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PREPARATION OF 1-PHENYLTHIO-1,3-DIENES BY REACTION OF 2,5-DIHYDROTHIOPHENES WITH BENZYNE THROUGH FRAGMENTATION OF SULFONIUM YLIDE INTERMEDIATES

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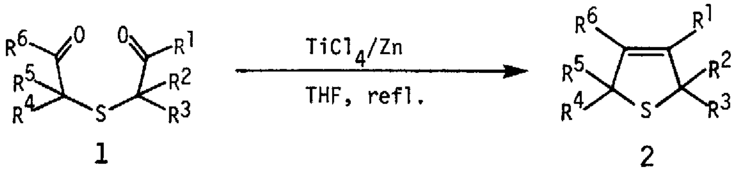
Summary: The reaction of a series of 2,5-dihydrothiophenes with benzyne, generated from 2-carboxybenzenediazonium chloride, affords 1-phenylthio-1,3-dienes in good yields through the fragmentation of sulfonium ylide intermediates.

We have recently developed a convenient synthesis of 2,5-dihydrothiophenes (2), which involves intramolecular reductive coupling of easily accessible diketo sulfides (1).[1] This allows the easy preparation of 2 in large quantities. We have been also interested in the synthetic use of the fragmentation of sulfonium ylides produced by reaction of cyclic sulfides with benzyne.[2] In this connection, we report here that the reaction of a series of 1 with benzyne affords 1-phenylthio-1,3-dienes (4) in good yields through the fragmentation of sulfonium ylide intermediates.



We have chosen 2-carboxybenzenediazonium chloride (3) as the benzyne precursor.[3] Thus, a mixture of 3,4-diphenyl-2,5-dihydrothiophene (2a; 1 mmol)[1] and 3 (1.2 mmol) was heated in refluxing 1,2-dichloroethane (50 ml) for 45 min in the presence of propylene oxide (0.3 ml) as the hydrogen chloride scavenger. Purification of the mixture by column chromatography on silica gel gave 1-phenylthio-2,3-diphenyl-1,3-butadiene (4a) in 76% yield, which consists of a mixture of Z- and E-isomers in the ratio 86:14. 3,4-Diphenylthiophene (5a) was also obtained in 8% yield as a minor product. In a similar way, several 3,4-diaryl-2,5-dihydrothiophenes 2b-e[1] were allowed to react with benzyne. Results summarized in Table 1 show that 1-phenylthio-1,3-dienes 4b-e are formed in good yields and also the Z-isomers are formed in preference to the corresponding E-isomers. 3,4-Diarylthiophenes 5b-e were also obtained in low yields in every case. In ^{1}H-NMR spectra (CDCl$_3$ as solvent), the vinyl hydrogen at C-1 of the Z-isomers of 4a-e, which is cis to the adjacent aryl substituent, appears at a lower field than that of the corresponding E-isomers.[4] For example, the vinyl hydrogen at C-1 of the Z-isomer of 4a appears at δ 6.87 as singlet, while that of the E-isomer at δ 6.40 as singlet; two vinyl hydrogens at C-4 of the Z-isomer appear at δ 5.32 and 5.89 as doublet, while those of the E-isomer at δ 4.93 and 5.13 as doublet.

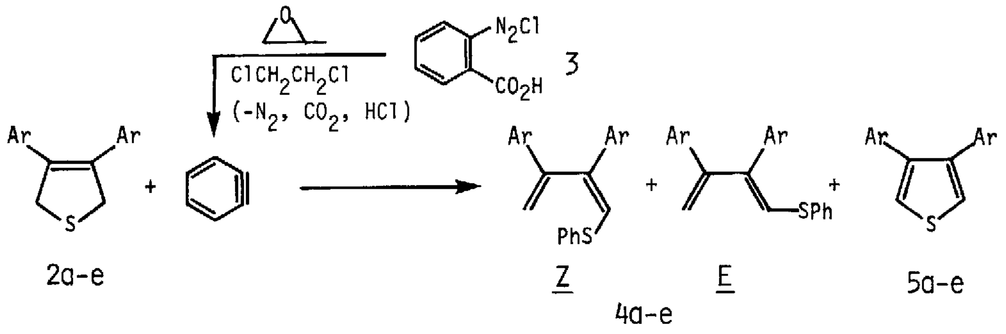
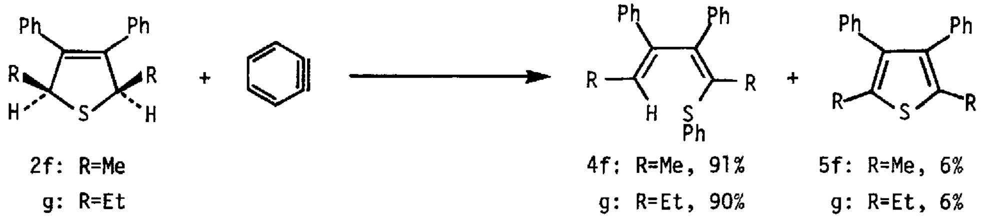


Table 1 Reaction of 3,4-Diaryl-2,5-dihydrothiophenes 2a-e with Benzyne[a)]

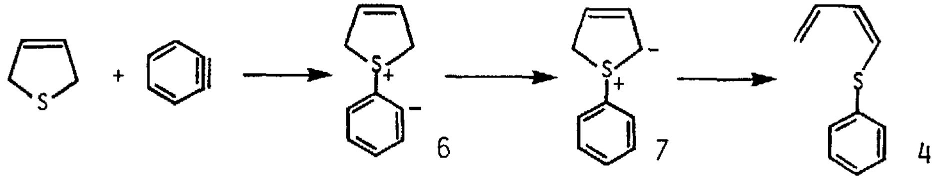
	a	b	c	d	e
Ar	C_6H_5	4-MeC_6H_4	4-MeOC_6H_4	3-Naphthyl	2-Thienyl
Yield of 4 (%)	76	86	62	74	76
Z:E	86:14	93:7	80:20	90:10	84:16
Yield of 5 (%)	8	12	20	21	12

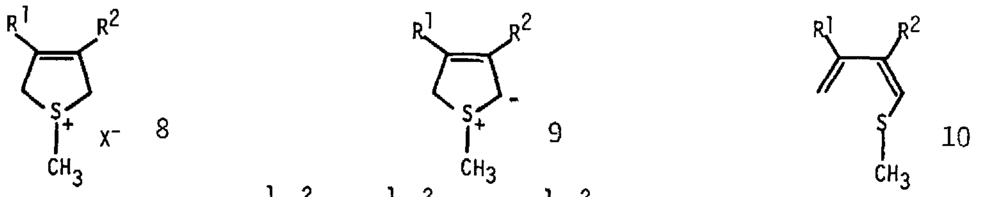
a) In every case 1.2 equiv of 3 was used.

The reaction of cis-2,5-dimethyl-3,4-diphenyl-2,5-dihydrothiophene (2f)[5] with benzyne cleanly gave a configurationally pure 1-phenylthio-1,3-diene in 91% yield in a stereospecific manner along with 2,5-dimethyl-3,4-diphenylthiophene (5f) in 6% yield. The thiodiene was tentatively assigned as 4f mainly on the basis of mechanistic grounds (vide infra); ^{1}H-NMR ($CDCl_3$) δ 1.90 (3H, d, MeCH=), 1.99 (3H, s, Me), 6.07 (1H, q, MeCH=), 6.9-7.5 (15H, m, Ph). Benzyne also cleanly reacted with cis-2,5-diethyl-3,4-diphenyl-2,5-dihydrothiophene (2d)[5] in a stereospecific manner to give the diene (4g) and the thiophene (5g) in 90% and 6% yields, respectively.



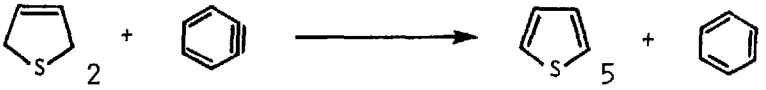
The initial step of the present reaction probably involves the formation of betaines 6, which then give rise to the ylide intermediates 7.[6] The fragmentation of 7 should lead to the final products 4 (substituents on the dihydrothiophene ring are omitted for simplicity in the scheme). This type of fragmentation is precedented.[7,8] Treatment of sulfonium salts 8 with base affords the ylides 9, which undergo the fragmentation to give the thiodienes 10 in varying yields.[7,9] The reaction is stereoselective and the dienes presumably have the configuration shown. The authors explained the stereoselctive formation of 10 on the principle of least motion.[10] An alternative explanation seems possible in the present case, however; the fragmentation can be presumed as an electrocyclic process of 6 electron system which occurs in a concerted disrotatory manner.[11] This well accounts for the stereospecific formation of a single configurational isomer from 2f and 2g. In the case of 2a-e, the Z-dienes initially formed may partially isomerize to the corresponding E-dienes by acid catalyst (hydrogen chloride formed from 3).





$R^1=R^2=Me$; $R^1=R^2=CO_2Me$; $R^1,R^2= -(CH_2)_4-$

The most probable explanation for the formation of thiophenes 5 involves the transfer of two hydrogens from dihydrothiophenes to benzyne to afford 5 and benzene, which presumably occurs in a concerted symmetry-allowed process.[12]



Next we examined the reaction of unsymmetrically substituted 2,5-dihydrothiophenes (2h-l)[1,5] with benzyne. Results are summarized in the scheme (see next page). The reaction of 2h and 2i with benzyne cleanly afforded thiodienes 4h (73%) and 4i (94%), respectively, which are configurationally pure. The reaction of 2j-l with benzyne becomes rather complex because two ylide intermediates are formed from one substrate since hydrogen exists at α- and α'-positions of the sulfide moiety and the fragmentation of each ylide results in the formation of positional isomers of thiodienes. Configuration of thiodienes 4h-l has not been rigorously established by ^{1}H-NMR analysis and tentatively assigned on mechanistic grounds.

In summary the reaction of 2,5-dihydrothiophenes 2, which has recently become readily obtainable, with benzyne provides a convenient synthesis of polysubstituted 1-phenylthio-1,3-dienes 4, which are synthetically of great importance, but are otherwise rather difficult to prepare.[13]

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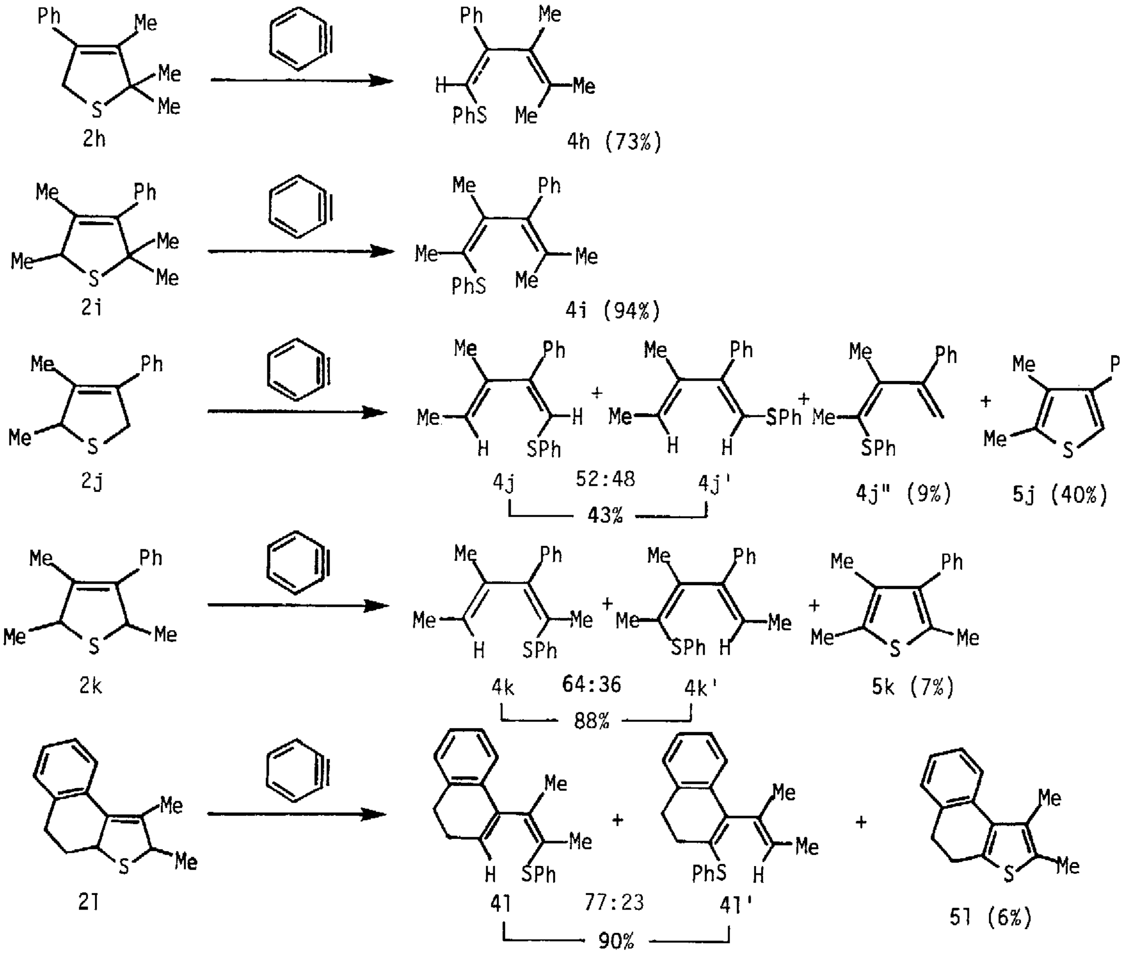

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