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REACTIONS OF BENZYNE WITH SULFUR COMPOUNDS

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REACTIONS OF BENZYNE WITH SULFUR COMPOUNDS

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The present review deals with the reactions of benzyne with all kinds of sulfur compounds, irrespective of their organic or inorganic nature. The references cover all of reactions reported after conclusive evidence for the existence of benzyne as the reactive intermediate had been obtained. Emphasis will be placed on both mechanistic and synthetic points of view.

Key words: Benzyne, carbon disulfide, elemental sulfur, mesoionic compounds, sulfides, sulfones, sulfonium ylides, sulfoxides, sulfur-containing heterocycles, thiocarbonyl compounds, thiophenes.

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1. INTRODUCTION

More than forty years have passed since the existence of benzyne as a reactive intermediate was established. Benzyne is a highly reactive and therefore short-lived intermediate with a singlet ground state, but its lifetime in an inert atmosphere should be indefinite since no unimolecular decay of benzyne is known. Thus, the lifetime of benzyne generated in low concentration in argon reaches about 0.02 sec, where benzyne collapses slowly to give biphenylene.¹ The lifespan of benzyne also lengthens when benzyne is bound to a polystyrene resin through an ester linkage and thus its dimerization is inhibited.² The most effective method for lengthening the lifetime of benzyne is to generate it in an argon matrix. The generation of benzyne by photolysis in an argon matrix at 8 K allows the determination of its infrared spectrum.^{3,4} A weak absorption at 2085 cm^{-1} , attributable to the stretching vibration of the carbon-carbon triple bond, has been detected.⁴

Many methods for generating benzyne are now available. Some of them are very convenient and can be carried out easily. A few precursor compounds are even commercially available. However, we need to choose the most appropriate method by considering carefully the chemical and physical properties of the substrate and the product of expectation.

Benzyne is a bifunctional intermediate like carbenes and singlet oxygen. Calculations reveal that the LUMO of benzyne is dramatically low-lying compared to that of 2-butyne by *cis*-bending of the triple bond.⁵ Because of this orbital property, benzyne is strongly electrophilic and reacts with a wide variety of nucleophiles. It undergoes [2 + 2] cycloadditions and/or ene reactions with alkenes, [2 + 4] cycloadditions with 1,3-dienes, and [2 + 3] cycloadditions with 1,3-dipoles, and add amines and other nucleophiles. Benzyne is also soft as an electrophile because of the weak, easily polarized third bond produced by overlap of the adjacent σ -hybrid orbitals at the dehydro carbons. This property cooperates with the soft nature of the sulfur atom, and thus benzyne is capable of reaction with a wide variety of sulfur compounds.

The purpose of the present review is to arrange the reactions of benzyne with sulfur compounds in a compact form. For this purpose, reactions with all sorts of sulfur compounds, are irrespective of their organic or inorganic nature, are treated. The reactions are classified depending on the sulfur-containing functional group of the substrate. All reactions which were reported after the presence of benzyne as the reactive intermediate had been established will be covered.

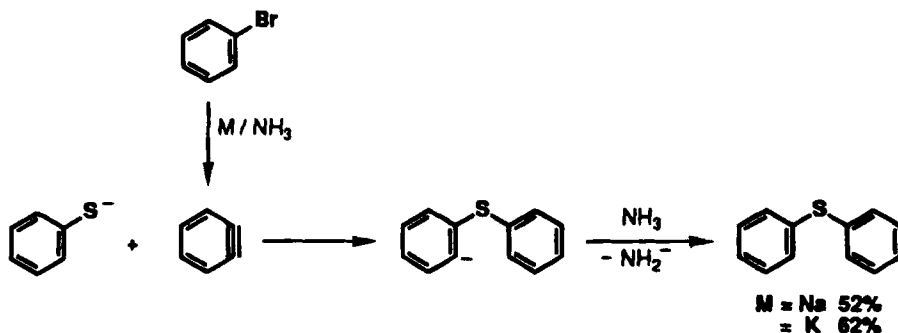
Many excellent reviews and monographs on the general chemistry of benzyne and related species are available.⁶⁻¹⁵

2. REACTIONS WITH THIOLATES

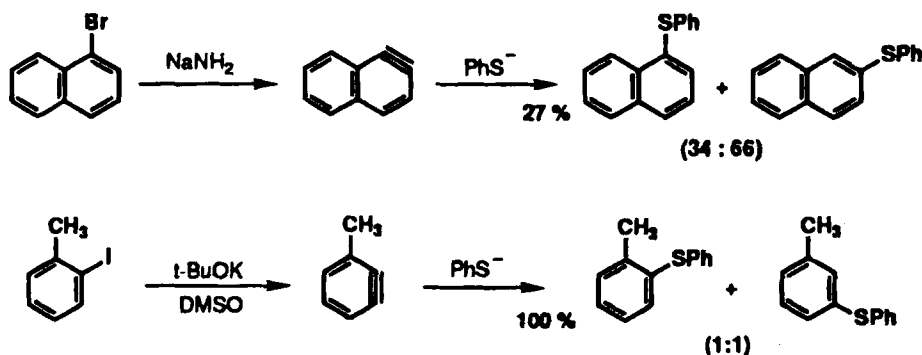
Several reports describe reactions of benzyne with thiolates, but no report has appeared on reactions where thiols are true reactants with benzyne.

A few papers describe the addition of arenethiolates to benzyne.¹⁶⁻¹⁸ Thus, treatment of bromobenzene with sodium in liquid ammonia in the presence of thiophenol affords diphenyl sulfide, the adduct of benzyne with benzenethiolate followed by protonation, in

52% yield along with aniline (10%) and diphenylamine (12%). The use of potassium also gives diphenyl sulfide in 62% yield.¹⁶ Curiously, however, sodium sulfide failed to add to benzyne under the above conditions. Neither thiophenol nor diphenyl sulfide formed, but adducts with ammonia, namely, aniline (33%) and diphenylamine (48%), were formed.¹⁶



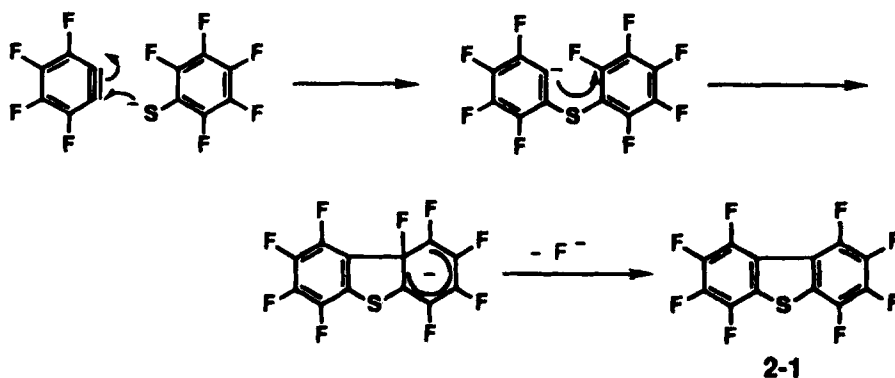
Addition of benzenethiolate to 1-naphthalene, generated by treatment of 1-bromonaphthalene with sodium amide, affords 1-naphthyl phenyl and 2-naphthyl phenyl sulfide in moderate yields in the ratio 34:46, while no regioselectivity was observed upon addition of benzenethiolate to 3-methylbenzyne, generated by treatment of *o*-iodotoluene with potassium *t*-butoxide in dimethyl sulfoxide, which gave phenyl *o*-tolyl and phenyl *m*-tolyl sulfide in the ratio 1:1.¹⁸



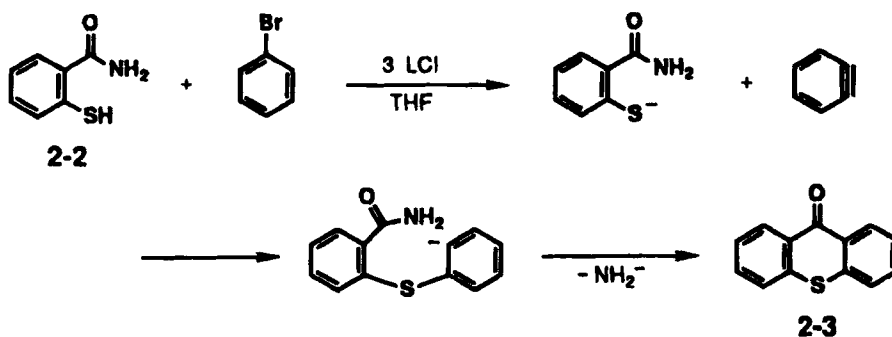
Competition experiments revealed that the nucleophilicity of benzenethiolate towards benzyne is 46 times larger than that of phenoxide which is comparable with that of chloride.¹⁹

Tetrafluorobenzyne, generated by treatment of pentafluorobromobenzene with butyllithium, reacts with pentafluorobenzenethiolate to give perfluorodibenzothiophene 2-1 in good yield.²⁰ The reaction, which probably proceeds as depicted below, is synthetically

interesting, but no application to the synthesis of other dibenzothiophenes has ever appeared.

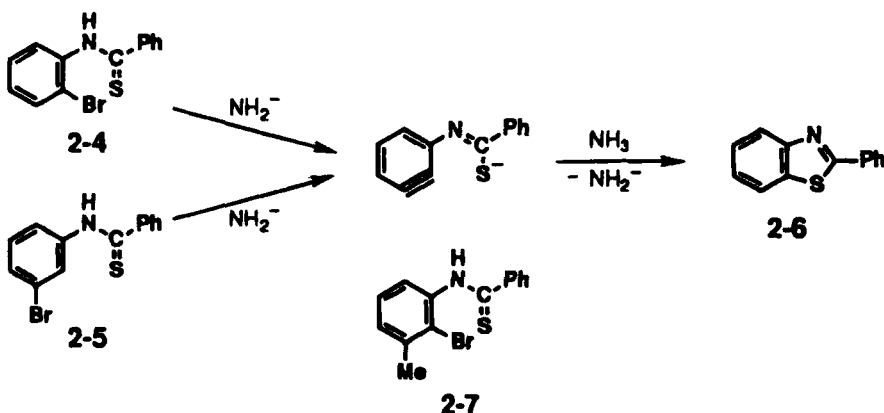


Treatment of a mixture of thiosalicylamide 2-2 and bromobenzene with 3 equiv. of lithium cyclohexylisopropylamide (LCI) affords 9-thioxanthenone 2-3 in 98% yield.²¹ The reaction involves addition of the thiolate to benzyne, followed by intramolecular condensation. Various methoxy and dimethoxy substituted derivatives of 2-3 can be obtained by this condensation.



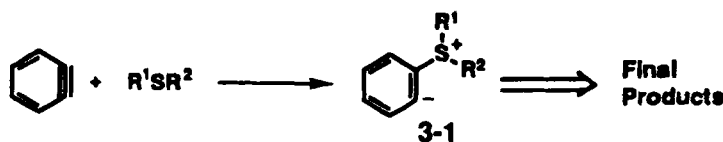
Treatment of the thioamide 2-4 with KNH_2 in liquid ammonia affords the benzothiazole 2-6 in 90% yield.^{22,23}

Treatment of the *m*-isomer 2-5 under the same conditions also gives the same thiazole 2-6 in 72% yield. Both reactions involve intramolecular addition of the thiolate to the benzyne moiety. No cyclization was observed with the thioamide 2-7 from which the generation of a benzyne intermediate is impossible. The intramolecular addition described above has been successfully applied to the preparation of various heterocyclic and carbocyclic compounds.



3. REACTIONS WITH ACYCLIC SULFIDES

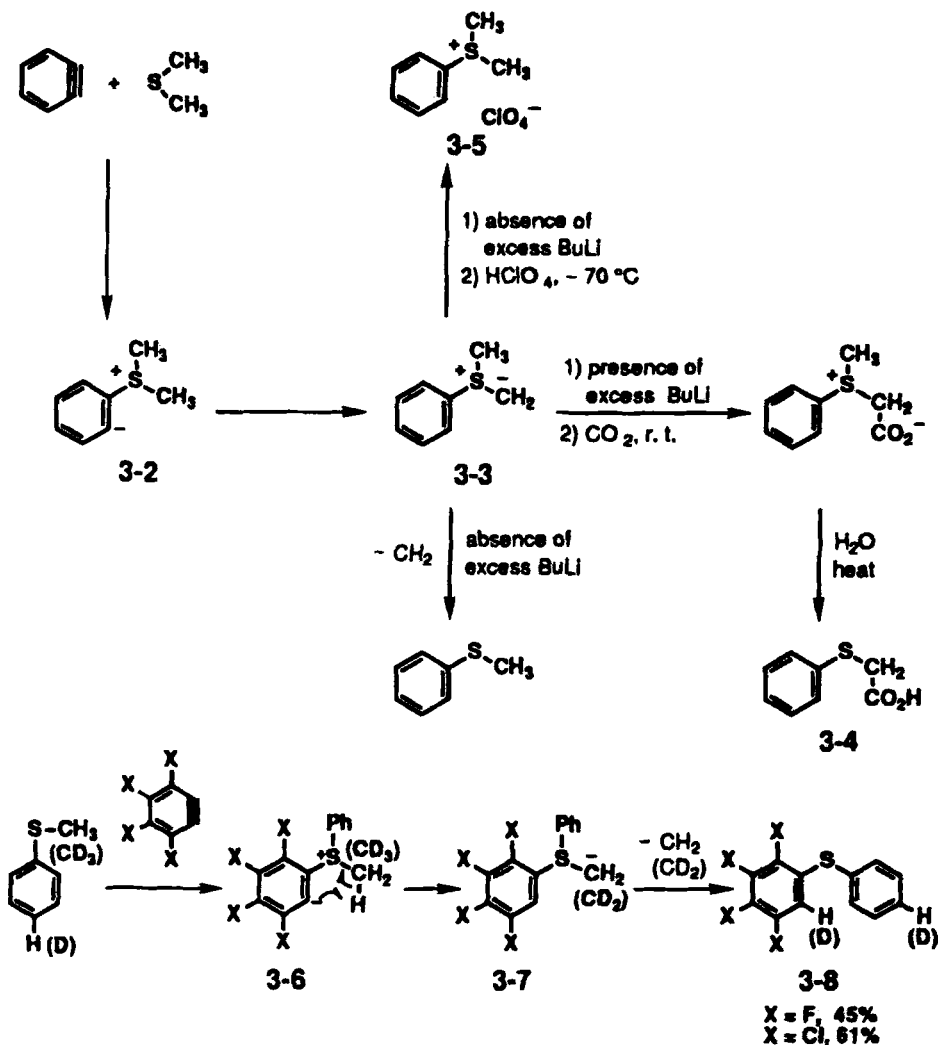
Reactions of benzyne with sulfides have been studied most extensively among those with sulfur compounds. The initial step of the reaction involves electrophilic addition of benzyne to the sulfur to give a betaine intermediate 3-1, which then collapse to the final products depending on the substituents on the sulfur, the reaction conditions, and sometimes the method used for generating benzyne.



3.1. Reactions with Dialkyl Sulfides and Alkyl Aryl Sulfides

The reaction of dimethyl sulfide with benzyne, generated by treatment of *o*-bromochlorobenzene with butyllithium, initially affords the betaine intermediate 3-2 which then undergoes proton transfer to give the ylide 3-3.²⁴ The ylide 3-3 produced in the presence of excess butyllithium is surprisingly stabilized by complexing with butyllithium and can be trapped even at room temperature by carboxylation to give the carboxylic acid 3-4. Meanwhile, in the absence of excess butyllithium, the ylide 3-3 rapidly decomposes to give thioanisole with loss of methylene, although 3-3 can be trapped at -70°C with perchloric acid to give the sulfonium perchlorate 3-5. Thioanisole can react further with benzyne.^{24,25} Thus, the reaction of thioanisole with the highly electrophilic tetrahaloben-

zynes affords phenyl tetrahalophenyl sulfides 3-8 by loss of methylene from the ylides 3-7 produced by proton transfer in the betaines 3-6. The proton transfer process was shown to be intramolecular by using deuterated thioanisole as the substrate.²⁵



When the sulfides possess an alkyl group carrying a β -hydrogen, the resulting betaines 3-9 undergo alkene elimination.^{24,26} Thus, the reaction of benzyne with diethyl sulfide affords ethyl phenyl sulfide and ethene in 74% and 72% yields, respectively, although it is not clear whether the elimination takes place via path (a), path (b), or path (c). A variety

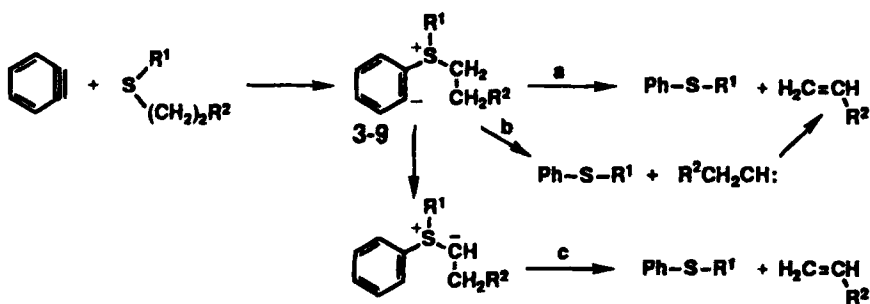
TABLE 3-1 Reactions of dialkyl, alkyl allyl, and alkyl phenyl sulfides with benzyne

starting sulfide (R ¹ SCH ₂ CH ₂ R ²)		products (yield, %)		recovery of sulfide (%)	ref.
R ¹	R ²	PhSR ¹	CH ₂ =CHR ²		
CH ₃	H	52 ^{a)}	52	25	26
C ₂ H ₅	H	74	72	22	26
C ₃ H ₇	C ₃ H ₇	51	50		24
C ₆ H ₁₃	C ₆ H ₁₃	70	70		24
CH ₂ Ph	H	54	50	30	26
CH ₂ Ph	CH ₃	60	55	20	26
CH ₂ CH = CH ₂	H	60	57	20	26
CH ₂ CH = CH ₂	CH ₃	59	55	16	26
CH ₂ CH = CH ₂	CH ₂ CH ₃	57	46	22	26
Ph-S-CH(CH ₃)CH ₂ CH ₃		21 ^{b)}	5 ^{b)}	43	26
Bu'-S-Bu'		12		44	26

^{a)}Ethyl phenyl sulfide was also formed in 3% yield.

^{b)}Diphenyl sulfide and butene were also formed.

of sulfides such as dialkyl, alkyl benzyl, and alkyl allyl sulfides undergo this type of elimination as summarized in Table 3-1.



The above elimination has been applied to the preparation of aryl phenyl sulfides. A wide variety of aryl ethyl sulfides react with benzyne, generated by aprotic diazotization of anthranilic acid, to give aryl phenyl sulfides 3-10 in excellent yields with elimination of ethene (Table 3-2).²⁷

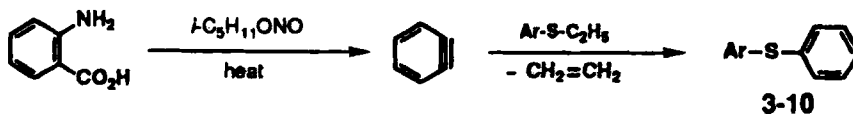
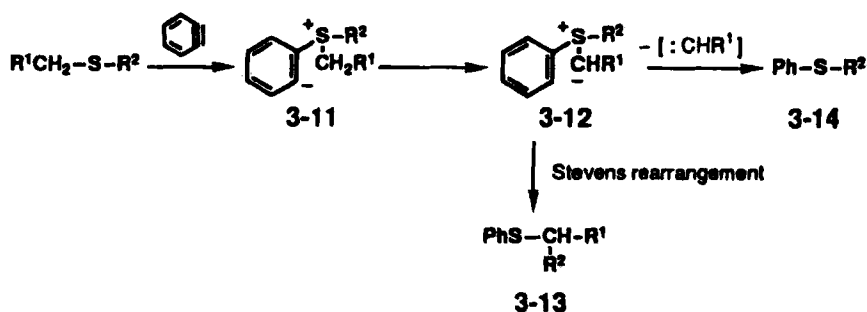


TABLE 3-2 Preparation of aryl phenyl sulfides (Ar-S-Ph) by reaction of benzyne with aryl ethyl sulfides

Ar	yield (%)	Ar	yield (%)
C ₆ H ₅	92	<i>p</i> -BrC ₆ H ₄	96
<i>o</i> -CH ₃ C ₆ H ₄	96	<i>p</i> -CH ₃ OC ₆ H ₄	87
<i>m</i> -CH ₃ C ₆ H ₄	93	2,4,6-(CH ₃) ₃ C ₆ H ₂	90
<i>p</i> -CH ₃ C ₆ H ₄	95	1-naphthyl	90
<i>p</i> - <i>t</i> -BuC ₆ H ₄	93	2-naphthyl	92
<i>p</i> -ClC ₆ H ₄	97		

The Stevens rearrangement of sulfonium ylides has been observed only with stabilized ylides. A phenyl or vinyl group on the α -carbon of the betaine intermediate **3-11** facilitates proton transfer to produce the ylide **3-12** since it can stabilize the negative charge of the ylide.²⁶ Ylides of this type may then undergo Stevens rearrangement in addition to an α -elimination to give **3-13** and **3-14**, respectively (Table 3-3).

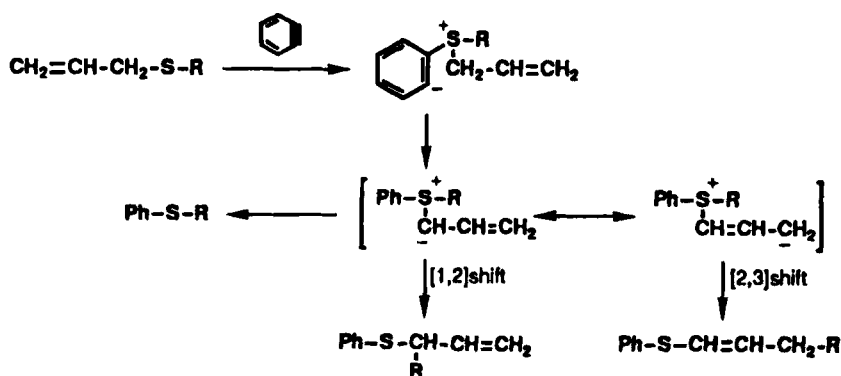
TABLE 3-3 Stevens rearrangement and elimination products of resonance-stabilized sulfonium ylides **3-12**

R ¹	R ²	products (yield, %)		recovery of sulfides (%)
		3-13	3-14	
C ₆ H ₅	CH ₃	14	24	10
C ₆ H ₅	C ₆ H ₅ CH ₂	20	11	20
<i>p</i> -O ₂ NC ₆ H ₄	CH ₃		20	50
<i>p</i> -O ₂ NC ₆ H ₄	C ₂ H ₅		12	55
CH ₂ =CHCH ₂ S	CH ₂ =CHCH ₂	55	6	35

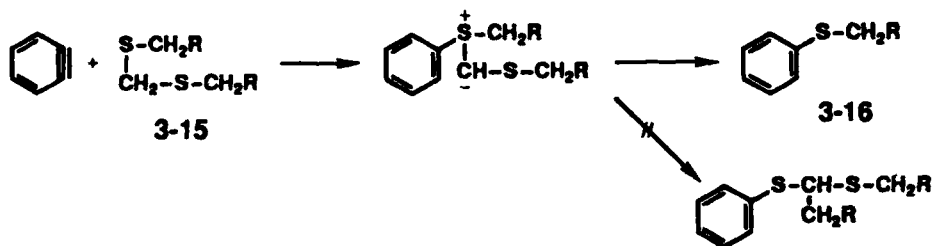
When the substrate is an allyl sulfide, a γ -Stevens rearrangement ([2,3] sigmatropic shift) also takes place along with a normal Stevens rearrangement ([1,2] shift) and α -elimination (Table 3-4).²⁶

TABLE 3-4 [1,2] vs. [2,3] shift of sulfonium ylides

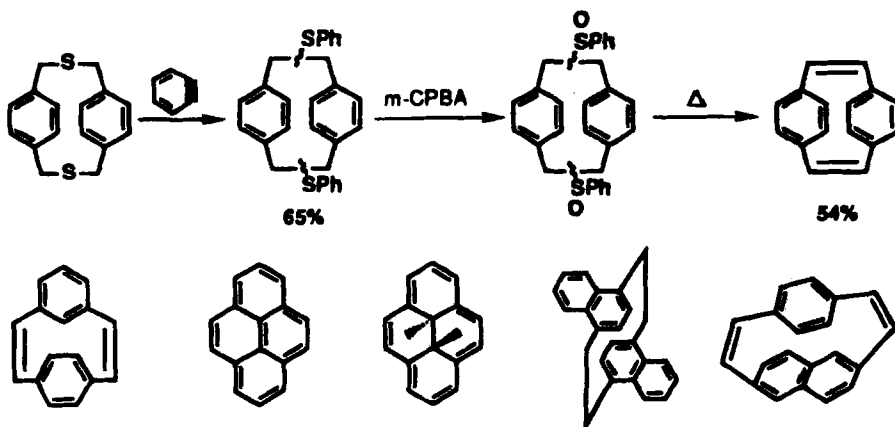
R	products (yield, %)		
	Ph-S-CH(R)CH=CH ₂	Ph-S-CH=CHCH ₂ R	Ph-S-R
CH ₃	12	19	12
C ₆ H ₅ CH ₂	49	7	
CH ₂ =CHCH ₂	52	12	5



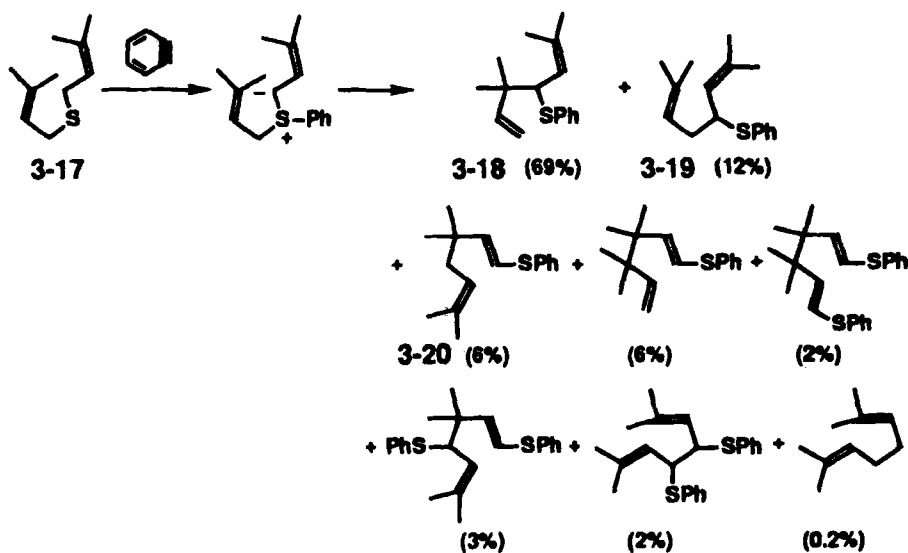
The reaction with the dithioacetals **3-15** gave the sulfides **3-16** as the sole products. No Stevens rearrangement was observed.²⁶



The benzyne-induced Stevens rearrangement was also successfully applied to the conversion of a wide variety of dithia[3.3]cyclophanes to the corresponding ring-contracted cyclophane-dienes.²⁸ A range of compounds given below were also prepared by this technique starting from the appropriate sulfides.²⁹⁻³¹

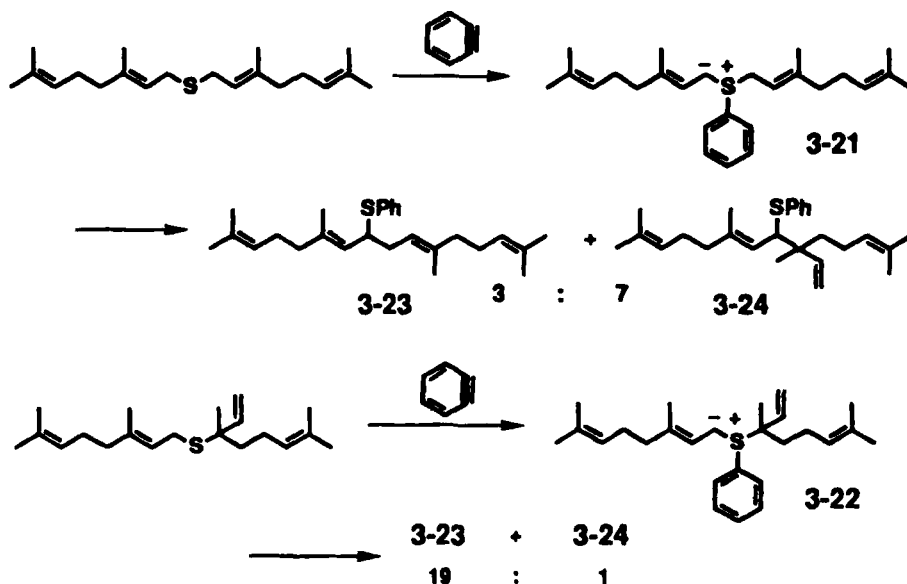


The reaction of the diallyl sulfide **3-17** with benzyne was reported to give the sulfides **3-18**, **3-19**, and **3-20** in the ratio 7:2:1.³² Careful quantitative product analysis revealed that the reaction affords eight products including the above three products in the proportions given below and the mechanism leading to these products was discussed in some detail.³³

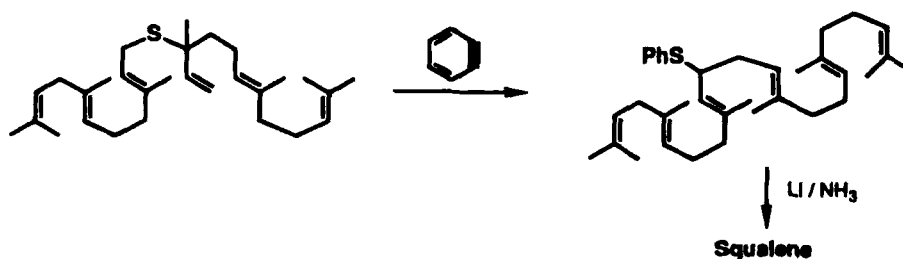


The benzyne-induced sulfonium ylide rearrangement is also useful for the preparation of nonisoprenoid as well as isoprenoid terpenes. The ylide **3-21**, produced by treatment of digeranyl sulfide with benzyne, rearranges to give **3-23** and **3-24** in a ratio of 3:7.³⁴ The ylide **3-22**, produced by treatment of geranyl linalyl sulfide with benzyne, rearranges

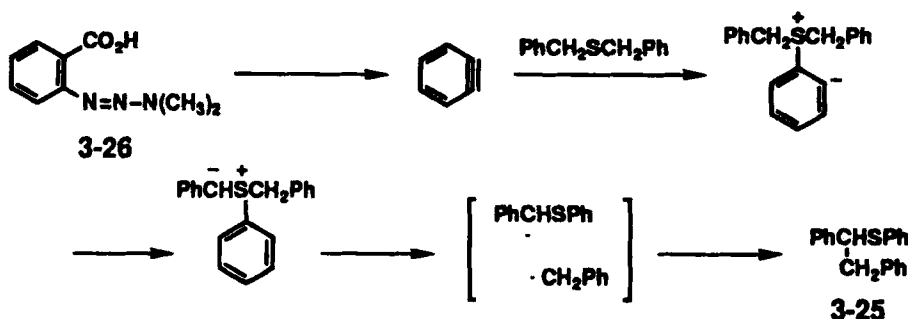
to form **3-23** and **3-24** in a ratio of 19:1. Reduction of **3-23** and **3-24** with lithium in liquid ammonia produces the isoprenoid and nonisoprenoid diterpenes, respectively.



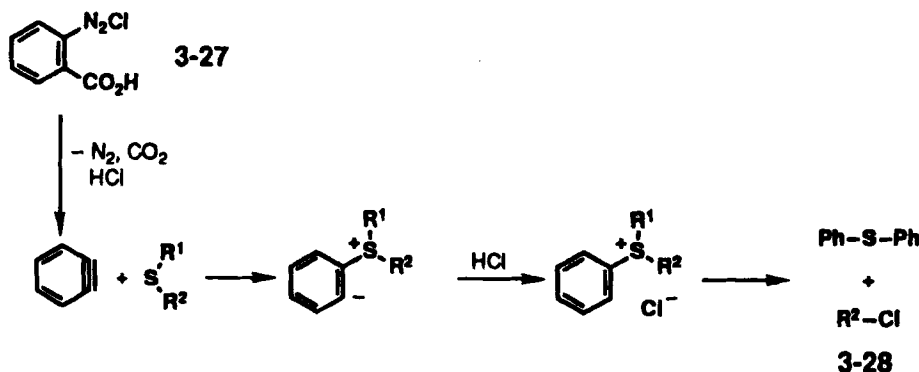
Successful application of the benzyne-induced sulfonium ylide rearrangement to squalene synthesis has also been reported.³⁵



The ylide produced from dibenzyl sulfide and benzyne collapses to phenyl 1,2-diphenylethyl sulfide (**3-25**) (20%) and benzyl phenyl sulfide (11%) by Stevens rearrangement and α -elimination, respectively.²⁵ The reaction of dibenzyl sulfide with benzyne, generated from 1-(2-carboxyphenyl)-3,3-dimethyltriazene (**3-26**),³⁶ also affords the sulfide **3-25** as the principal product.³⁷ When the reaction was monitored by ¹H NMR, nuclear spin polarization in the Stevens rearrangement product **3-25** was observed, thus suggesting that the rearrangement occurs through a radical dissociation-recombination mechanism.



The reaction of alkyl phenyl sulfides and related sulfides with benzyne, generated by thermolysis of 2-carboxybenzenediazonium chloride (3-27) in the presence of 2-methyloxirane, provides a new method for carbon-sulfur bond cleavage and affords diphenyl sulfide and alkyl chlorides 3-28 in good yields.³⁸ This indicates that the formation of ylides from betaines by intramolecular proton transfer (or the elimination of alkenes from the ylides) is slow enough to allow addition of hydrogen chloride (produced from 3-27) to these intermediates to give the sulfonium chlorides. The final step involves nucleophilic carbon-sulfur bond cleavage by chloride ion. The yields of 3-28 do not depend on the presence or absence of 2-methyloxirane which acts as the hydrogen chloride scavenger produced from 3-27 (Table 3-5).



Although the reaction of benzyne with thioanisole gives diphenyl sulfide with elimination of methylene, the fate of the methylene is not clear. In the reaction of benzyne with sulfides carrying a carboxyl group, e.g., *o*-(methylthio)benzoic acid, the methylene is transferred to the carboxyl group to give the methyl ester 3-29.³⁹ Thus, reaction of *o*-(methylthio)benzoic acid with benzyne, generated by aprotic diazotization of anthranilic acid, affords the methyl ester 3-29 in 56% yield along with thioxanthone in 2% yield. The formation of these products can be formulated as depicted below. *o*-(Ethylthio)benzoic acid behaves similarly, but affords the ethyl ester 3-30 in lower yield (26%) probably because of elimination of ethene from the betaine or ylide is a more favorable and faster

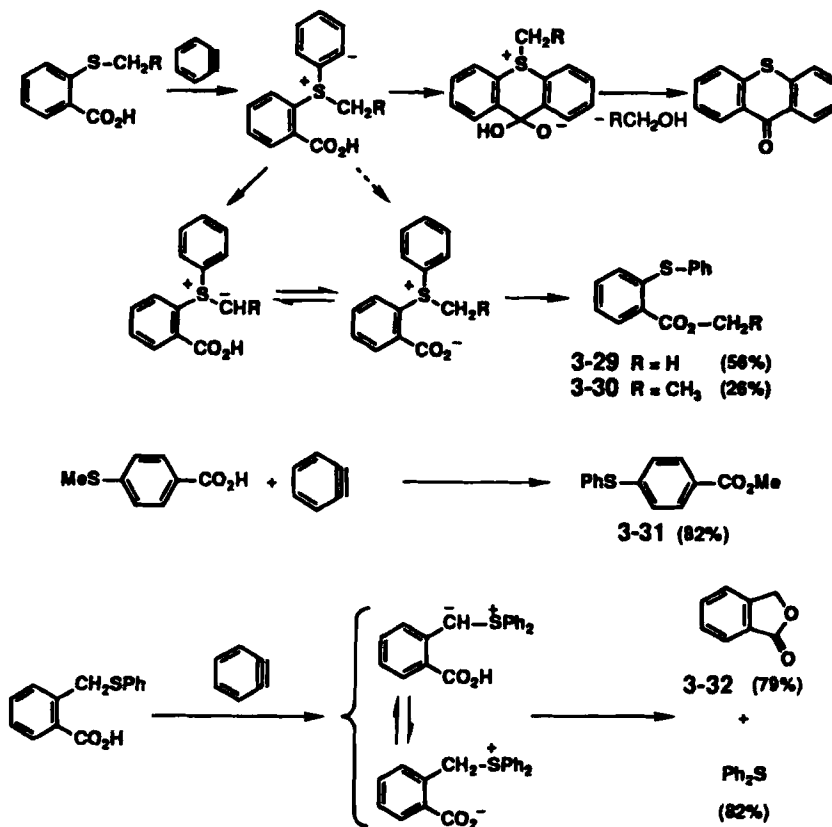
TABLE 3-5 Reactions of sulfides with benzyne generated from 2-carboxybenzene diazonium chloride (3-27)^{a)}

sulfide	methyloxirane	products, yield (%)			
Ph-S-C ₁₆ H ₃₃	present	Ph-S-Ph	88	C ₁₆ H ₃₃ Cl	85
Ph-S-C ₁₆ H ₃₃	absent	Ph-S-Ph	93	C ₁₆ H ₃₃ Cl	88
Ph-S-CH ₂ Ph	present	Ph-S-Ph	94	PhCH ₂ Cl	78
Ph-S-CH ₂ Ph	absent	Ph-S-Ph	85	PhCH ₂ Cl	84
C ₁₆ H ₃₃ -S-C ₁₆ H ₃₃ ^{b)}	present	Ph-S-Ph	93	C ₁₆ H ₃₃ Cl	86
		Ph-S-C ₁₆ H ₃₃	6		
PhCH ₂ -S-CH ₂ Ph ^{b)}	present	Ph-S-Ph	89	PhCH ₂ Cl	66
PhCH ₂ -S-C ₁₆ H ₃₃	present	Ph-S-C ₁₆ H ₃₃	74	PhCH ₂ Cl	65
		Ph-S-CH ₂ Ph	8	C ₁₆ H ₃₃ Cl	11

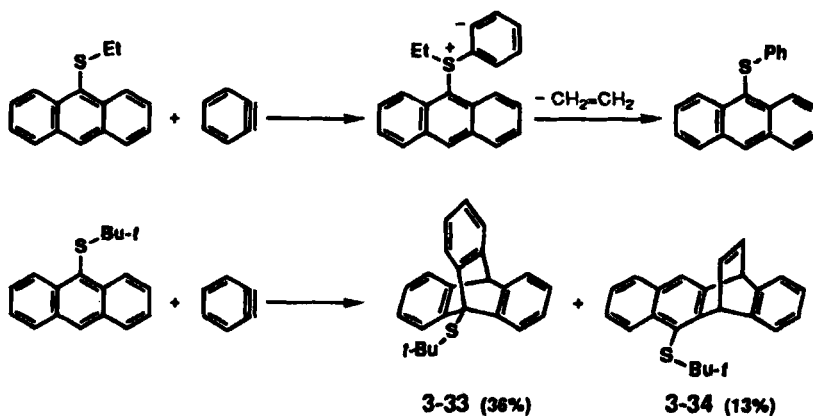
^{a)}1.1 Equiv. 3-27 was used unless otherwise stated.

^{b)}2.8 Equiv. 3-27 was used.

process than that of methylene. The above methylene transfer may not be intramolecular because the reaction of benzyne with *p*-(methylthio)benzoic acid, where intramolecular methylene transfer is improbable, affords the ester 3-31 in good yield (82%). The reaction of benzyne with *o*-(phenylthiomethyl)benzoic acid undergoes intramolecular cyclization to give the lactone 3-32 (79%) and diphenyl sulfide (82%).

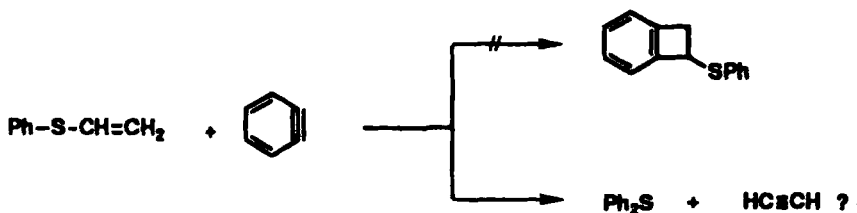


The reaction of benzyne with 9-(ethylthio)anthracene affords 9-(phenylthio)anthracene with elimination of ethene. Meanwhile, the reaction with 9-(*tert*-butylthio)anthracene, where attack of benzyne on the sulfur is sterically inhibited, affords Diels-Alder adducts with an anthracene nucleus, **3-33** and **3-34**, in 36% and 13% yields, respectively.⁴⁰



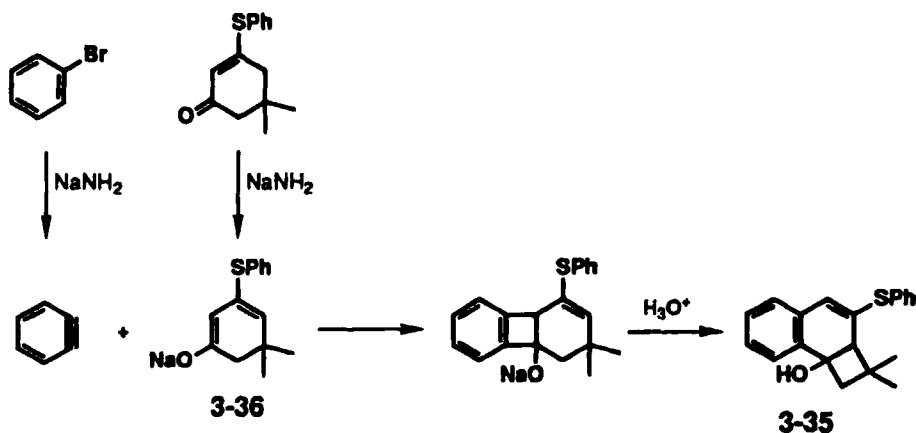
3.2. Reactions with Unsaturated Sulfides

The [2 + 2] cycloaddition of benzyne with alkenes is the reaction that has been studied most extensively from a mechanistic point of view. Many alkenes undergo [2 + 2] cycloaddition with benzyne to give benzocyclobutene derivatives in moderate yields, although alkenes which carry an alkyl group possessing an α -hydrogen may undergo an ene reaction preferentially. However, we have already seen that the initial reaction of benzyne with allyl sulfides occurs exclusively on the sulfur atom but not at the double bond, thus indicating that divalent sulfur is much more reactive toward benzyne than a carbon-carbon double bond. Thus, the reaction of benzyne with phenyl vinyl sulfide affords diphenyl sulfide (44.5%), probably with loss of ethyne. No [2 + 2] cycloaddition product is formed.⁴¹

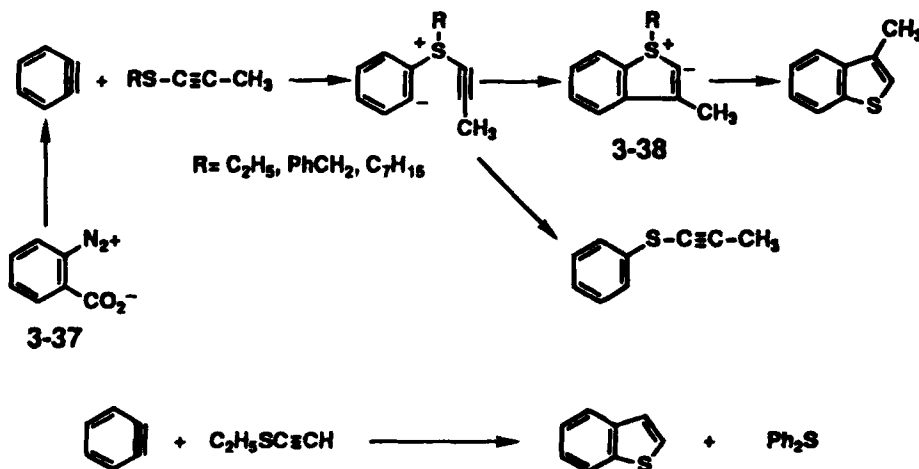


Benzyne, generated under strongly basic conditions, reacts with β -alkylthio or β -arylthio substituted cyclohexenone enolates to give arynic condensation products, e. g., **3-35**.⁴²

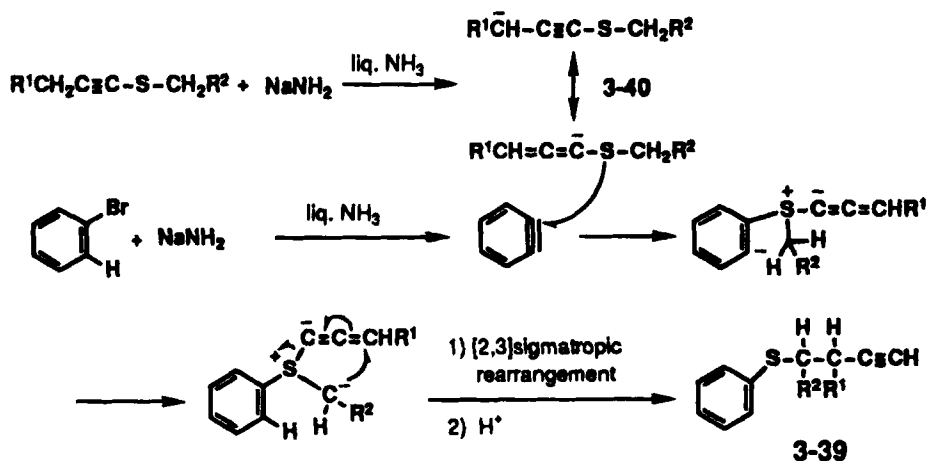
The reaction proceeds via the initial addition of the benzyne to the enolate 3-36 as shown below.



Benzyne, generated by thermolysis of benzenediazonium-2-carboxylate (3-37), reacts with alkythioalkynes to afford 3-methylbenzothiophene and 1-phenylthio-1-propyne in about 30% combined yield.⁴³ Similarly, reaction with ethylthioethyne affords benzothiophene (13%) and diphenyl sulfide (6%). The formation of benzothiophenes may best be explained by cyclization of the betaine intermediate leading to the vinyl ylide 3-38 which then collapses to the final products.



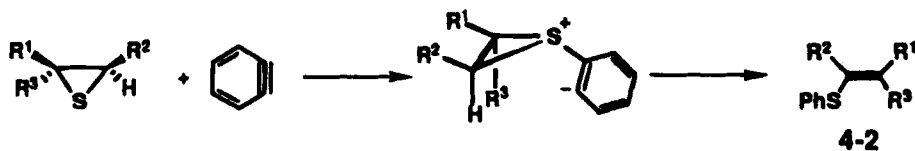
The reaction of benzyne, generated by treatment of bromobenzene with sodium amide in liquid ammonia, with 1-alkynyl sulfides produces the sulfides 3-39 in low to moderate yields.⁴⁴ Under these conditions, the starting sulfides are deprotonated to give the anions 3-40, which react with benzyne to give the final products in the manner proposed below.



4. REACTIONS WITH CYCLIC SULFIDES


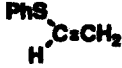

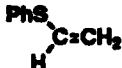

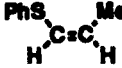
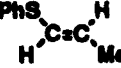

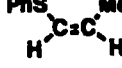
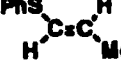

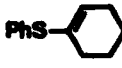

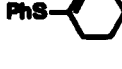


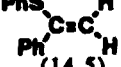
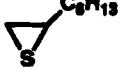
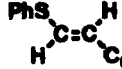
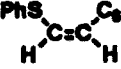

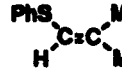

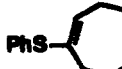



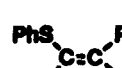
4.1. Reactions with Saturated Cyclic Sulfides

The reaction of thiiranes, the smallest cyclic sulfides, with benzyne, generated by thermolysis of the diazonium chloride **3-27** in the presence of 2-methyloxirane or of the diazonium-carboxylate **3-37**, provides a new synthesis of phenyl vinyl sulfides.⁴⁵ The reaction is applicable to a wide variety of thiiranes and affords phenyl vinyl sulfides in good yields in a stereo- and regioselective manner (Table 4-1). Thus, the reaction of the parent thiirane with benzyne generated from **3-27** and **3-37** affords phenyl vinyl sulfide in a respective yield of 74% and 75% (entries 1 and 2). The reactions with *cis*- and *trans*-2, 3-diphenylthiiranes produce *cis*- and *trans*-(phenylthio)stilbenes in 79% and 71% yields, respectively, with retention of the stereochemistry of the thiiranes (entries 11 and 12). The reactions with 2-methyl- and 2-hexylthiirane afford the sulfides, PhSCH=CHR (R = CH₃, C₆H₁₃), exclusively (entries 3, 4, and 8). No isomeric sulfides PhSC(R)=CH₂ are formed. Thus, the reaction is also regioselective. These results can best be explained by assuming that the initial betaine intermediates undergo ring opening with retention of the configuration of the starting thiirane and that subsequent elimination of the more acidic proton on the less substituted carbon takes place.



The reaction of 3,4,5,6-tetrafluorobenzyne with thiolane affords 2,3,4,5-tetrafluorophenyl vinyl sulfide, probably by fragmentation of an ylide intermediate.⁴⁶ However, applica-

TABLE 4-1 Preparation of phenyl vinyl sulfides by reaction of benzyne with thiiranes

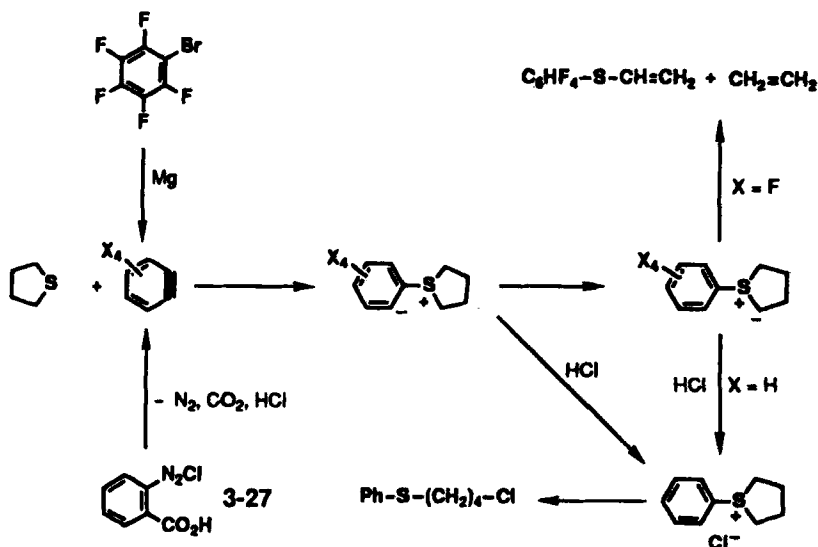
entry	thiirane	source of benzyne	phenyl vinyl sulfides (yield, %)
1		3-27	 (74)
2		3-37	 (75)
3		3-27	 +  (77) ^a
4		3-37	 +  (75) ^a
5		3-27	 (89)
6		3-37	 (64)
7		3-27	 (58) +  (14.5)
8		3-27	 +  (90) ^a
9		3-27	 (78.5)
10		3-27	 (77)
11		3-27	 (79)
12		3-27	 (71)

^aThe *cis:trans* ratio was not reported.

TABLE 4-2 Reactions of cyclic sulfides with benzyne generated from 3-27

cyclic sulfide	2-methyloxirane	products (yield, %) Ph-S-(CH ₂) _n -Cl
thietane	present	n = 3 70
thietane	absent	n = 3 70
thiolane	present	n = 4 63
thiolane	absent	n = 4 65
thiane	present	n = 5 79
thiane	absent	n = 5 70

tion of the reaction to benzyne, generated by thermolysis of 3-27, affords 4-chlorobutyl phenyl sulfide in 63% yield.³⁸ None of the expected phenyl vinyl sulfide was obtained. The yield of the sulfide was not affected by the presence or absence of 2-methyloxirane which can act as a scavenger of the hydrogen chloride produced from 3-27. This indicates that either the ylide formation from the betaine or the ylide fragmentation is slow enough to allow the addition of hydrogen chloride to the intermediate to give a sulfonium chloride as observed in the reaction with alkyl phenyl sulfides. Thietane and thiane also react with the above benzyne in the same manner to give the corresponding ω-chloroalkyl phenyl sulfides in good yields (Table 4-2).



Betaine intermediates, produced by reaction of benzyne with 2-substituted 1,3-dithiolanes, collapse in two ways to give the ylides 4-1 and 4-2.⁴⁷ The ylides 4-1 undergo fragmentation to dithioesters 4-3 with loss of ethene, while the ylides 4-2 decompose to give phenyl vinyl sulfide and thioaldehydes. Thus, the reaction of benzyne with 2-phenyl-1,3-dithiolane affords phenyl vinyl sulfide (17%), diphenyl sulfide (5%), phenyl dithiobenzoate (23%), and benzaldehyde (5~20%) with 20% recovery of the starting material. The

diphenyl sulfide originates from further reaction of phenyl vinyl sulfide with benzyne, while benzaldehyde may come from hydrolysis or oxidation of thiobenzaldehyde. The results of reactions with a series of 2-substituted dithiolanes are given in Table 4-3. In any cases, no unstable thioaldehydes could be isolated. However, the reaction with the spiro compound 4-4 allows the isolation of a thiocarbonyl compound, ethylene trithiocarbonate, in 15% yield along with phenyl vinyl sulfide (36%) and benzo-1,3-dithiole-2-thione (4-5) (5%). Compound 4-5 is the product of further reaction of benzyne with ethylene trithiocarbonate as discussed later.

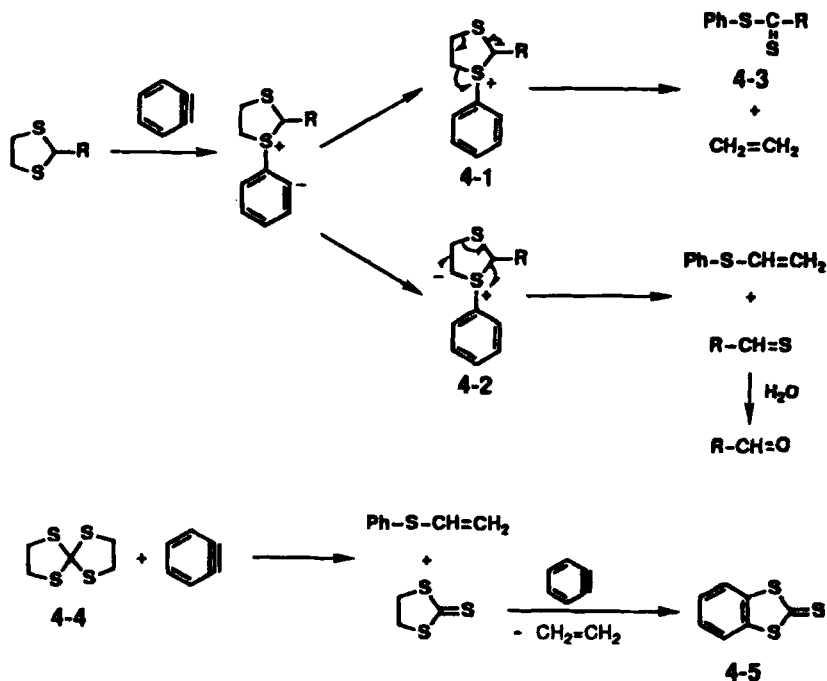
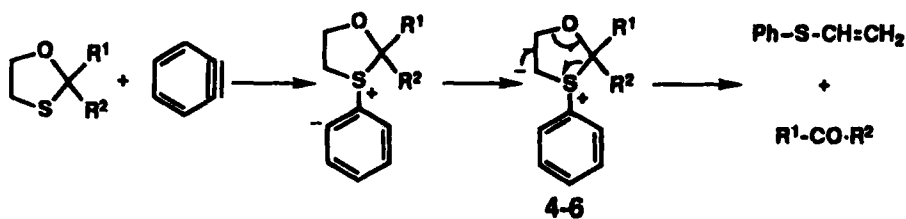


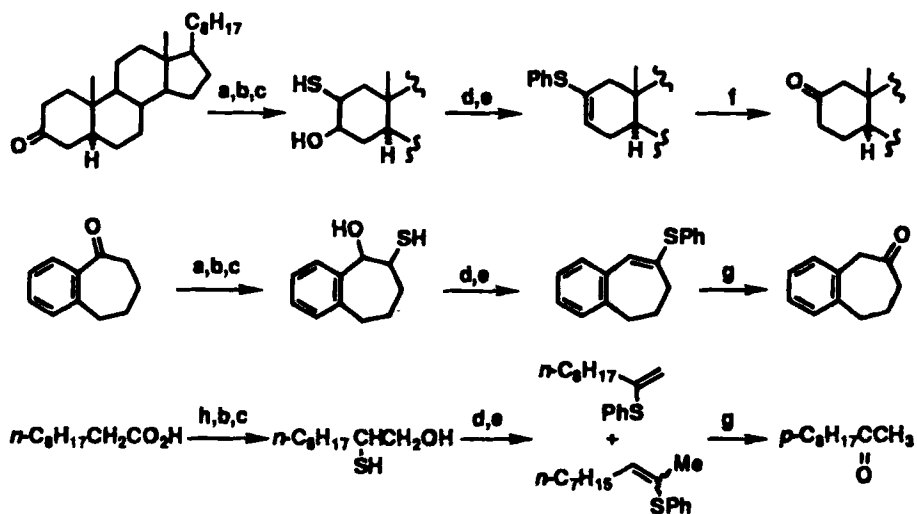
TABLE 4-3 Reactions of 2-monosubstituted 1,3-dithiolanes with benzyne

R	yield (%)	
	dithioester	phenyl vinyl sulfide
C_6H_5	23	17
<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4$	29	11
<i>p</i> - $\text{CH}_3\text{OC}_6\text{H}_4$	34	15
<i>p</i> - ClC_6H_4	25	9
<i>m</i> - ClC_6H_4	23	9
<i>o</i> - ClC_6H_4	9	9
1-naphthyl	29	21
2-thienyl	22	7
CH_3CH_2	9	39
$\text{CH}_3\text{CH}_2\text{CH}_2$	9	39

2-Monosubstituted and 2,2-disubstituted 1,3-oxathiolanes, a typical form of masked aldehydes and ketones, react with benzyne, generated by thermal decomposition of 3-27 in the presence of 2-methyloxirane, with sole formation of the ylides 4-6, which cleanly undergo fragmentation giving rise to phenyl vinyl sulfide and the corresponding carbonyl compounds in good yields.⁴⁸ Thus, the reaction provides a unique method for the deprotection of masked carbonyl compounds. The results of the reactions with some simple oxathiolanes are given in Table 4-4. The results of its application to the preparation of various aryl vinyl sulfides also are given in Table 4-5. The reaction is virtually stereospecific (entries 3 and 5). The formation of the alcohol derivative in entries 4 and 6 indicates that the fragmentation of the ylide is slow in these cases, and that it is captured by hydrogen chloride produced from 3-27 to give the sulfonium chloride whose hydrolysis would lead to the final product, an alcohol.



Application of the reaction to 1,2-carbonyl transposition is also possible as exemplified in the examples given below.⁴⁸



- a: Br₂. b: EtOC(S)S⁻K⁺. c: LiAlH₄. d: cyclohexanone-ZnCl₂ (Na₂SO₄).
 e: benzyne. f: (I) HBr, (II) HgCl₂ (THF-H₂O). g: HgCl₂ (CH₃CN-H₂O).
 h: (I) SOCl₂, (II) NBS-HBr, (III) aq. NaHCO₃.

TABLE 4-4 Reactions of 2-mono- and 2,2-disubstituted 1,3-oxathiolanes with benzyne

R ¹	R ²	yield (%)	
		Ph-S-CH=CH ₂	R ¹ -CO-R ²
C ₆ H ₅	H	57	71
<i>p</i> -CH ₃ OC ₆ H ₄	H	50	76
<i>p</i> -ClC ₆ H ₄	H	49	49
C ₆ H ₅	C ₆ H ₅	67	82
C ₆ H ₅	C ₆ H ₅	(+) ^{a)}	100
CH ₃	CH ₃	71	(+) ^{a)}

^{a)}The yield was not determined.

TABLE 4-5 Reactions of 2,2-pentamethylene-1,3-oxathiolanes with benzyne

entry	oxathiolane	products (yield, %)			
1			(85) ^{a)}		
2			(70)		
3			(83) ^{b)}		
4			(7) ^{c)}		(88) ^{d)}
5			(86.5)		
		(<i>E</i> : <i>Z</i> = 98:2)			
6			(50)		(30) ^{d)}
		(<i>E</i> : <i>Z</i> = 14:86)			

^{a)}No *cis*-isomer was formed.

^{b)}The *Z*-isomer was found in trace amount.

^{c)}A mixture of *E*- and *Z*-isomers.

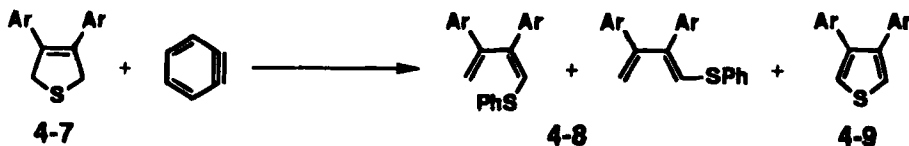
^{d)}A mixture of diastereomers.

TABLE 4-6 Reactions of 3,4-diaryl-2,5-dihydrothiophenes with benzyne

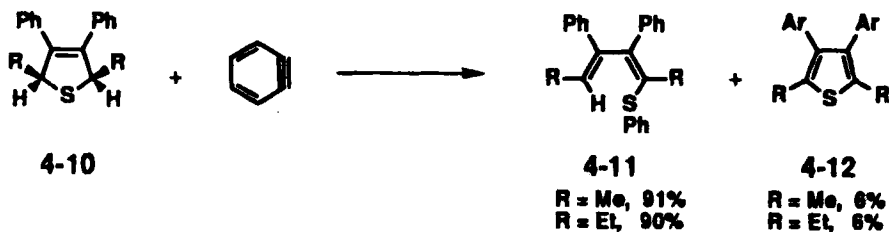
Ar	C ₆ H ₅	4-MeC ₆ H ₄	4-MeOC ₆ H ₄	3-naphthyl	2-thienyl
yield of 4-8 (%)	76	86	62	74	76
Z:E	86:14	93:7	80:20	90:10	84:16
yield of 4-9 (%)	8	12	20	21	12

4.2. Reactions with Unsaturated Cyclic Sulfides

Fragmentation of the ylides produced by reaction of 2,5-dihydrothiophenes with benzyne provides a convenient synthesis of polysubstituted 1-phenylthio-1,3-dienes. Thus, the reaction of a series of 3,4-diaryl-2,5-dihydrothiophenes **4-7** with benzyne, generated from **3-27**, affords 3,4-diaryl-1-phenylthio-1,3-dienes **4-8** in 74–86% yield along with 3,4-diarylthiophenes **4-9** in 8–21% yield (Table 4-6).⁴⁹



Similarly, reaction with 2,5-dialkyl-3,4-diphenyl-2,5-dihydrothiophenes **4-10** affords the corresponding 1,3-dienes **4-11** in high yields along with the thiophenes **4-12** in low yields.



Retention of the original stereochemistry of the starting dihydrothiophenes in the diene formation may indicate that the fragmentation of the ylides occurs in a concerted disrotatory manner. The formation of some *E*-isomers (Table 4-6) is probably due to acid-catalyzed isomerization of the *Z*-isomers initially formed; hydrogen chloride generated from **3-27** should act as the acid catalyst.

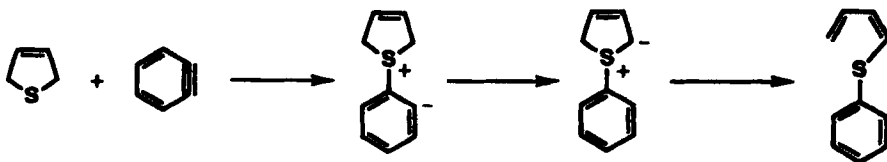
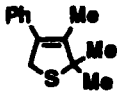
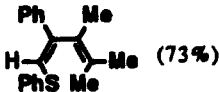
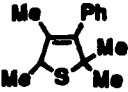
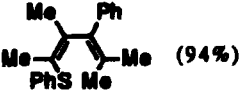
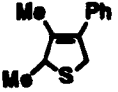
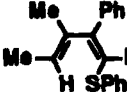
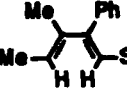
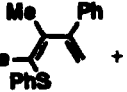
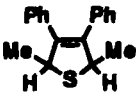
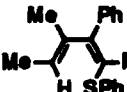
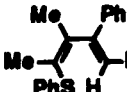
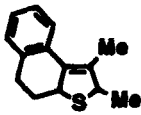
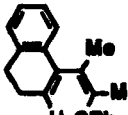
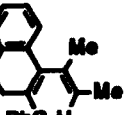
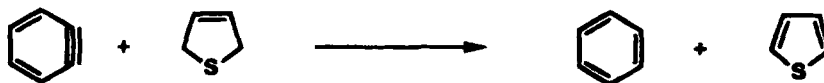


TABLE 4-7 Preparation of polysubstituted 1-phenylthio-1,3-dienes

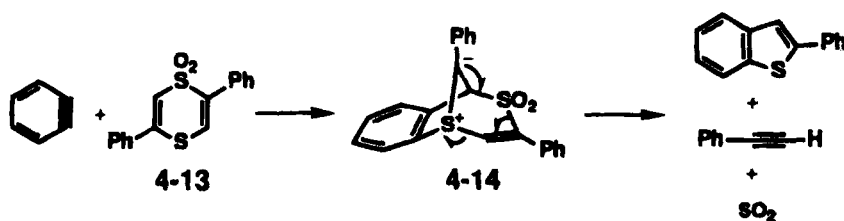
dihydrothiophene	products (yield, %)
	 (73%)
	 (94%)
	 (43%, 52:48) +  (9%) +  (40%)
	 (88%, 64:36) +  (7%)
	 (90%, 77:23) +  (6%)

The formation of thiophenes is assumed to be the result of hydrogen transfer from dihydrothiophenes to benzyne, which presumably occurs in a concerted symmetry-allowed process.

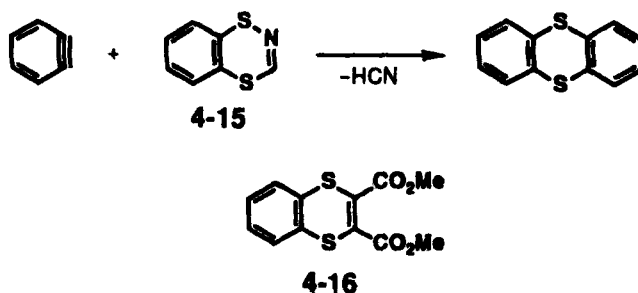


Examples of the application of this reaction to the synthesis of other 1-phenylthio-1,3-dienes are given in Table 4-7.

The 1,4-dithiin derivative **4-13** reacts with benzyne, generated by aprotic diazotization of anthranilic acid, probably in a 1,3-dipolar cycloaddition manner, to give the ylide intermediate **4-14**, which gives rise to 2-phenylbenzothiophene (28%), phenylethyne, and sulfur dioxide on fragmentation.⁵⁰



The benzodithiazine 4-15 reacts with benzyne to give thianthrene in low yield with elimination of hydrogen cyanide.⁵¹ This type of addition-elimination reaction of 4-15 with dimethyl butynedioate takes place effectively to give the benzodithiin 4-16 in high yield.



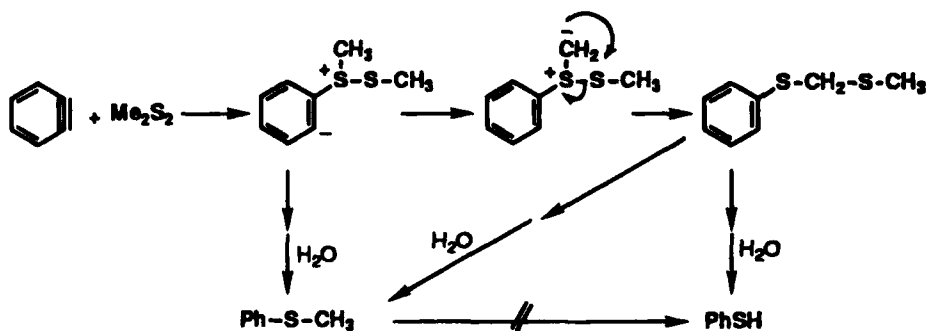
5. REACTIONS WITH DISULFIDES

Dialkyl disulfides undergo S-S bond fission upon the reaction with benzyne to give *S*-phenyl compounds. Reaction of dimethyl disulfide with benzyne, generated from bromobenzene and sodium in liquid ammonia, gives thiophenol (28%), thioanisole (8%), and diphenyl sulfide (5%) along with aniline (32%), diphenylamine (8%), and a small amount of biphenyl.⁵² Diethyl, diisopropyl, dibutyl, and di-*t*-butyl sulfide also react with benzyne to give similar products (Table 5-1). The mechanism shown below was proposed for the *S*-phenyl compound formation.

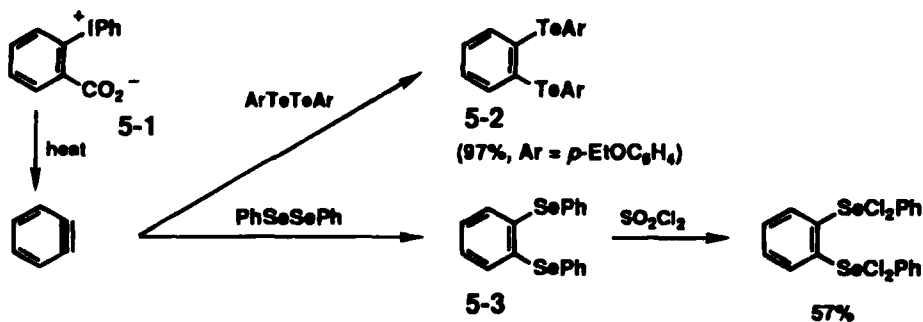
TABLE 5-1 Reactions of dialkyl disulfides RSSR with benzyne^{a)}

R	PhSH	PhSR	Ph ₂ S	PhNH ₂	Ph ₂ NH	Ph ₂
CH ₃	28	8	5	32	8	s
C ₂ H ₅	16	40	s	10	9	s
<i>i</i> -C ₃ H ₇	19	s	s	39	s	s
<i>n</i> -C ₄ H ₉	23	s	s	40	s	s
<i>t</i> -C ₄ H ₉	21	4	s	45	3	s

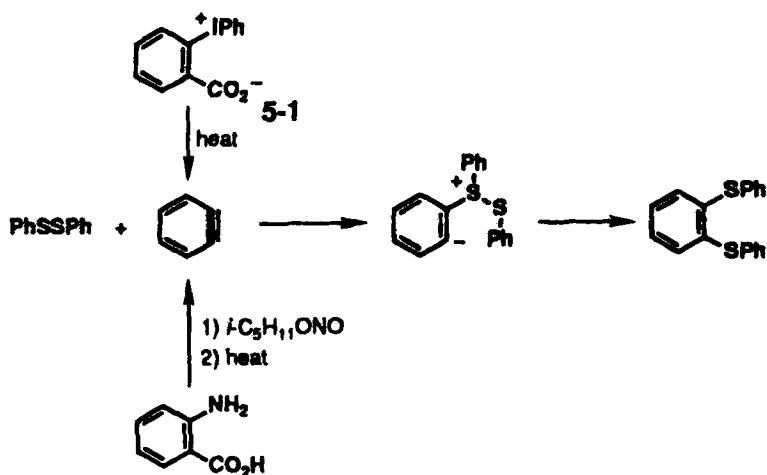
^{a)}s stands for formation in a small amount.



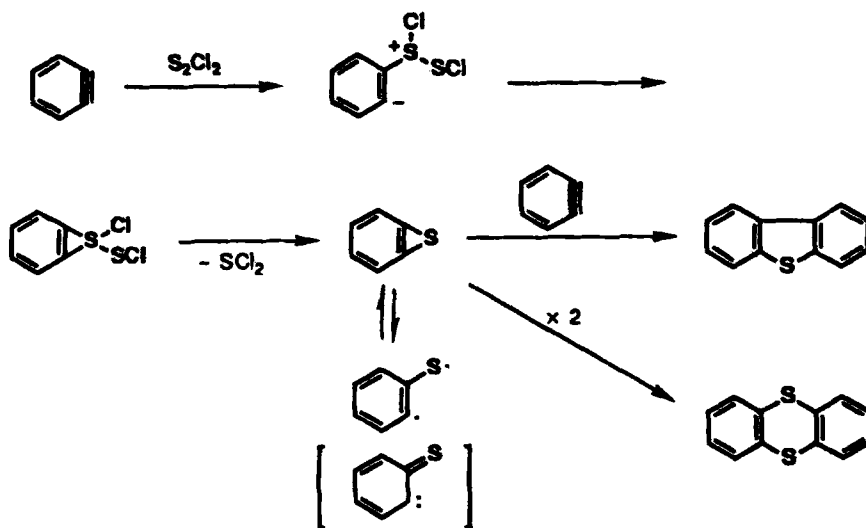
It has been reported that benzyne, generated by thermolysis of diphenyliodonium-2-carboxylate **5-1**, inserts into the Se-Se and Te-Te bonds of diphenyl diselenide and bis(*o*-ethoxyphenyl) ditelluride to give compounds **5-2** and **5-3**, respectively, in good yields, although it fails to insert into the S-S bond of diphenyl disulfide.⁵³



Reinvestigation of the reaction of benzyne with diphenyl disulfide revealed that benzyne, generated by thermolysis of **5-1** and also by aprotic diazotization of anthranilic acid, can insert into the S-S bond to give *o*-bis(phenylthio)benzene in 8% and 14% yield, respectively, with a large amount of recovered disulfide.⁵⁴ 4-Chloro-, 3,5-dichloro-, and 4-nitrobenzyne also undergo this reaction to give the corresponding insertion products in 25%, 19%, and 30% yield, respectively.



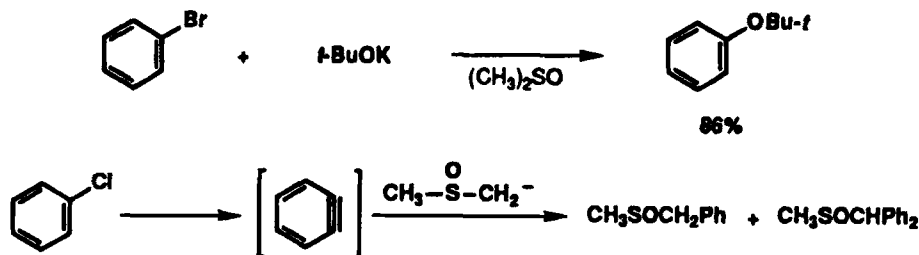
The reaction with disulfur dichloride, which also possesses an S-S bond, is also known. Benzyne generated from 3-27 reacts with disulfur dichloride to give dibenzothiophene (8–10%) and thianthrene (26–35%).⁵⁵ A mechanism involving ligand coupling of a sulfurane intermediate leading to benzothirane or its equivalent with loss of sulfur dichloride has been proposed for this reaction.



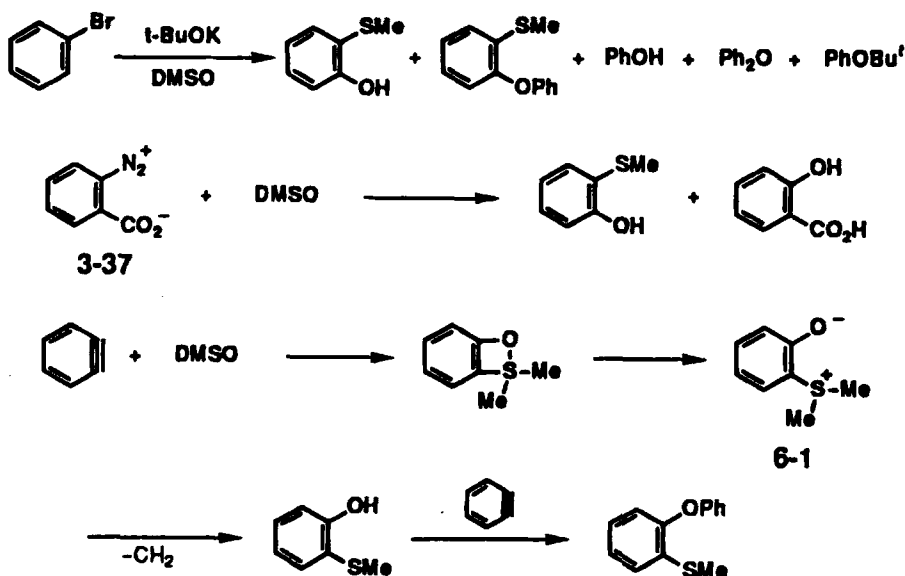
6. REACTIONS WITH SULFOXIDES

The products of the reaction of benzyne with sulfoxides may vary greatly depending on the conditions under which benzyne is generated.

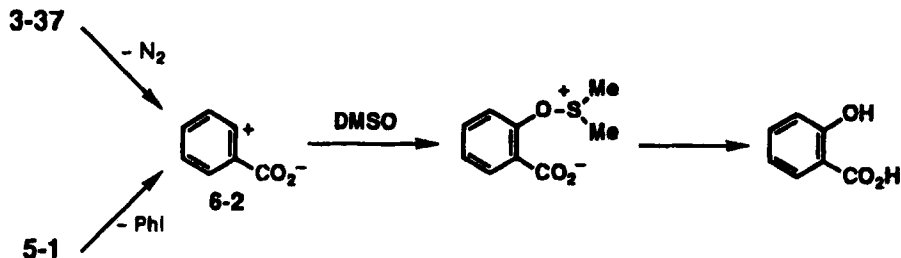
The reaction of bromobenzene with *t*-BuOK in dimethyl sulfoxide (DMSO) takes place unusually rapidly to give *t*-butyl phenyl ether in 86% yield.⁵⁶ On the other hand, the reaction of chlorobenzene with dimethylsulfonium (6.7 equiv.) in DMSO affords benzyl methyl sulfoxide in 41% yield; when a smaller amount of dimethylsulfonium (2.5 equiv.) was used, benzhydryl methyl sulfoxide (8.7%) was formed together with benzyl methyl sulfoxide. The intermediacy of benzyne has been suggested for these reactions.⁵⁷



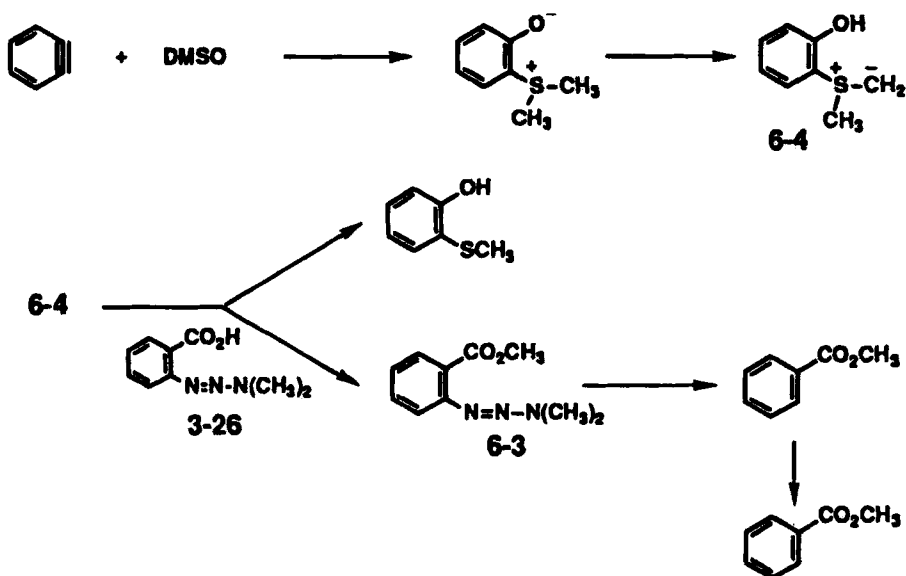
A careful product analysis of the reaction of bromobenzene with *t*-BuOK in DMSO revealed that the reaction produces *o*-(methylthio)phenol (7%), *o*-(methylthio)phenyl phenyl ether (5%), phenol (5%), and diphenyl ether (6%) in addition to *t*-butyl phenyl ether (52%).⁵⁸ *o*-(Methylthio)phenol (14%) was also formed along with salicylic acid (11%) by the reaction of DMSO with benzyne generated from the diazoniumcarboxylate 3-37. The formation of the sulfur-containing compounds can best be explained by assuming [2 + 2] cycloaddition of benzyne with DMSO. In fact, the reaction of DMSO with benzyne generated from 3-37 at 36–40°C allowed the isolation of the inner salt 6-1 as the picrate in separate work.⁵⁹



Meanwhile, thermolysis of the iodoniumcarboxylate **5-1** in DMSO gives salicylic acid in 20% yield.⁶⁰ The formation of salicylic acid from **5-1** and also from **3-37** may be rationalized as the result of trapping of the intermediates **6-2** with DMSO.

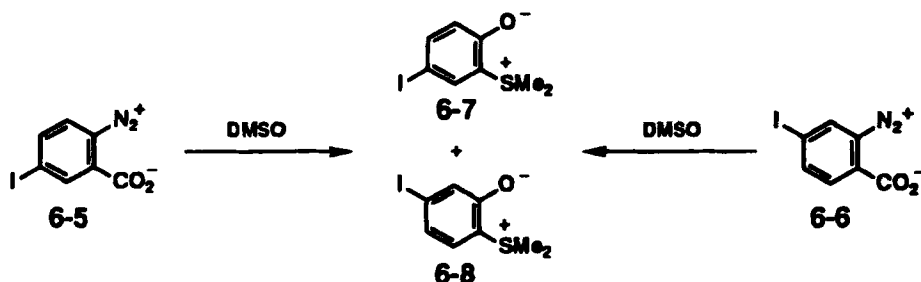


Thermolysis of the triazene **3-26** in DMSO at 150–160 °C gives *o*-(methylthio)phenol (28%), methyl benzoate (6%), and 3,3-dimethyl-1-(2-methoxycarbonylphenyl)triazene (**6-3**) (9%) along with *N,N*-dimethylaniline (23%) and *N*-methyldiphenylamine (1.5%).⁶¹ The formation of the first three products can be again explained by assuming [2 + 2] cycloaddition of benzyne to DMSO as depicted below, although the amines arise from the reaction of benzyne with dimethylamine produced from **3-26**.

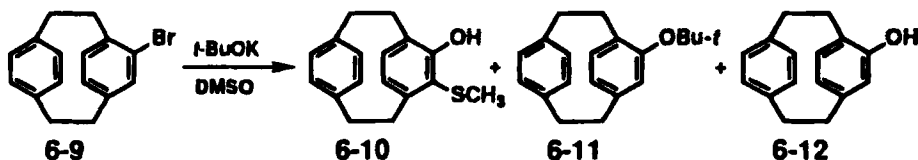


The intermediacy of benzyne in the formation of the inner salt **6-1** was also apparent from the following observations. 4-Iodobenzenediazonium-2-carboxylate (**6-5**) and 5-iodobenzenediazonium-2-carboxylate (**6-6**) should give rise to a mixture of **6-7** and **6-8**

in the same ratio on reaction with DMSO since both precursor compounds generate the same 3-iodobenzynes. Actually, thermal decomposition of these compounds in DMSO, followed by treatment with picric acid, gave the same picrates that which formed from isomeric mixtures of 6-7 and 6-8, probably in the same ratio.⁶⁰

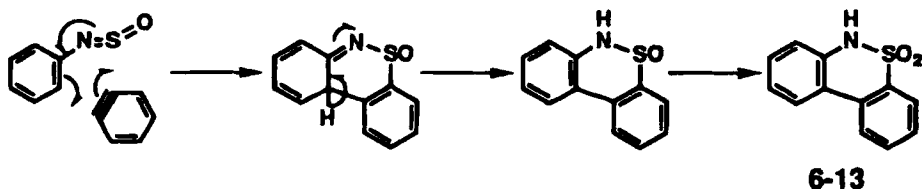


The formation of an *o*-(methylthio)phenol derivative is also observed when benzyne is a part of a [2.2]paracyclophane system. Thus, treatment of the bromocyclophane 6-9 with *t*-BuOK in DMSO affords the *o*-(methylthio)phenol 6-10 (10%) along with the ether 6-11 (4%) and the phenol 6-12 (14%).⁶²



Although the reaction of diphenyl sulfoxide with benzyne, generated by treatment of *o*-bromofluorobenzene with magnesium, affords diphenyl sulfide in 13% yield, it is not clear if benzyne is involved in the diphenyl sulfide formation.⁶⁰

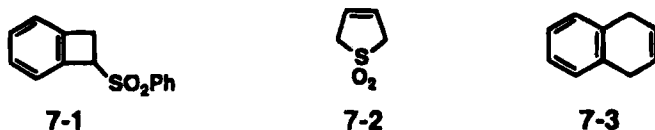
Thionylaniline which is not a sulfoxide is known to react with benzyne to give the thiazine derivative 6-13, though in low yield.⁶³



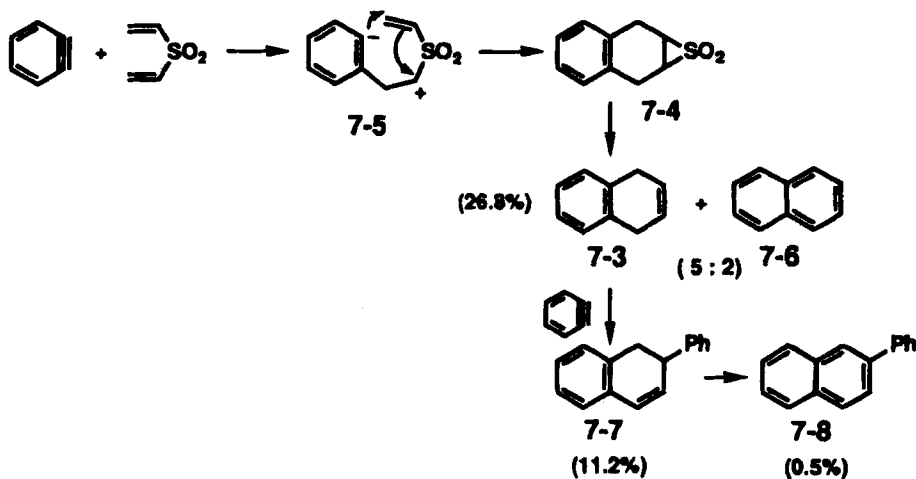
7. REACTIONS WITH COMPOUNDS CONTAINING A SULFONE MOIETY

Reactions of benzyne with sulfones in which the sulfone moiety actually takes part in reactions with benzyne have never been reported. In all of the reactions reported only an unsaturated substituent of the sulfone participates in reactions with benzyne.

Attempted reaction of phenyl vinyl sulfone with benzyne failed to give the expected [2 + 2] cycloadduct **7-1**, probably because of the electron-withdrawing nature of the PhSO₂ group.⁴¹ The reaction of sulfolene **7-2** with benzyne, generated from **3-37**, gives 1,4-dihydronaphthalene (**7-3**) in low yield; this arises from Diels-Alder reaction of benzyne with 1,3-butadiene produced by thermolysis of sulfolene.⁶⁴

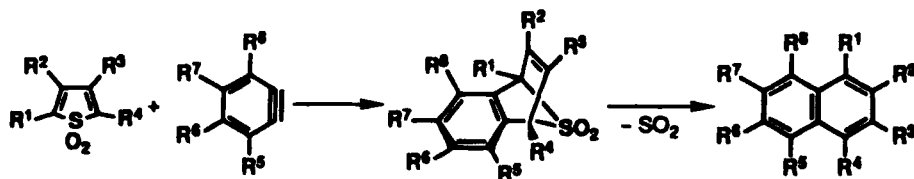


A nonconjugated diene, divinyl sulfone, reacts with benzyne to give a homo Diels-Alder adduct **7-4** initially, probably via the zwitterionic intermediate **7-5**. Then **7-4** extrudes sulfur dioxide to give 1,4-dihydronaphthalene **7-3**. Dehydrogenation of **7-3** and also ene reaction of **7-3** with benzyne, followed by dehydrogenation, explain the other observed products **7-6**, **7-7**, and **7-8**.⁶⁵

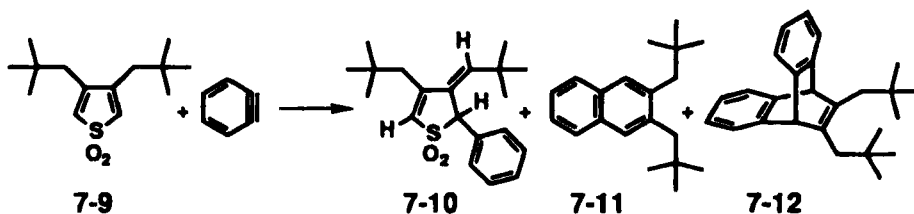


Thiophene 1,1-dioxides are no longer aromatic and behave as typical dienes toward benzyne. The Diels-Alder reaction of benzyne with thiophene dioxides provides a new method for the construction of the naphthalene ring since the initial adducts spontaneously

extrude sulfur dioxide to give naphthalene derivatives.^{66,67} Table 7-1 summarizes the results of reactions of benzyne with thiophene dioxides.



The reaction of benzyne with 3,4-dineopentylthiophene 1,1-dioxide (**7-9**) is of interest; it affords the ene reaction product **7-10** in 68% yield along with the Diels-Alder adducts **7-11** (20%) and **7-12** (7.5%).⁶⁸ This is the first instance where an ene reaction has been observed with a thiophene dioxide derivative. The barrelene **7-12** is the product of the Diels-Alder reaction of benzyne with **7-11** on the more congested benzene ring, but not the unsubstituted and hence less hindered one.



8. REACTIONS WITH COMPOUNDS CONTAINING A C=S BOND

8.1. Reactions with Carbon Disulfide

Benzyne generated by elimination of CO_2 and CO from phthalic anhydride at 700°C in the gas phase reacts with carbon disulfide to give 1,2-benzodithiole-3-thione (**8-1**) (39%) and 1,3-benzodithiole-2-thione (**8-2**) (26.6%) as the major products.^{69,70} Dibenzothiophene, thianthrene, and dibenzotetrathiafulvalene (**8-4**) are other sulfur-containing minor products. 1,3-Dipolar cycloaddition of benzyne to CS_3 (formed from CS_2 and the sulfur provided by prior decomposition of CS_2 to CS and S under high energy conditions) has been proposed to explain the formation of compounds **8-1** and **8-2**. The formation of thianthrene and dibenzothiophene was explained as the result of the reaction of benzyne with sulfur, while formation of **8-4** was explained as the result of the dimerization of 1,3-benzodithiol-2-ylidene carbene (**8-3**), produced by 1,3-dipolar cycloaddition of benzyne to carbon disulfide.

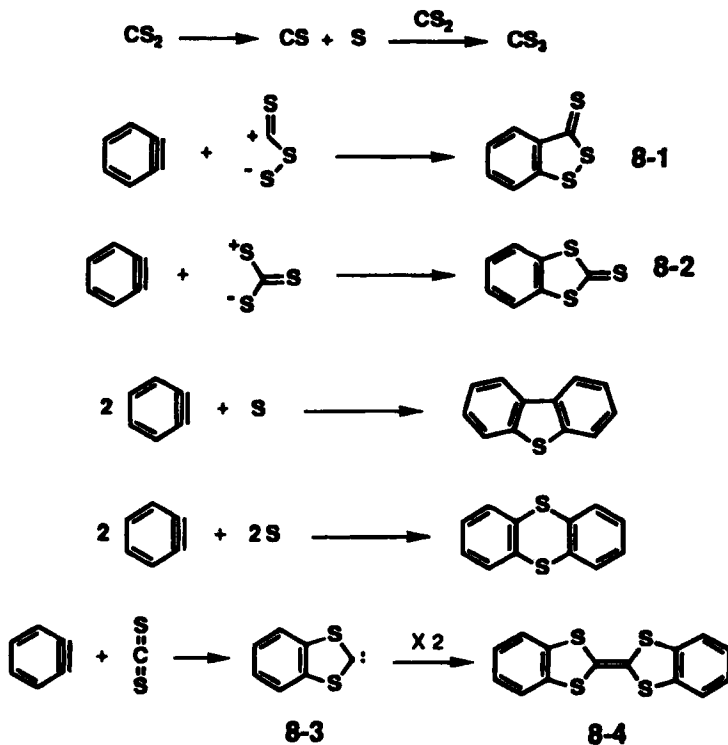
TABLE 7-1 Reactions of thiophene 1,1-dioxides with benzynes

benzyne	thiophene 1,1-dioxide	product	yield (conv. yield) %
			72 (94)
			65 (96)
			40 (97)
		— a)	
			9 (19)
			23 (36)
			64 (95)
			23 (78) ^{b)}
			25 (45)
			29 (51)
			19 (46) ^{c)}
			40

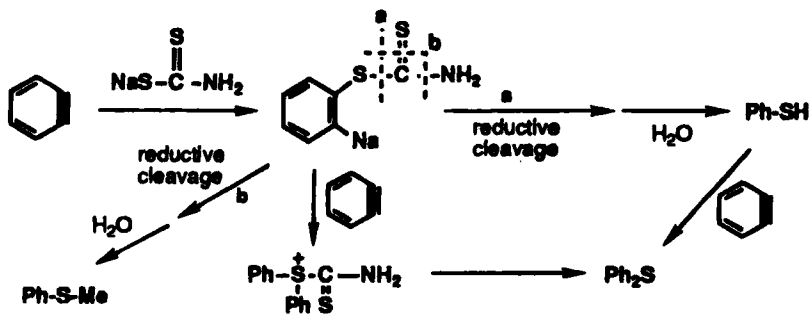
^{a)}Tetrachlorothiophene 1,1-dioxide was recovered quantitatively, and instead perchloroacridone (23%) and isoamyl tetrachlorophenyl ether (52%) were obtained.

^{b)}Tetramethylnaphthalene was not obtained.

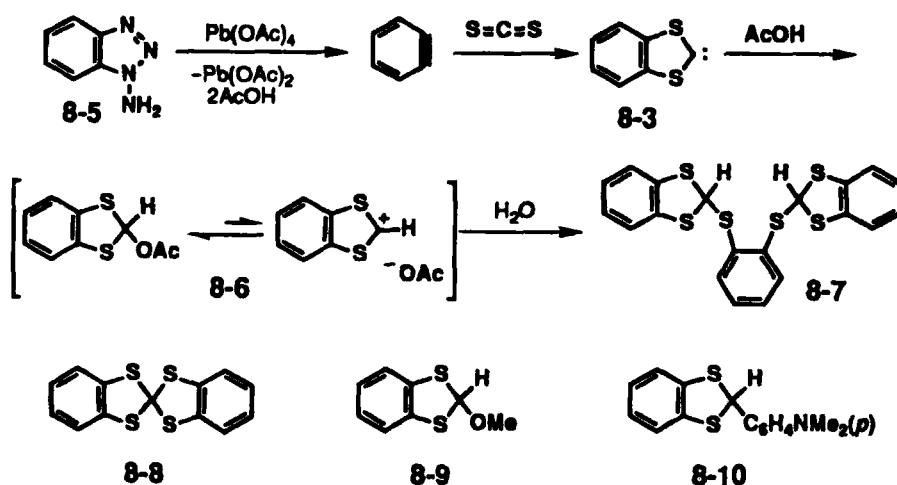
^{c)}Although dimethyldibenzobarrelene (ca. 4%) was formed, it could not be isolated in pure crystalline form.



The reaction of carbon disulfide with benzyne generated from bromobenzene and sodium amide in liquid ammonia affords thiophenol, thioanisole, and diphenyl sulfide in addition to aniline and diphenylamine.⁷¹ However, in this case the reactant which actually reacts with benzyne is not carbon disulfide but the adduct of carbon disulfide with sodium amide. A mechanism involving reductive C-S bond cleavage of the initial adduct has been proposed to explain the formation of the sulfur-containing products.

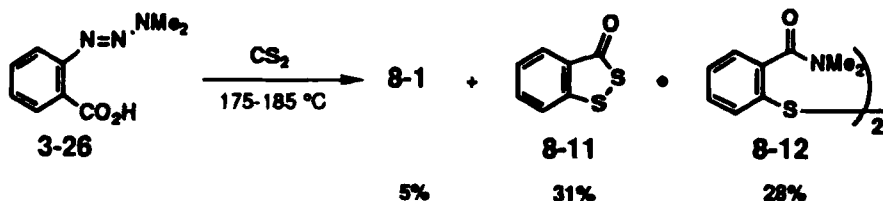


Later, it was made clear that the reaction of benzyne with carbon disulfide in the liquid phase affords the carbene **8-3** by 1,3-dipolar cycloaddition.⁷² The reaction was examined in detail by using a series of precursor compounds.⁷³ Oxidation of 1-aminobenzotriazole (**8-5**) with $\text{Pb}(\text{OAc})_4$ in a mixture of carbon disulfide and dichloromethane affords **8-7** (67%) and **8-8** (6%), while the oxidation in carbon disulfide alone gives a higher yield (89%) of **8-7** along with a trace amount of **8-8**. The formation of **8-7** is explained by 1) formation of the carbene **8-3** by 1,3-dipolar cycloaddition of benzyne to carbon disulfide, 2) formation of the adduct **8-6** by addition of acetic acid (formed from $\text{Pb}(\text{OAc})_4$) to the carbene, and 3) hydrolysis of **8-6** during work-up. The mechanism of the formation of the spiro compound **8-8** is not clear. Oxidation of **8-5** in a 1:1 mixture of carbon disulfide and methanol affords 2-methoxy-1,3-benzodithiole (**8-9**), the adduct of the carbene **8-3** with methanol, in 78% yield, while oxidation in the presence of *N,N*-dimethylaniline produces a 15% yield of the benzodithiole **8-10**, a product arising from **8-6** and the aniline.

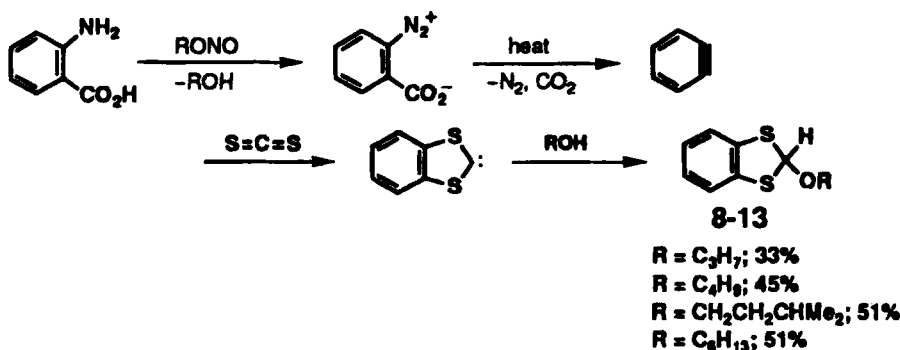


Thermolysis of benzenediazonium-2-carboxylate (**3-37**) in a refluxing mixture of carbon disulfide and dichloromethane affords **8-4** (22%), **8-7** (1%), **8-8** (2%), and 1,3-benzodithiole-2-one (2%). Apparently the formation of **8-4** is explained as the result of the dimerization of the carbene **8-3**. Benzyne generated from 2-carboxybenzenediazonium chloride (**3-27**) reacts with carbon disulfide to give **8-7** as the principal product.

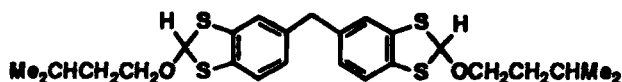
However, the products produced by reaction of carbon disulfide with benzyne generated from 1-(2-carboxyphenyl)-3,3-dimethyltriazene (**3-26**) cannot be explained by initial formation of the carbene **8-3**. Thus, heating this precursor compound with carbon disulfide at 175–185°C in a stainless steel bomb affords **8-1** (5%), **8-11** (31%), and **8-12** (28%) by an uncertain mechanism.



The reaction of carbon disulfide with benzyne, generated by aprotic diazotization of anthranilic acid, in the presence of alcohols provides a very convenient one-pot synthesis of 2-alkoxy-1,3-benzodithioles (**8-13**).⁷⁴ Thus, slow addition of a solution of anthranilic acid (0.30 mol) in dioxane (100 ml) to a stirred and refluxing solution of isoamyl nitrite (0.36 mol), isoamyl alcohol (0.60 mol), and carbon disulfide (150 ml) in 1,2-dichloroethane (800 ml) and work-up of the resulting mixture in an appropriate way gives 37 g (51%) 2-(3-methylbutoxy)-1,3-benzodithiole. In a similar way, a series of 2-alkoxy-1,3-benzodithioles can be synthesized. The reaction is also applicable to substituted benzyne⁷⁵ and 4,4'-methylenebis(benzyne);⁷⁶ it produces 2-alkoxy-1,3-benzodithioles (**8-14**) carrying substituent(s) on the benzene ring and the bisbenzodithiole **8-15**, respectively. The 2-alkoxy-1,3-benzodithioles prepared in this way can be converted to a wide variety of other 1,3-benzodithiole derivatives and related compounds and thus serve as convenient reagents in organic synthesis.⁷⁷



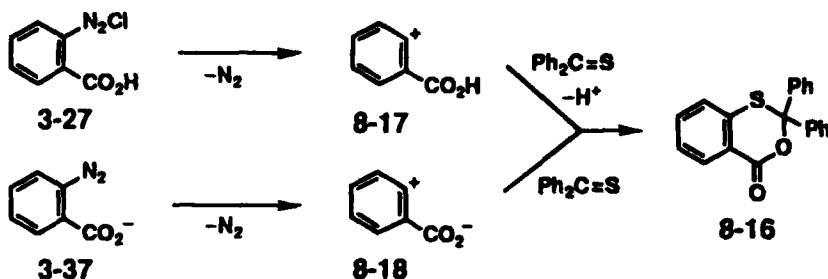
	R ¹	R ²	R ³	R ⁴	Yield(%)
 8-14	Me	H	H	H	65
	H	Me	H	H	35.5
	H	Cl	H	H	34
	H	I	H	H	49
	H	NO ₂	H	H	46
	H	H	-CH=CH-CH=CH-	H	24
	Cl	Cl	Cl	Cl	73
	Br	Br	Br	Br	57



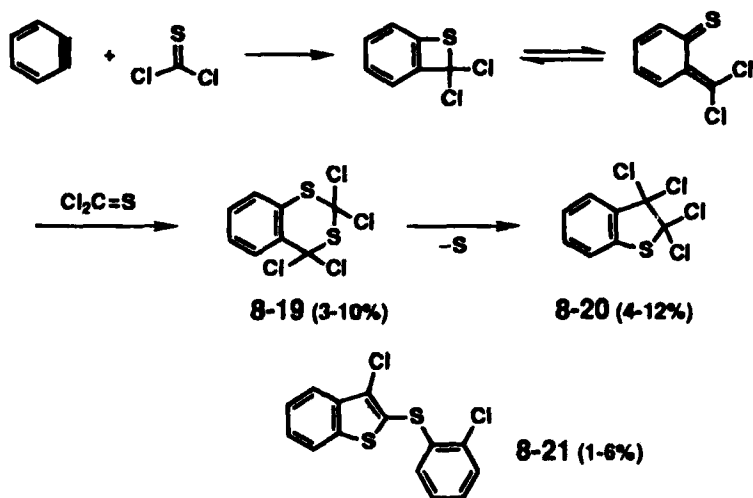
8-15 (14%)

8.2. Reactions with Thioketones

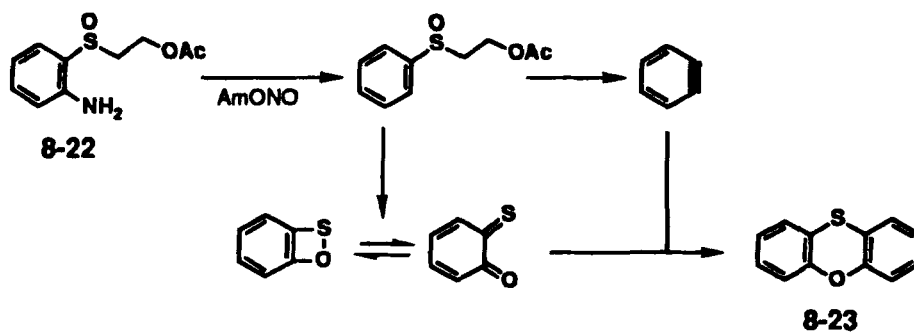
Benzyne is expected to undergo [2 + 2] cycloaddition with thioketones providing a convenient synthesis of benzothietes since it can undergo [2 + 2] cycloaddition with ketones.^{78,79} However, the properties of thioketones are difficult to reconcile with the properties of the precursor compounds of benzyne and also with the reaction conditions where benzyne is generated; acidic or basic conditions and the presence of oxidizing reagents or strong nucleophiles should be avoided. Because of this limitation, no report describing the reaction of benzyne with a thioketone in the actual sense has appeared. Thus, for example, attempted reaction of thiobenzophenone with benzyne using **3-27** and **3-37** as the precursors affords **8-16** in 44.5% and 40% yields, respectively.⁸⁰ The formation of **8-16** is explained as the result of reactions of thiobenzophenone with **8-17** and **8-18** which are intermediates of benzyne formation. Other diaryl thioketones behave similarly.⁸¹



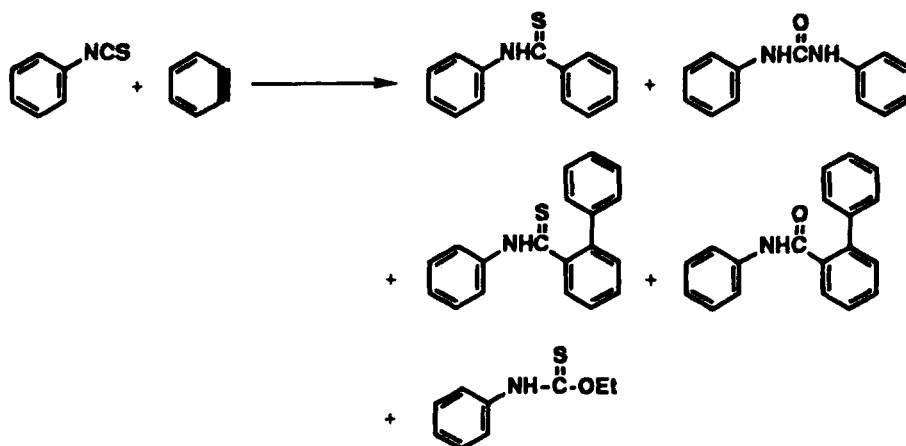
Thiophosgene, though not a true thioketone, reacts with benzyne, generated from **3-37**, to give **8-19** (3–10%), **8-20** (4–12%), and **8-21** (1–6%).⁸² The formation of **8-19** can be rationalized by [2 + 2] cycloaddition of benzyne with thiophosgene, ring opening of the resulting benzothiete, and [2 + 4] cycloaddition of the quinone methide to benzyne. Compound **8-20** should be produced from **8-19** by elimination of sulfur, although the mechanism of the formation **8-21** is not clear.



Aprotic diazotization of the sulfinylaniline **8-22** produces biphenylene and dibenzo-1,4-thioxine **8-23**.^{83,84} The formation of **8-23** is rationalized by formation of benzoxathiete and its ring opening to monothio-*o*-benzoquinone, followed by cycloaddition to benzyne formed concomitantly by a competing pathway. Evidence for the intermediacy of benzyne was given by trapping experiments; reactions in the presence of 1,3-diphenylisobenzofuran and 9,10-dimethylantracene afford the expected benzyne adducts in reasonable yields.

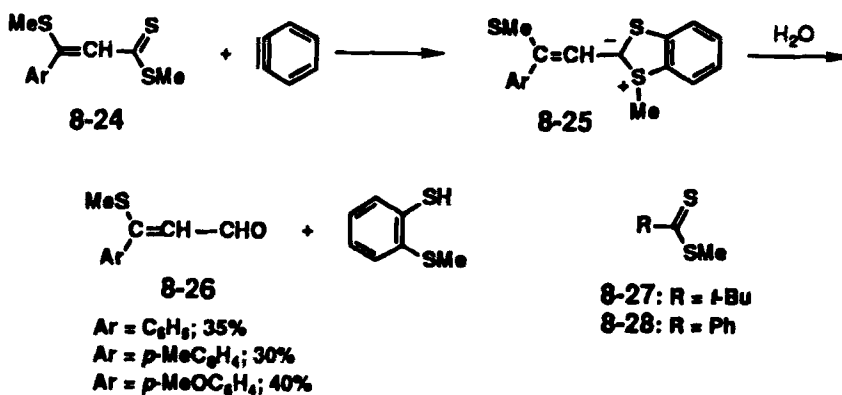


Phenyl isothiocyanate, though not a thioketone, was reported to react with benzyne, generated by treatment of fluorobenzene with phenyllithium, to give the compounds shown below.⁸⁵



8.3. Reactions with Dithioesters and Related Compounds

Benzynes react with dithioesters and related compounds in a 1,3-dipolar cycloaddition manner to give five-membered sulfonium ylides as the initial adducts. Thus, benzyne generated by aprotic diazotization of anthranilic acid reacts with the α,β -unsaturated dithioesters **8-24** probably to give five-membered sulfonium ylides **8-25** as the initial adducts.⁸⁶ The ylides **8-25** then collapse to the aldehydes **8-26** and *o*-(methylthio)thiophenol **8-27** by hydrolysis with contaminating water. The dithioesters **8-27** and **8-28** are also converted to the corresponding aldehydes on reaction with benzyne.



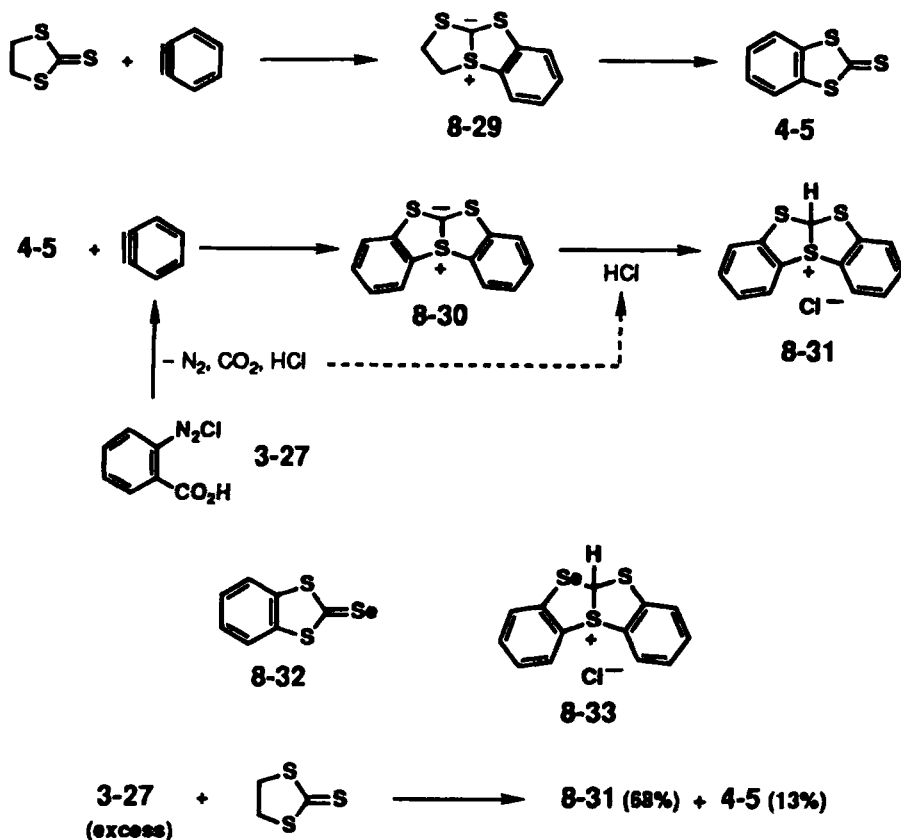
As already described in Section 4, ethylene trithiocarbonate reacts with benzyne, generated by aprotic diazotization of anthranilic acid, thermolysis of diphenyliodonium-2-carboxylate (**5-1**), or oxidation of 1-aminobenzotriazole (**8-5**) to give 1,3-benzodithiole-2-thione (**4-5**), though in low yields (8–13%).^{87–89} The reaction probably proceeds via the initial formation of the ylide **8-29**. The low yield of **4-5** may be attributed to further reaction of **4-5** with benzyne, to give the ylide **8-30** which does not have any favorable collapsing pathways. In fact, the reaction of **4-5** with benzyne, generated by aprotic diazotization of anthranilic acid, gives a complex mixture from which no pure compounds could be isolated.⁹⁰ However, the reaction of **4-5** with benzyne, generated by thermolysis of **3-27**, gives a 91% yield of the sulfonium chloride **8-31** which possesses a novel ring structure.⁹¹ The chloride **8-31** is apparently the product of trapping of the ylide **8-30** by hydrogen chloride produced from **3-27**. In a similar way, 1,3-benzodithiole-2-selone (**8-32**) reacts with benzyne generated from **3-27** to give the sulfonium chloride **8-33** in 82% yield. A synthetically more important one is the reaction of ethylene trithiocarbonate with excess **3-27**, which gives the salt **8-31** directly in 68% yield in one pot together with **4-5** (13%) which is the intermediate leading to **8-31**.

TABLE 8-1 Reactions of thiadiazolethiones 8-34 with benzyne

8-34		yield of 8-35 (%)	
R ¹	R ²	method A ^{a)}	method B ^{b)}
CH ₃	CH ₃	58	53
C ₆ H ₅	H	64	61
C ₆ H ₅	CH ₃	63	98
C ₆ H ₅	COCH ₃	73	94
<i>p</i> -BrC ₆ H ₄	H	41	71
<i>p</i> -BrC ₆ H ₄	CH ₃	59	91

^{a)}Method A: Diphenyliodonium-2-carboxylate 5-1 as benzyne source.

^{b)}Method B: Aprotic diazotization of anthranilic acid as benzyne source.

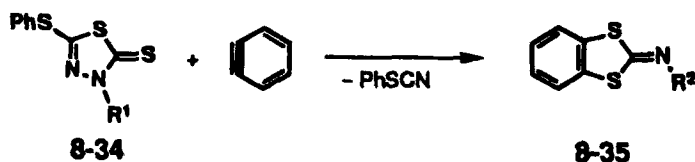


1,3-Dipolar cycloaddition of thiadiazolethiones 8-34 with benzyne, followed by elimination of phenyl thiocyanate, gives 2-imino-1,3-benzodithioles 8-35 in good yields (Table 8-1).⁹²

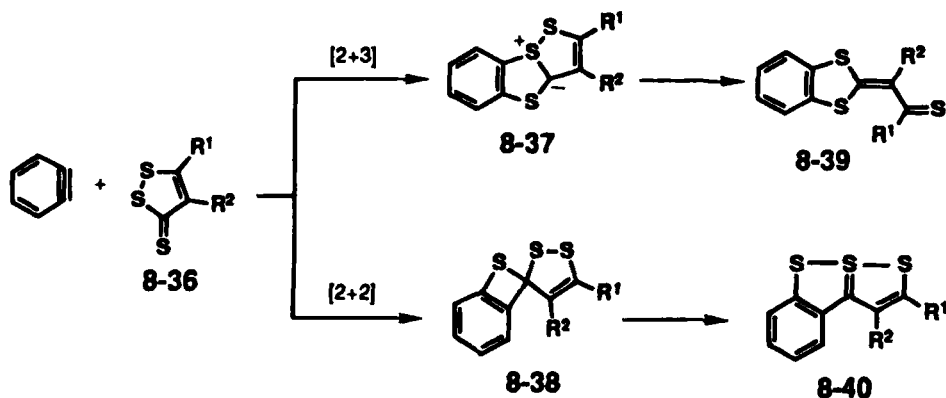
TABLE 8-2 Reactions of 1,2-dithiole-3-thiones **8-36** with benzyne

8-36		yield (%)		benzyne source ^{a)}	references
R ¹	R ²	8-39	8-40		
C ₆ H ₅	H	28	—	A	87,88
C ₆ H ₅	H	trace	—	B	87
C ₆ H ₅	H	7	—	C	87
C ₆ H ₅	H	55	—	D	87
C ₆ H ₅	H	37	18	C	89,92
C ₆ H ₅	H	46	15	A	89,92
Me	Me	37	0.5	C	89,92
Me	Me	35	1	A	92
p-MeC ₆ H ₄	H	52	34	C	92
p-MeC ₆ H ₄	H	45	—	A	89,92
p-ClC ₆ H ₄	H	44	3	C	89,92
p-ClC ₆ H ₄	H	44	3	A	89,92
p-MeOC ₆ H ₄	H	33	—	C	89,92
p-MeOC ₆ H ₄	H	29	—	A	89,92
C ₆ H ₅	Me	66	—	C	89,92
C ₆ H ₅	Me	72	—	A	89,92
C ₆ H ₅	Me	67	—	A	93,94
-(CH ₂) ₄ -		51	—	C	92
-(CH ₂) ₄ -		59	—	A	92

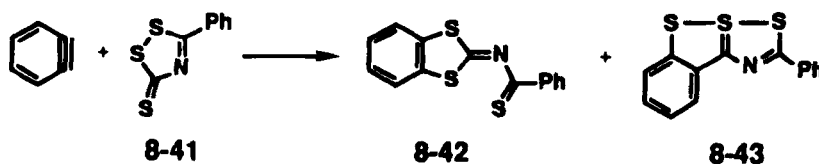
^{a)}A: Aprotic diazotization of anthranilic acid. B: Benzenediazonium-2-carboxylate. C: Diphenyliodonium-2-carboxylate. D: Oxidation of 1-aminobenzotriazole.



A series of 1,2-dithiole-3-thiones **8-36** also react with benzyne, generated from several precursors, to give 1,3-benzodithioles **8-39** and, in some cases, trithiapentalenes **8-40** (Table 8-2).^{87-89,92-94} The dithioles **8-39** are formed by 1,3-dipolar cycloaddition, probably via the ylide intermediates **8-37**, the trithiapentalenes **8-40** by [2 + 2] cycloaddition via the spiro compounds **8-38**.



The same reaction also takes place between benzyne and 8-41, an aza analog of 8-36. Benzyne generated from 5-1 gives 8-42 and 8-43 in 33% and 1% yield, respectively, and benzyne formed by aprotic diazotization of anthranilic acid gives 8-42 in 45% yields.^{89,92}

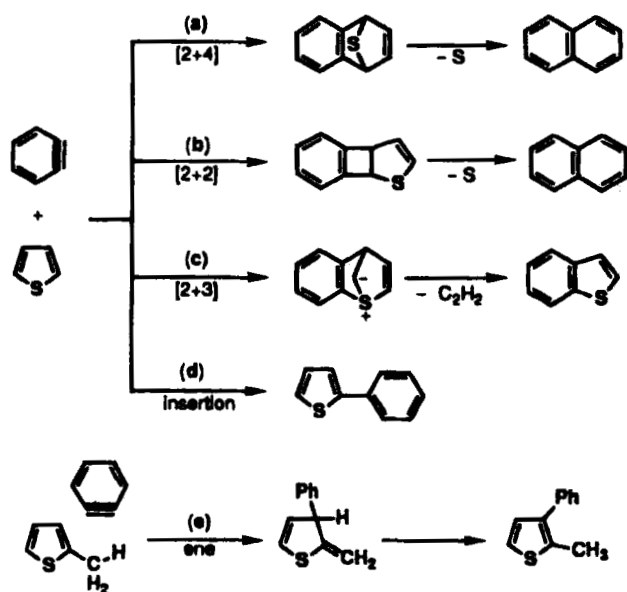


9. REACTIONS OF BENZYNE WITH AROMATIC FIVE-MEMBERED HETEROCYCLIC COMPOUNDS

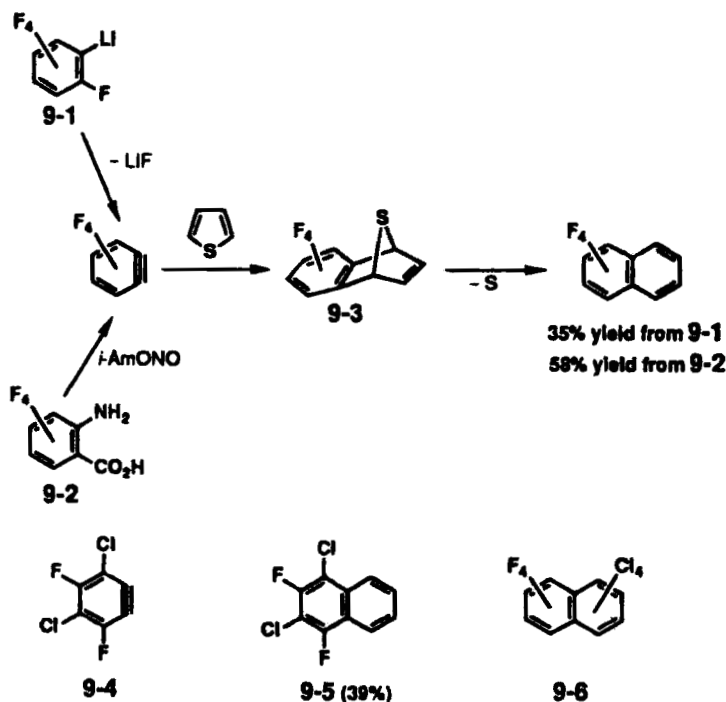
9.1. Reactions with Thiophenes

Thiophene is considered to be the most aromatic of the five-membered heterocycles, and as such its reactivities as ene or diene are low. However, benzyne is capable of reacting with thiophenes in many ways including (a) [2 + 4] cycloadditions, (b) [2 + 2] cycloadditions, (c) [2 + 3] cycloadditions, (d) C-H insertions, and (e) ene reactions for compounds with thenyl hydrogens, but the reactions usually give complex mixtures in low yields and are usually not of synthetic importance.

The strongly electrophilic 3,4,5,6-tetrafluorobenzyne undergoes [2 + 4] cycloaddition with thiophene to give the adduct 9-3 which extrudes sulfur to produce 1,2,3,4-tetrafluoronaphthalene in reasonable yield.⁹⁵⁻⁹⁷ When the benzyne was generated from 9-1, a product assumed to be 9-3 was isolated in a small amount along with 1,2,3,4-tetrafluoronaphthalene.^{95,96} 3,5,2,6-Dichlorodifluorobenzyne 9-4 also reacts with thiophene to give the naph-

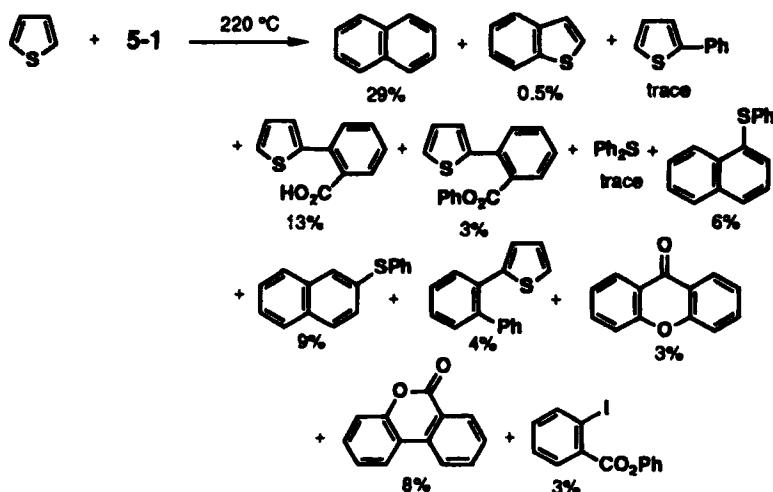


thalene **9-5** in 39% yield.⁹⁸ 3,4,5,6-Tetrafluorobenzynes can react even with tetrachlorothiophene to give the naphthalene **9-6**, though in low yield.⁹⁶

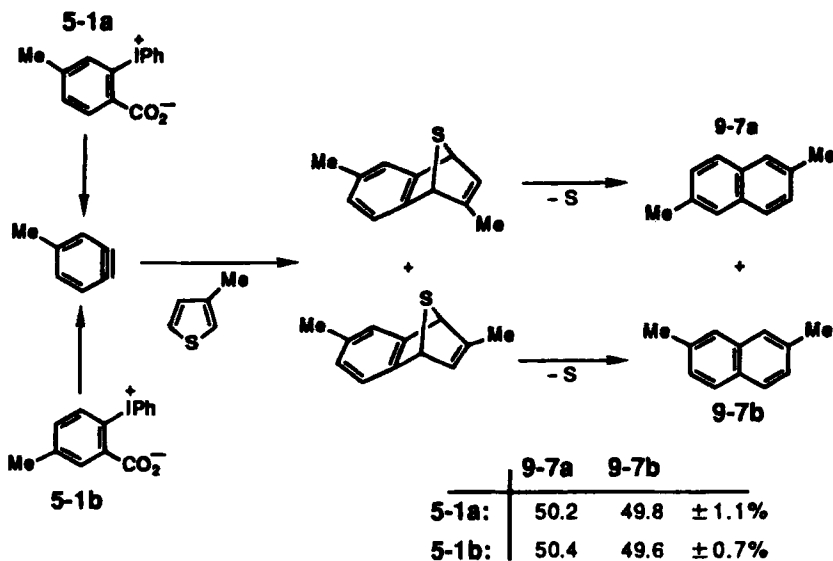


The reaction of benzyne with thiophene was examined in detail with six different benzyne precursors, (1) benzenediazonium-2-carboxylate, (2) benzothiadiazole dioxide, (3) diphen-

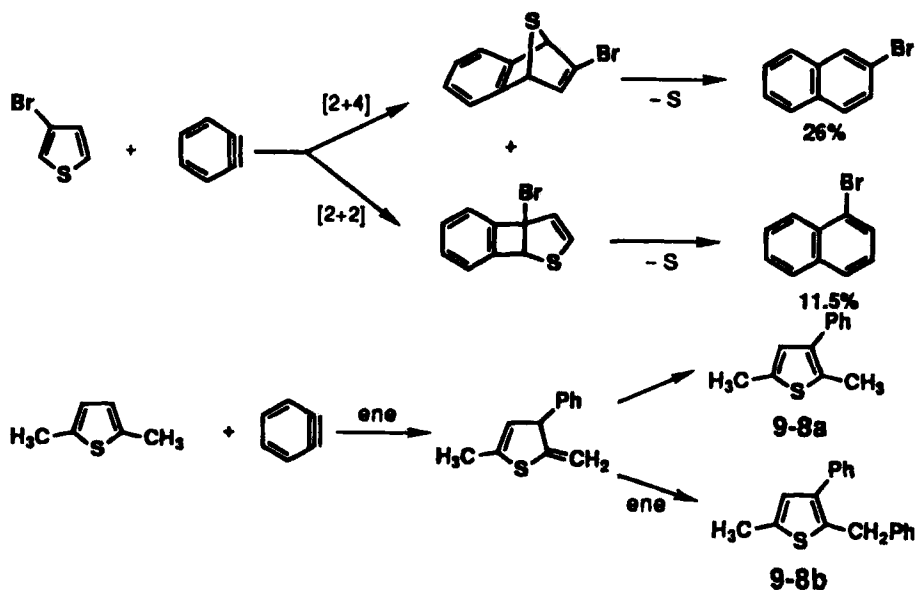
yliodonium-2-carboxylate, (4) *o*-fluorophenylmagnesium bromide (*o*-fluorobromobenzene + Mg), (5) *o*-fluorophenyllithium (*o*-fluorobromobenzene + BuLi), and (6) the nitrene produced by oxidation of 1-aminobenzotriazole.⁹⁹⁻¹⁰² The most satisfactory system proved to be diphenyliodonium-2-carboxylate (5-1) at 220 °C, where the yield of the product derived from benzyne + thiophene approached 50%, the major product being naphthalene (29%). All of the products produced by this reaction are given below.¹⁰¹



In the above reaction naphthalene arises from [2 + 4] cycloaddition, benzo[*b*]thiophene from [2 + 3] cycloaddition, and 2-phenylthiophene from C-H insertion. The following observations provide evidence that the naphthalene formation is due to [2 + 4] cycloaddition; the benzyne generated from 5-1a and the one from 5-1b react with 3-methylthiophene to give mixtures of 9-7a and 9-7b in equal proportions.¹⁰¹

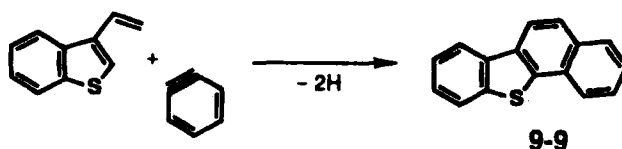


The reactions of 11 mono- and disubstituted thiophenes with benzyne generated from **5-1** were studied under a standard set of conditions.¹⁰² The major products were naphthalenes whose substitution patterns indicated that both [2 + 4] and [2 + 2] cycloaddition occurred, with the former predominating. However, it was found that a significant proportion of naphthalenes is formed by [2 + 2] cycloaddition in the case of 3-halothiophenes such as 3-bromo- and 3,4-dibromothiophene. And also, in several reactions, benzothiophenes are formed in low yields by [2 + 3] cycloaddition, probably via sulfonium ylide intermediates. In addition, ene and especially double ene products were formed with alkylthiophenes. For example, the reaction with 2,5-dimethylthiophene affords the ene product **9-8a** and the double ene product **9-8b** in 7% and 13% yield, respectively.

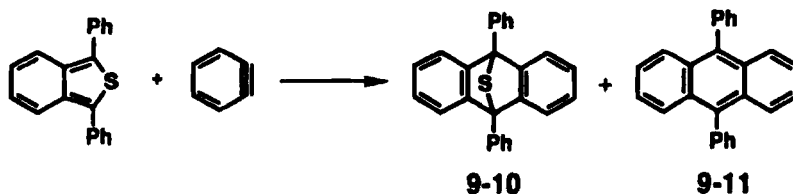


The reaction of benzyne with thiophene in the gas phase has also been reported.¹⁰³⁻¹⁰⁵ Benzyne generated from phthalic anhydride at 690 °C reacts with thiophene to give naphthalene and benzo[*b*]thiophene by [2 + 4] and [2 + 3] cycloaddition, respectively, as well as 2-phenylthiophene by C-H insertion.¹⁰⁴

3-Vinylbenzo[*b*]thiophene undergoes [2 + 4] cycloaddition with benzyne (generated from *o*-fluorobromobenzene + Mg) to give **9-9** in 14% yield.¹⁰⁶

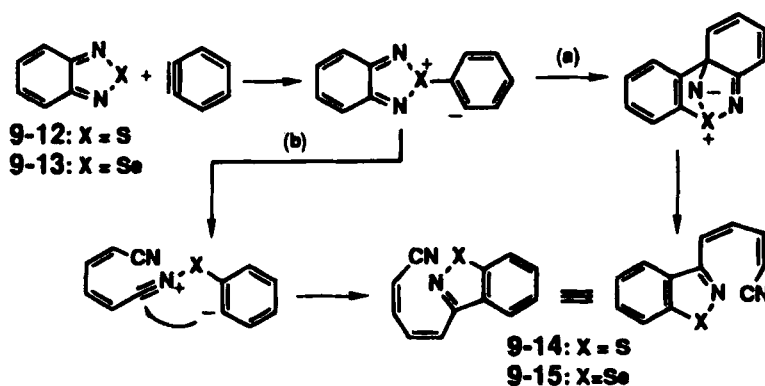


Benzyne, generated from *o*-fluorophenylmagnesium bromide, undergoes [2 + 4] cycloaddition with 2,5-diphenylbenzo[*c*]thiophene to give **9-10** and **9-11** in 9% and 14% yield, respectively, with 42% recovery of starting material.¹⁰⁷



9.2. Reactions with Other Five-membered Sulfur-containing Aromatic Heterocyclic Compounds

The benzothiadiazole **9-12** reacts with benzyne to give **9-14** in low yields (5% yield with benzyne from **3-37** and 10% yield with benzyne from the oxidation of 1-aminobenzotriazole).^{63,108} The same reaction occurs with benzoselenadiazole **9-13** to give **9-15** in good yields (88% yield with benzyne from **3-37** and 85% yield with benzyne from oxidation of 1-aminobenzotriazole). The plausible mechanisms given below were proposed to account for the formation of **9-14** and **9-15**.



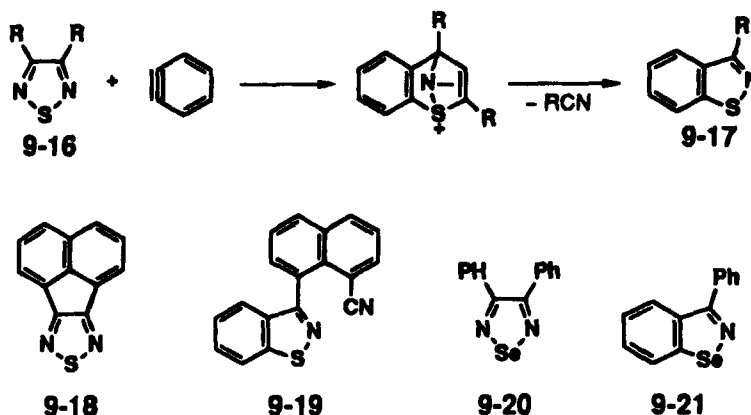
A series of thiadiazoles **9-16** react with benzyne, generated from **3-37**, to give the benzoisothiazoles **9-17** (Table 9-1).^{109,110} The fused thiadiazole **9-18** also affords the thiazole **9-19** in 88% yield. A mechanism involving a 1,3-dipolar cycloaddition of benzyne across

TABLE 9-1 Reactions of 1,2,5-thiadiazoles with benzyne

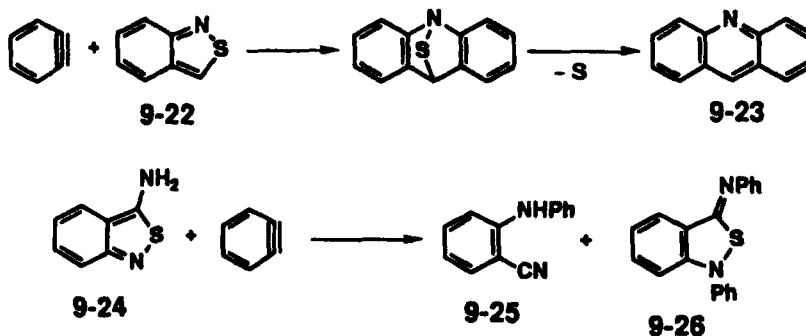
thiadiazole 9-16 R	benzoisothiazole 9-17 yield (%) ^a
H	25 (74)
Me	31 (62)
Cl	35 (55)
OEt	75 (83)
CN	36 (60)
(CH ₂) ₄ (R,R)	30 (53)

^aThe figure in parenthesis is corrected for recovered thiadiazole.

a C=N-S group was proposed to explain the formation of **9-17** and **9-19**. The selenazole **9-20** with benzyne likewise affords the benzoselenazole **9-21** in 90% yield.



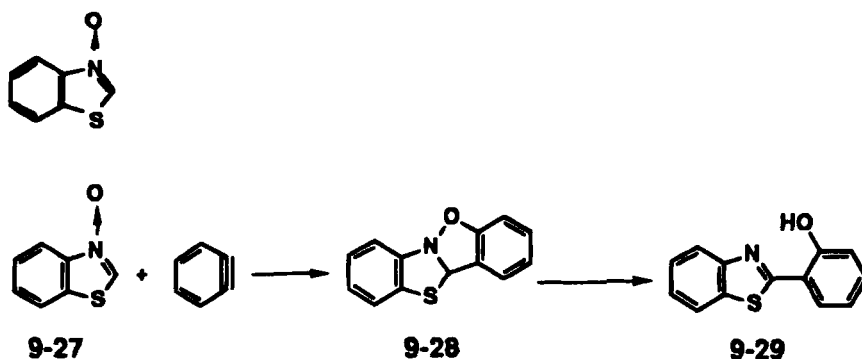
The reaction of the benzoisothiazole **9-22** with benzyne (2 equiv.) affords acridine (**9-23**) in 5% yield with 37% recovery of **9-22**.¹⁰ On the other hand, the reaction with the amine derivative **9-24** gives **9-25** and **9-26**, though in low yields (5% and 4%, respectively).



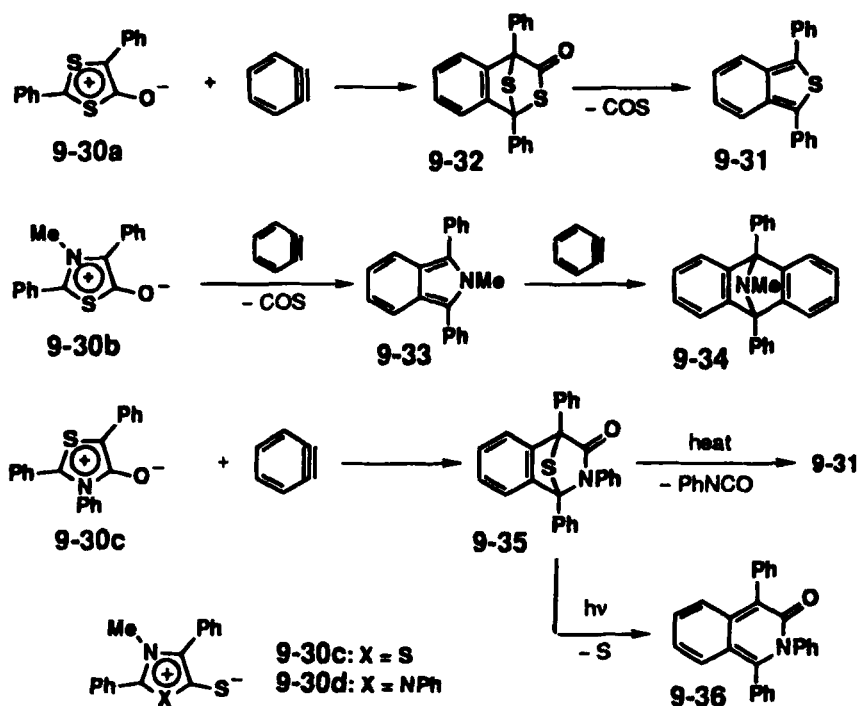
Benzoisothiazole 3-oxide (**9-27**) undergoes 1,3-dipolar cycloaddition with benzyne, generated from **3-37**, to give **9-28** whose ring opening affords **9-29** as the final product in a reasonable yield.¹¹

9.3. Reactions with Mesoionic Compounds

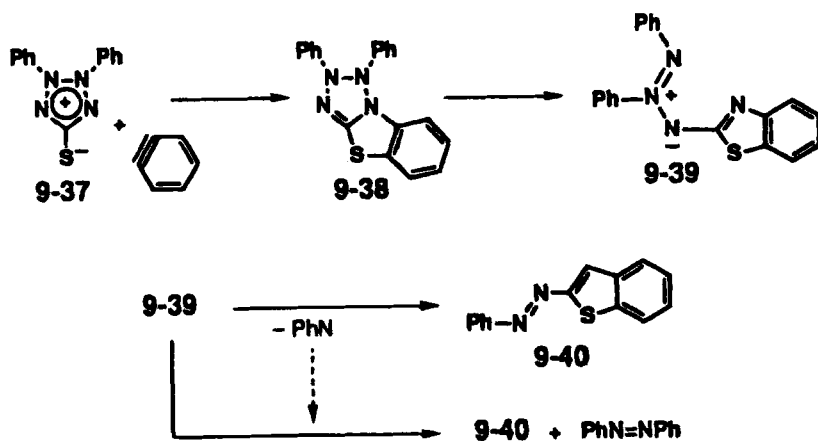
Reactions of benzyne, generated by oxidation of 1-aminobenzotriazole with $\text{Pb}(\text{OAc})_4$, with mesoionic compounds have been studied in some detail. Treatment of the mesoionic



compound **9-30a** with benzyne affords the isobenzothiophene **9-31** in 36% yield along with *o*-dibenzoylbenzene and an adduct ($C_{23}H_{18}O_3S_2$, 21%) of the intermediate **9-32** with acetic acid produced from $Pb(OAc)_4$.^{112,113} The corresponding reaction with **9-30b** gives the isoindole **9-33** (4%) and the iminoanthracene **9-34** (11%).^{112,113} The reaction with **9-30c** allows the isolation of the initial adduct **9-35** in 78% yield, which is converted to **9-31** on thermolysis in 67% yield and to **9-36** on photolysis in 60% yield.¹¹³ The reaction of **9-30c** and **9-30d** with benzyne gave inconclusive results, probably because of the oxidation of these substrates by $Pb(OAc)_4$.



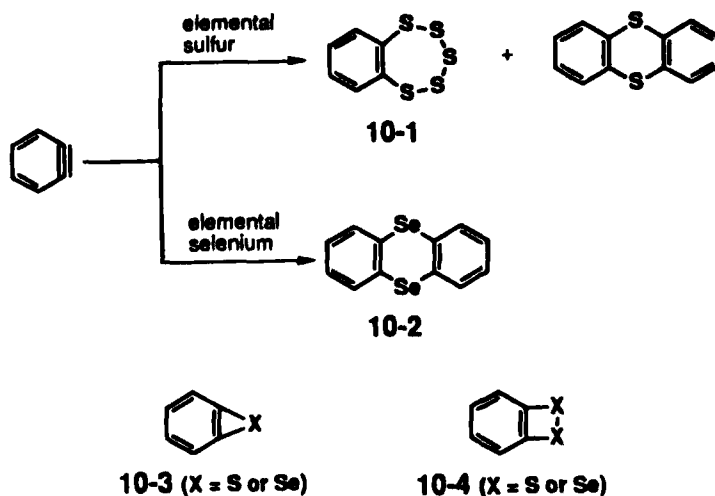
Benzyne generated by aprotic diazotization of anthranilic acid undergoes a 1,3-dipolar cycloaddition with dehydrodithione **9-37** to give the azimine **9-39** in 39% yield.^{114,115} When the reaction was conducted at higher temperature, azobenzene (9%) and 2-(phenylazo)benzothiazole (**9-40**) (11%) were obtained by thermal decomposition of **9-39**.¹¹⁶



10. REACTIONS WITH ELEMENTAL SULFUR

As already touched upon in Section 8.1, benzyne seemingly reacts with sulfur to give dibenzothiophene and thianthrene.⁶⁹

The reaction of benzyne with elemental sulfur in the liquid phase has also been reported.¹¹⁷ Benzyne, generated by thermolysis of **5-1** in refluxing *o*-dichlorobenzene, reacts with sulfur to give benzopentathiepin (**10-1**) and thianthrene in 6% and 5% yield, respectively. The reaction with benzyne, generated by thermolysis of **3-27**, likewise gives **10-1** (4%) and thianthrene (12%). Elemental selenium also reacts with benzyne generated from **5-1** to give selenanthrene (**10-2**) in 26% yield, thus providing a one-pot synthesis of **10-2**; precursor compound **5-1** is commercially available. For the formation of thianthrene and selenanthrene, intermediates such as **10-3**, **10-4**, and their equivalents may be involved.



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