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REACTIONS OF BENZYNE WITH SULFIDES HAVING A CARBOXYL GROUP. A NOVEL SYNTHESIS OF ESTER AND LACTONE

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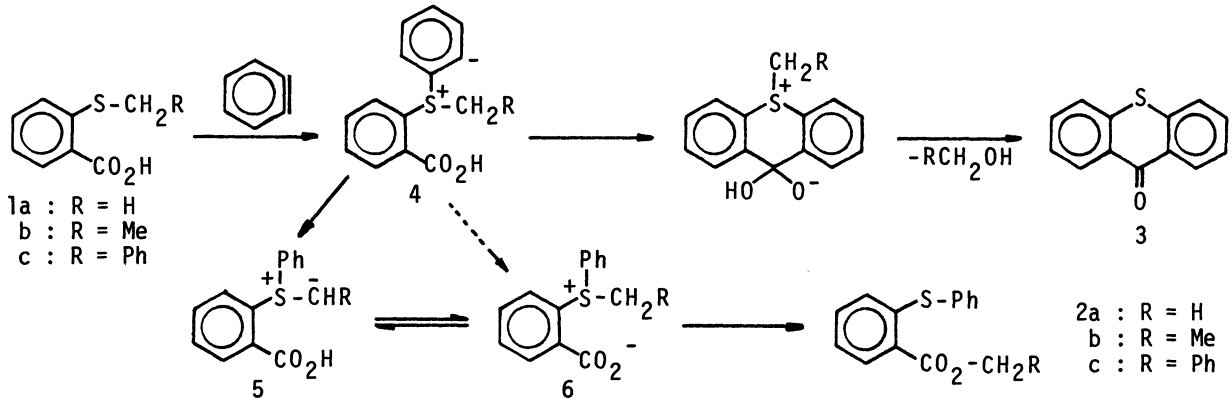
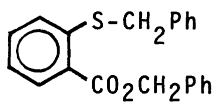
Reactions of benzyne with *o*- and *p*-(alkylthio)benzoic acids afford alkyl *o*- and *p*-(phenylthio)benzoates in varied yields, while reaction with *o*-(phenylthio)methylbenzoic acid gives phthalide and diphenyl sulfide in good yields.

Reaction of benzyne with sulfide is one of promising and the most straightforward method for producing a sulfonium ylide.$^{1)}$ There has been no report concerning the synthetic use of the ylide generated by this method, however, probably because the reaction was investigated mainly from a mechanistic point of view. As a first step of our study directed toward the synthetic use of this ylide, we examined the reaction of benzyne with a sulfide having a carboxyl group. In 1969 Heaney et al. reported that the ylide produced from tetrachlorobenzyne and thioanisole reacts with tetrachlorophthalic acid to give dimethyl tetrachlorophthalate.$^{2)}$

Aprotic diazotization of anthranilic acid followed by thermolysis of the resulting benzenediazonium-2-carboxylate is the method chosen as a source of benzyne.$^{3)}$ To a gently refluxing solution of *o*-(methylthio)benzoic acid (**1a**)$^{4)}$ (10 mmol) and isoamyl nitrite (12.5 mmol) in 1,2-dichloroethane (100 ml) was added dropwise a solution of anthranilic acid (12 mmol) in dioxane (10 ml) over a period of 20 min. After completion of the addition, the mixture was refluxed for 30 min. Workup of the mixture by column chromatography on silica gel afforded methyl *o*-(phenylthio)benzoate (**2a**) (56%), bp 140 °C/0.9 mmHg (Kugelrohr) (mp 46-47.5 °C),$^{5)}$ and thioxanthone (**3**) (2%). The ester (**2a**) must be produced from the ylide (**5**) via (**6**) by methylene transfer to the carboxyl group (**6** may be produced from the betaine **4** directly). Compound **3** must be produced as depicted.$^{6)}$

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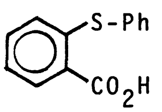
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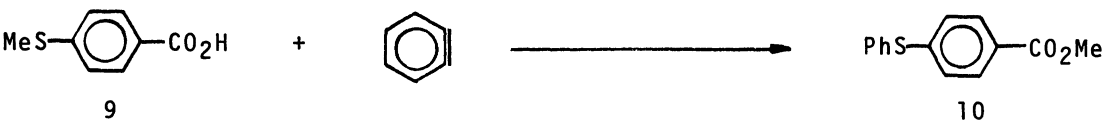

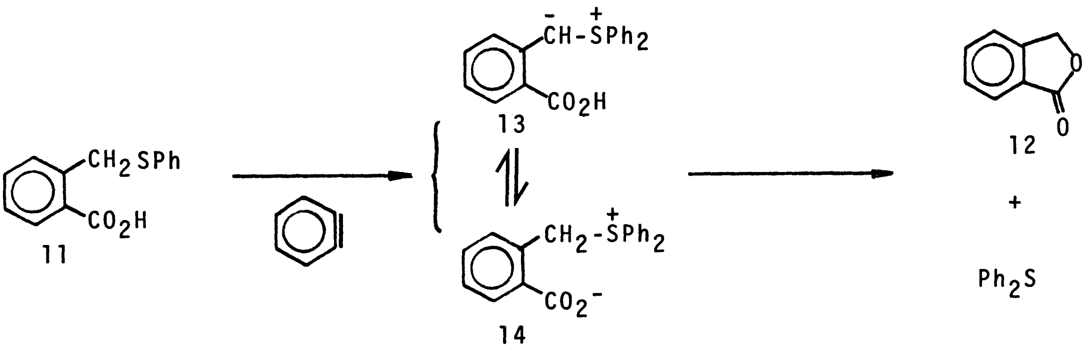

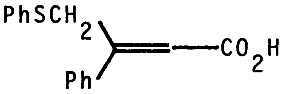
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In a similar way, benzyne reacted with *o*-(ethylthio)benzoic acid (**1b**)[4] to give the ester (**2b**) (26%), bp 150 °C/1 mmHg (Kugelrohr) (lit.,[7] mp 38 °C) and **3** (3%). In the reaction with *o*-(benzylthio)benzoic acid (**1c**),[4] however, benzyl *o*-(benzylthio)benzoate (**7**)[8] (16%), mp 111.5-112 °C and a small amount of *o*-(phenylthio)benzoic acid (**8**), mp 166.5-167 °C (lit.,[9] mp 166-167 °C) were obtained in addition to the expected ester (**2c**)[8] (32%), mp 42.5-43 °C. In compound **7** the benzyl group of **1c** remains unchanged, though the carboxyl group is benzylated, while in compound **8** the carboxyl group remains untouched, though the benzyl group is displaced by a phenyl group. The formation of these products indicates that the transfer of alkylidene group to the carboxyl group in the ylides occurs both intra- and inter-molecularly, despite the presence of a geometry that would appear to favor an intramolecular reaction. In fact, even in the reaction with *p*-(methylthio)benzoic acid (**9**)10) where intramolecular reaction is unlikely, methyl *p*-(phenylthio)benzoate (**10**) (82%), mp 73-74 °C (lit.,11) mp 69-70 °C) was obtained, when 1.7 mol. equiv. of anthranilic acid was employed (the use of 1.2 mol. equiv. of anthranilic acid gave **10** in 63% yield).

The reaction was next applied to the synthesis of lactone. Thus, *o*-(phenylthio)methylbenzoic acid (**11**)12) was first chosen as a model compound, since we thought that the ylide (**13**) could undergo an intramolecular cyclization via (**14**) to give phthalide (**12**) with elimination of diphenyl sulfide. Expectedly the reaction worked satisfactorily to give **12** (79%), mp 70.5-71 °C, and diphenyl sulfide (82%). When the reaction was applied to 4-(phenylthio)butanoic acid,13) however, the expected γ-butyrolactone was not obtained, although diphenyl sulfide (82%) was produced.14) The both E- and Z-isomers of the carboxylic acid (**15**) were also prepared,15) and allowed to react with benzyne. The both isomers gave a complex mixture disappointingly.16)

The method developed here for preparation of ester and lactone is new and unique, although it seems to have somewhat limited utility. In any event the results suggest that the ylides generated from benzyne and sulfides can be used in organic synthesis in many ways and may stimulate additional efforts in this field.

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References

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3) F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth.*, **48**, 12 (1967).

4) These compounds were prepared from thiosalicylic acid and the corresponding alkyl halides in good yields.

5) W. G. Bentrude and J. C. Martin, *J. Am. Chem. Soc.*, **84**, 1561 (1962).

6) Compound **3** (4%), mp 212-212.5 °C, was also obtained along with methyl *o*-(phenylthio)benzoate (42%), when methyl *o*-(methylthio)benzoate was allowed to react with benzyne.

7) A. Mustafa and O. H. Hishmat, *J. Am. Chem. Soc.*, **75**, 4647 (1953).

8) ^{1}HNMR ($CDCl_3$): **7** δ 4.15 (s, 2H), 5.38 (s, 2H), 7.1-7.6 (m, 13H), and 7.9-8.1 (m, 1H): **2c** δ 5.40 (s, 2H), 6.7-8.7 (m, 13H), and 7.9-8.2 (m, 1H).

9) I. Goldberg, *Ber.*, **37**, 4526 (1905).

10) This compound was prepared from *p*-(methylthio)benzaldehyde by oxidation with silver oxide in a good yield.

11) D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, **22**, 323 (1957).

12) M. Rajsner, Z. Vejdgelek, V. Seidlova, and M. Protiva, Czech. Patent 105,353, (1963); *Chem. Abstr.*, **60**, 1656 (1964).

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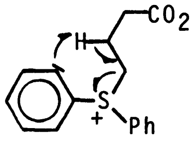
14) Diphenyl sulfide must be produced along with 3-butenoic acid in a fashion like (**16**). This type of reaction is not unprecedented: H. Hellmann and D. Eberle, *Ann.*, **662**, 188 (1963).



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15) The Wittig reaction of phenyl phenacyl sulfide with ethoxycarbonylmethylenetriphenylphosphorane afforded a mixture of E- and Z-isomers (ca. 3:1, 80%) of the expected olefin. Each isomer was separated by column chromatography and then hydrolyzed. Although E isomer, mp 136.5-137.5 °C, ^{1}HNMR ($CDCl_3$) δ 3.80 (s, 2H), 6.78 (s, 1H), 7.0-7.5 (m, 10H), and ca. 8.5 (broad s, 1H), was obtained in a pure form, Z isomer could not be obtained in a pure form since alkaline hydrolysis was accompanied by *cis-trans* isomerization, and therefore Z isomer containing ca. 30% of E isomer was employed for the reaction with benzyne.

16) Diphenyl sulfide (30-40%) and the phenyl ester of **15** (4-5%) were identified products. The E isomer of the phenyl ester, mp 72.5-73.5 °C, was identified by comparison with an authentic sample which was prepared from the E isomer of the carboxylic acid **15** and phenol in the presence of *N*,*N*'-dicyclohexylcarbodiimide.

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