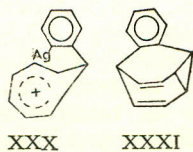
Other workers⁶² have assigned a different structure to XXVII. In their opinion the spectral data better fit the structure XXIX for this cycloadduct which results due to 2+2 cycloaddition. According to them the nonplanar geometry of cycloheptatriene a 2+2 addition only is unhindered, and precludes other possible modes of additions.



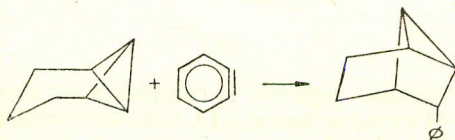
Addition to Cyclooctatetraene: Benzyne on treatment with cyclooctatetraene gives a number of adducts.³⁰



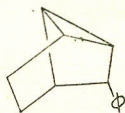
It is found that the product ratio is remarkably affected by Ag-ion catalysis which indicates involvement of a benzyne-A⁺ complex (XXX).



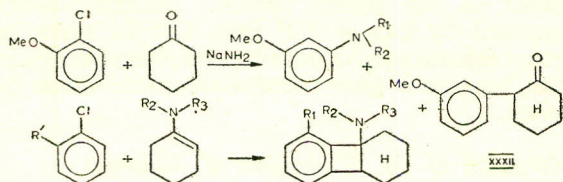
Warner,³¹ however, believes that the proposed complex³⁰ does not explain the nonformation of sterically preferable bullvolene (XXXI) which should be easily formed if the reaction goes via the above complex. It is argued that the σ-bound Ag is in a poor position to interact with the π-electrons of the homotropylium ion segment in which the majority of the π-electron density is beneath the ring.



Reaction with Sigma Bonds (Highly Strained Polycyclic Molecules):⁴⁶ The reactivity of benzyne is demonstrated by its reaction with σ-bonds.^{41,46} Thus the addition of benzyne to tricyclo(4.1.0.2.7)heptane takes place through the backside approach to highly strained ring and attacks the C—C single bond. The possibility of frontside attack of benzyne is eliminated by the catalytic reduction of the adduct formed from benzyne and tricycloheptane.



Reaction with Ketones:⁴³ Benzyne generated from halobenzenes by treating with sodamide in THF

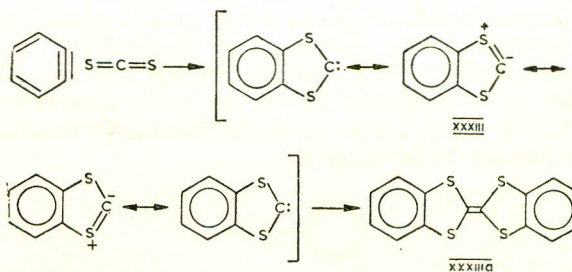


or in secondary cyclic amines reacts with cyclohexanone or its enamine to give 2-aryl-cyclohexanone XXXII (product of ene reaction) which otherwise

is prepared in low yields by difficult routes, and products of 2+2 addition.

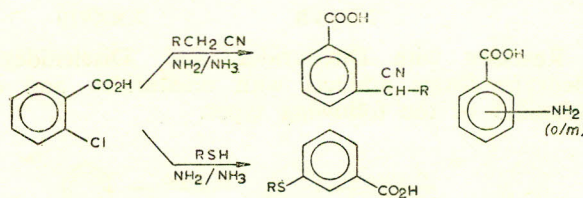
Tetrahalogenated benzyne⁵⁹ react with carbonyl compounds to give products of 1,2-addition across the C=O bond, and also a 1,4-addition leading to the formation of 2 H-chromenes.

Reaction with Sulphur Compounds: Benzyne generated from phthalic anhydride at 700°C under N₂ reacts with CS₂ to form (XXXIIIa)

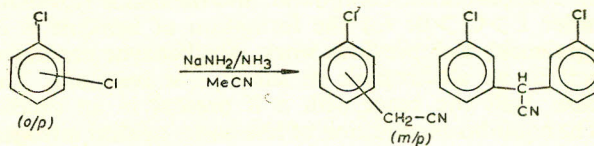


The reaction is thought to proceed via a carbenoid species (XXXIII) as shown above.

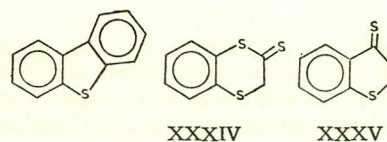
Cyanomethylation: ^{11-13,33} *o*-Chlorobenzoic acid when treated¹² with sodamide in liquid ammonia in the presence of a nitrile or mercaptan yields the corresponding benzylnitriles, sulphides and amines.



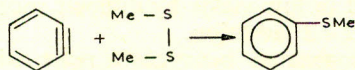
This cyanomethylation reaction¹³ is an extension of earlier reported¹² examples of general benzyne-carbanion phenylation reaction to form the benzyne-cyanide derivatives. It includes the examples of halogeno compound having the alkoxy groups in the benzene ring. The latter type of derivatives serve as important starting materials for the synthesis of isoquinoline derivatives. The reaction proceeds as follows:



Benzyne generated by the pyrolytic fragmentation of phthalic anhydride at 700°C reacts with CS₂ to form

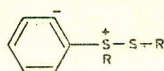


dibenzothiophene (XXXIV) 3.1%, (26.6%) and XXXV (39.0%).

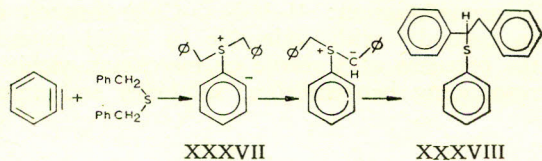


In the liquid phase^{35,36} reaction with carbon disulphide and benzyne generated from PhBr/NaNH₂-NH₃ gives PhSH, PhSMe, Ph₂S, PhNH₂, Ph₂NH. Benzyne and dialkyl sulphides give addition-cleavage products PhSH and PhSR. Use of carbon dioxide in place of CS₂ gave PhOH only and no benzyne alcohol is formed which eliminates a free radical mechanism.

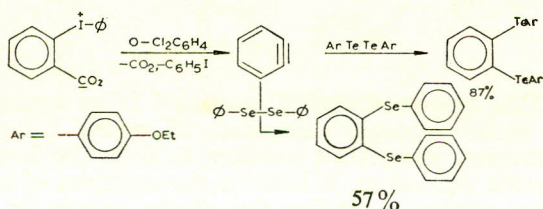
Benzyne in its reaction with disulphides³⁷ gave PhSH, PhSMe, Ph₂S, PhNH₂, Ph₂NH and Ph₂. The reaction is presumed to via an ionic intermediate XXXVI. 1-(2-Carboxyphenyl)-3,3-dimethyltetrazene on heating to 190°C gives:



benzyne which reacts with benzyl sulphide to give XXXVIII via the following ionic pathway:

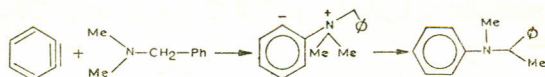


Reaction with Ditellurides and Diselenides:⁴⁵ Benzyne forms adducts with ditellurides and diselenides of the following types.



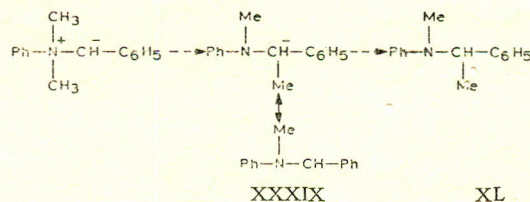
Under the same conditions cleavage of PhSSPh did not take place.

Reaction with Amines: In examples studied the benzyne is generated⁴² by the action of a strong base on a haloaromatic compound, and the halide reactivity order F > Cl > Br for the formation of benzyne is in agreement with previous work. The benzyne generated acts as an electrophile in subsequent reactions. The base itself can react with it if present in an excess. The equilibrium addition of less basic, neutral nitrogen lone-pair to benzyne is favoured by high amine concentrations:



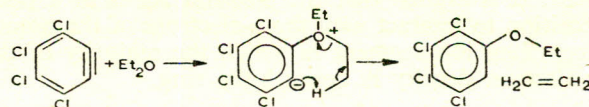
PMR studies of the above reaction product show stimulated emission and enhanced absorption in the chemical shift for the benzylic protons of the product. Such chemically induced nuclear polarization (CIDNP) multiplet effects, with downfield emission and upfield absorption occur when singlet radical pairs are direct product precursors.⁴² This, therefore,

indicates a radical pair such as XXXIX, is involved in the formation of XL.



This radical pair explains the observed results reasonably well. The yield of the product varies with changes in the base or the halobenzene used. The reaction of trihalobenzenes⁴⁴ with PhLi and *s*-amines, e.g. morpholine, piperidine, and R₂NH (R = Me, Et, iso-Pr) gave the corresponding 1,3,5-tris(dialkyl amino)benzene and 1-halo-2,4-(bisdialkylamino)benzenes. Dihaloalkylamino benzenes react similarly. The reaction proceeds via benzyne intermediate.

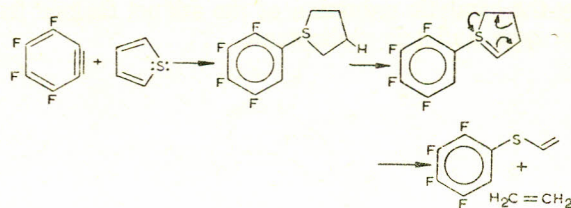
Reaction with Ethers and Thioethers:⁵¹ Ethers and thioethers are cleaved by benzyne. The electrophilicity of the latter is increased by substitution with halogens, and it will easily coordinate with the electron-rich ether oxygen.



XLI

The reaction sequence is completed by abstraction of a β-H from the betain XLI, followed by elimination of ethylene. No deuterium incorporation takes place in D₂O, which indicates a concerted process with irreversible first step of the reaction sequence. *n*-Butyl methyl ether, butyl methyl ether, cyclohexylmethyl ether all yield 2,3,4,5-tetrachloroanisole.

In a similar fashion, cleavage of thiophene takes place:



Other reactions of perhalogenated dehydrobenzene are similar to the parent species. Tetrafluorobenzene generated by loss of LiF from C₆F₅Li reacts with phenyl lithium to give nonafluorobiphenyl derivatives. With benzene it gives tetrafluorobenzobenzene derivatives.

Discussion of the Mechanism of Additions

As regards the mode of 2+2 addition of benzyne to mono-ene is concerned it is noteworthy that this addition is stereoselective and not stereospecific,

pointing to a non-concerted addition in confirmation with the Woodward-Hoffmann rules,⁵⁶ in which formation of second bond competes with the bond rotation. According to these rules a concerted thermal $2S+2S$ reaction is forbidden, while a concerted $2S+2A$ cycloaddition is allowed. The latter process would generate a *trans*-benzocyclobutene from *cis*-olefin and *cis* product from the *trans*-olefin.

Generally in the addition to mono-enes predominantly retention is observed. In order to explain this if a contribution from a concerted $2S+2A$ process is postulated then a contribution from some correspondingly more stereospecific $2S+2S$ reaction is also needed. Some workers⁵⁵ have involved the concept of triplet benzyne to explain this stereoselective reaction. But benzyne triplets are not detected by electron spin resonance, therefore, this explanation is unattractive and should be invoked only when there is no other better explanation. In view of this it is not necessary to have triplet benzyne to explain the results. They are best explained by a non-concerted, stepwise process. These arguments are further endorsed by the fact that temperature, length of heating, dilution or use of ethyl iodide as a solvent have no appreciable effect on the ratio of *cis* or *trans* products. The formation of 'ene' product, more so, in case of *trans*-olefins is, however, better explained by a concerted process, in which the orientation of the *trans*-olefin is best suited to the incipient 6-membered transition state in which the bulky substituents of the olefin are farthest from the reaction site, and do not hinder the partial bond overlap of the orbitals in the transition state.

In case of $2+4$ cycloaddition of benzyne to conjugated dienes there is the positive evidence of a concerted and stereospecific process, for ground state singlet benzyne with 2-electrons in the lower symmetric orbital. It is found that there is a considerable difference in the reactivity of benzyne with *trans-trans* and *cis-trans* dienes which discredits a non-concerted mechanism. These results are in harmony with those of Bartlett⁵⁸ about cycloaddition of 1,1-dichloro-2,2-difluoroethylene to butadiene wherein it has been observed that the difference in the fact between 1,2 and 1,4-addition is only the energy difference between *cisoid* and *transoid* butadienes. Thus it follows that $2+4$ cycloaddition of benzyne with 1,3-dienes has been shown to be stereospecific, while the $2+2$ cycloaddition of benzyne with a cyclic alkenes is stereoselective only and not stereospecific.

Electronic Configuration

Benzyne is generally represented by the same formulation as benzene with a triple bond, but this is only for the sake of simplicity. The actual structure of benzyne is unknown. However, a number of speculations and calculations regarding electronic picture of this molecule have been made.

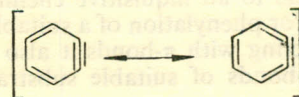
(a) It can be formulated in the same way as an acetylene, involving sp hybridization of the 2 C-atoms concerned.

(b) It may be formed by the overlap of sp^2 hybridized orbitals.

The first possibility looks unattractive at the outset, because, incorporation of a linear structure in the

6-membered ring would involve quite a bit of deviation from original bond angle accompanied by considerable strain. But this argument is put forward by various renowned workers that from the analogy of cyclopropene it is conceivable that benzyne molecule with this strained structure may have a transitory existence.

Second alternative with all C-atoms sp^2 hybridized and the coplanar orbitals with one electron each undergoing sideways overlap offers a good arrangement so much as the aromatic character and geometry of benzene moiety is left intact. The extreme reactivity of benzyne can be explained in terms of a weak sideways overlap of these sp^2 orbitals. This concept is widely accepted. It, however, is not meant to restrict the resonance in the benzene nucleus, rather a more complete picture would involve resonance hybrid XLVIII as shown:

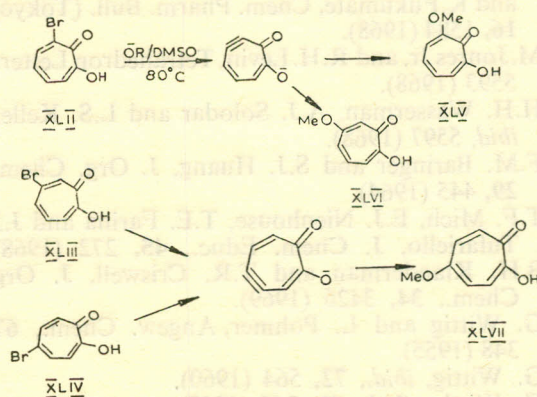


XLVIII

The third alternative is to represent it by a diradical. Particularly so if the spins of the two electrons are parallel. But no features of a diradical are shown by benzyne thus this possibility is ruled out. Also self-consistent field molecular orbital calculations⁶⁰ for *o*-benzyne in a geometry constrained to be that of benzene show its ground electronic state to be singlet. The same conclusion is drawn from the intermediate neglect of differential overlap (INDO) theory. From the LCAO-MO-SCF⁶¹ calculations the estimated energy for the abstraction of 2H from benzene is 157 kcal/mol and the strain energy⁶⁶ for I is reported as 60 kcal/mol. It is quite likely that the amount of work which is being done on this molecule will unravel the mystery of its triple bond in the near future.

Nonbenzenoid Dehydro-Derivatives

Certain dehydro-derivatives⁴⁷ of non-benzenoid aromatic compounds are also known. Thus dehydro-tropolones are postulated as intermediates in the reaction of some halo-tropolones with alkoxide⁴⁷ in aprotic medium.



XLII ———→ XLV+XLVI 96% yield
 XLIII ———→ XLV+XLVI 94% „
 XLIV ———→ XLVI+XLVII 97% „

The intermediacy of dehydro-tropolone is confirmed by trapping them with diphenylisobenzofuran and sodium azide.

Benzynes analogues of bi- and tricyclic aromatic hydrocarbons and other heteroaromatic systems are also known⁷⁰ and behave in a similar fashion.

From above it follows that benzyne is a good and convenient source of organic compounds in good yields which otherwise are obtainable only via long and cumbersome routes.^{43,49,50,59,63,64} It also offers a challenge to the intellectual genius of the chemists to investigate its various pathways to the formation of novel products. Since benzyne chemistry is comparatively 'young' (20 years), one can easily visualise the scope it offers to an inquisitive chemist. It offers convenient way for phenylation of a suitable substrate. Apart from reacting with π -bonds it also enters into reaction with σ -bonds of suitable substrates.

References

- R. Stoermer and B. Kahlert, *Chem. Ber.*, **35**, 1633 (1902).
- G. Wittig, *Naturwissenschaften*, **30**, 696 (1942).
- J.D. Roberts, H.E. Simmons Jr., L.A. Carlsmith and C.W. Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953).
- R. Huisgen and H. Rist, *Naturwissenschaften*, **41**, 358 (1954); *Ann. Chem.*, **594**, 137 (1955).
- H.H. Wasserman and J.M. Fernandez, *J. Am. Chem. Soc.*, **76**, 5322 (1968).
- E.M. Arnett, *J. Org. Chem.*, **25**, 324 (1960).
- H.E. Simmons Jr., *J. Am. Chem. Soc.*, **83**, 1657 (1961).
- Varda Usieli and Shalom Sarel, *J. Org. Chem.*, **38**, 1703 (1973).
- T.E. Stevens, *ibid.*, **33**, 855 (1968).
- C.D. Campbell and C.W. Rees, *J. Chem. Soc. (C)*, 742 (1969).
- T. Kametani and K. Ogasawara, *ibid.*, (C), 2208 (1967).
- E.R. Biehl and H. Ming Li, *J. Org. Chem.*, **31**, 602 (1966).
- T. Kametani, K. Ogasawara, T. Terui, K. Yamaki and K. Fukumate, *Chem. Pharm. Bull. (Tokyo)*, **16**, 1584 (1968).
- M. Jonres Jr. and R.H. Levin, *Tetrahedron Letters*, 5593 (1968).
- H.H. Wasserman, A.J. Solodar and L.S. Keller, *ibid.*, 5597 (1968).
- F.M. Baringer and S.J. Huang, *J. Org. Chem.*, **29**, 445 (1964).
- T.F. Mich, E.J. Nienhouse, T.E. Farina and J.J. Tufariello, *J. Chem. Educ.*, **45**, 272 (1968).
- B.H. Klanderman and T.R. Criswell, *J. Org. Chem.*, **34**, 3426 (1969).
- G. Wittig and L. Pohmer, *Angew. Chem.*, **67**, 348 (1955).
- G. Wittig, *ibid.*, **72**, 564 (1960).
- G. Wittig, *ibid.*, **69**, 245 (1957).
- N. Rabjohn, *Organic Synthesis Collection* (J. Wiley, New York, 1963), vol. IV, p. 965.
- L. Friedman, R.J. Osiewicz and P.W. Rabideau, *Tetrahedron Letters*, 5735 (1968).
- G. Ahlgren and B. Akermark, *ibid.*, 3947 (1970).
- I.F. Mikhailova, T.N. Sajeheva and V.A. Barkhash, *Zh. Org. Khim.*, **6**, 1426 (1970); *cf. Chem. Abstr.*, **73**, 87544.
- J. Nakayama, O. Simamura and Moyoshida, *J. Chem. Soc. (D)*, 1222 (1970).
- C. Ruchardt and C.C. Tan, *Angew. Chem. Intern. Ed. (Engl)*, **9**, 522 (1970).
- F.M. Logullo, Ph.D. dissertation, Case Institute of Technology, Pasadina, Calif. (1965).
- L. Friedman and F.M. Logullo, *J. Org. Chem.*, **34**, 3089 (1969); *J. Am. Chem. Soc.*, **85**, 1549 (1963); *ibid.*, **89**, 3071 (1967).
- E. Vedejs and R.A. Shepherd, *Tetrahedron Letters*, 1863 (1970).
- P. Warner, *ibid.*, 723 (1971).
- H.H. Wasserman and L.S. Keller, *Chem. Commun.*, 1483 (1970).
- T. Kametani, K. Kigasawa, M. Hiiragi, T. Aoyama and O. Kusama, *J. Org. Chem.*, **36**, 327 (1971).
- I. Murata and Y. Sugihara, *Chem. Letters*, 625 (1972); *cf. Chem. Abstr.*, **77**, 126299n.
- E. K. Fields and S. Meyerson, *Interin. J. Sulfur Chem. (C)* **6**, 51 (1971); *cf. Chem. Abstr.*, **76**, 24357s.
- I. Tabushi, K. Okazaki and R. Oda, *Tetrahedron Letters*, 3827 (1967).
- I. Tabushi, K. Okazaki and R. Oda, *ibid.*, 3591 (1967).
- H. Iwamura, M. Iwamura and T. Nishide, *ibid.*, 63 (1971).
- E.K. Fields and S. Meyerson, *ibid.*, 719 (1971).
- E.K. Fields and S. Meyerson, *ibid.*, 629 (1970).
- M. Jonus and M.R. Decamp Jr., *J. Org. Chem.*, **36**, 1536 (1971).
- A.R. Lepley, R.H. Becker and A.G. Giumanini, *ibid.*, **36**, 1222 (1971).
- T. Kametani, S. Nognchi, I. Agata, K. Kigasawa, M. Hiirugi, T. Hayasaka and O. Kusama, *J. Chem. Soc. (C)*, 1047 (1971).
- F. Effenberger, E. Auer and P. Fischer, *Chem. Ber.*, **103**, 1440 (1970).
- N. Petragnani and V.G. Toscano, *ibid.*, **103**, 1652 (1970).
- P.G. Gassman and G.D. Richmond, *J. Am. Chem. Soc.*, **92**, 2090 (1970).
- T. Yamatani, M. Yasunami and K. Takose, *Tetrahedron Letters*, 1725 (1970).
- R. Neidlein and P. Witerzene, *Pharmazie*, **26**, 81 (1971).
- S. Hayashi, N. Ishikawa, Y. Gosei, K. Kyokaishi, *J. Unir. Yaki Dotei Karaku Kankair*, **28**, 533 (1970). *cf. Chem. Abstr.*, **73**, 45241c.
- J.S. Wilt, E. Vasiliaskas, *J. Org. Chem.*, **35**, 2310 (1970).
- H. Heany and J.M. Jablonski, *Tetrahedron Letters*, 4455 (1968).
- E. Wolthius and W. Cady, *Angew. Chem. Intern. Educ.*, **6**, 555 (1967).
- C.F. Huebner and E.M. Donoghue, *J. Org. Chem.*, **33**, 1678 (1968).

54. C.D. Campbell and C.W. Rees., J. Chem. Soc. (C), 748 (1969).
55. I. Tabushi, H. Yamada, Z. Yushida and H. Kuroda, Tetrahedron Letters, 1093 (1971).
56. R. Hoffmann and R.B. Woodward, Accounts of Chem., Res., **1**, 17 (1968).
57. R.W. Atkin and C.W. Rees., J. Chem. Soc. (D), 152 (1969).
58. J.S. Swenton and P.D. Bartlett, J. Am. Chem. Soc., **90**, 2056 (1968).
59. H. Heany, J.M. Jablonski, C.T. McCarty and A.P. Price, Am. Chem. Soc., Div. Petrol. Chem. Preprn., **14**, C-28 (1969); *cf* Chem. Abstr., **73**, 130842u.
60. D.L. Wilhite and J.L. Whitten, J. Am. Chem. Soc., **93**, 2858 (1971).
61. P. Millie and S. Lionel, Interin. J. Quantum Chem., 187 (1971); Chem. Abstr., **74**, 91264f.
62. L. Lombardo and D. Wege, Tetrahedron Letters, 3981 (1971).
63. J. Ciabattanoi, J.E. Crowley and A.E. Kende, J. Am. Chem. Soc., **89**, 2778 (1967).
64. T. Miwa, M. Kato and T. Tamano, Tetrahedron Letters, 1761 (1969).
65. T. Miwa, M. Kato and T. Tamano, *ibid.*, 2743 (1968).
66. E. Haselbach, Helv. Chim. Acta., **54**, 1981 (1971); Chem. Abstr., **76**, 13638n.
67. H. Gotthardt, R. Huisgen and R. Knorr, Chem. Ber., **101**, 1056 (1968).
68. F.L. Hatch and D. Peter, J. Chem. Soc. (D), 1499 (1968).
69. E. Wolthius, B. Bouma, J. Modderinan and L. Sysma, Tetrahedron Letters, 407 (1970).
70. Th. Kauffmann, H. Fischer, R. Nuernberg, M. Westweber and R. Wirthwein, *ibid.*, 2911 (1967).