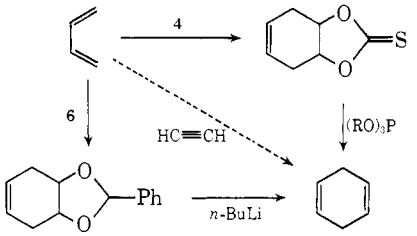
2-Phenyl- and 2-Thiono-1,3-dioxol-4-ene. Alternatives to Acetylene as Dienophiles in the Diels–Alder Reaction

Sir:

Acetylene, although potentially valuable as a dienophile, has only limited utility in the Diels–Alder reaction due to its sluggish reactivity and the difficulty associated with its handling.[1] We wish to report two simple procedures which are equivalent to the use of acetylene as a dienophile in the Diels–Alder reaction.

Scheme I outlines the general approaches which em-

Scheme I



ploy either vinylene thionocarbonate (**4**) or 2-phenyl-1,3-dioxol-4-ene (**6**) as dienophiles. Subsequent treatment of the thionocarbonate or 2-phenyl-1,3-dioxolane adducts with trivalent phosphorus[2] or *n*-butyllithium,[3] respectively, will yield the corresponding olefin.

The reaction sequences (Scheme I) present obvious advantages when compared to other dienophiles. Vinyl acetate or vinyl bromide is not very satisfactory due to low dienophilicity[1] and the lack of regiospecificity in the subsequent elimination reaction; vinylene carbonate would require, following initial Diels–Alder reaction, several additional steps to prepare the corresponding olefin.[4]

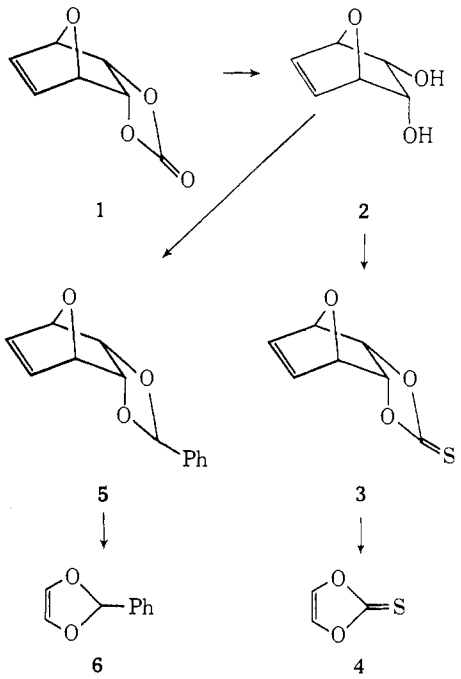
Recently, a low-yield conversion (phosphorus pentasulfide) of vinylene carbonate to vinylene thionocarbonate (**4**) has been reported.[5a] Previously an attempt to prepare **4** *via* the pyrolysis of **7** was reported to yield only polymeric products.[5b]

The utility of the retrodiene reaction for the synthesis of olefins[6] prompted us to examine other dienes for a general route to 2-substituted 1,3-dioxol-4-enes. The great facility with which furan Diels–Alder adducts undergo the retro reaction[7] and the high volatility of furan makes this an attractive approach for the synthesis of 1,3-dioxol-4-enes.

The cyclic carbonate (**1**) was synthesized in 25% yield in a Diels–Alder reaction between vinylene carbonate and furan.[8,9] Hydrolysis of **1** (1.0 *M* KOH at 100° for 1 hr) proceeded quantitatively to yield **2**.

The diol **2** was converted to **3** (mp 159°) in *ca.* 60%

Scheme II



yield upon treatment with *N,N*-thionocarbonyldiimidazole in refluxing toluene. Thermolysis of **3** at 160° (in a sublimation apparatus open to the air) afforded **4** in almost quantitative yield (contaminated with a small quantity of **3**). Resublimation at 120° afforded pure **4** as long white needles (with a faint garlic-like odor): mp (sealed tube) 46°; nmr (CCl_4–Me_4Si) δ 7.51 (s); uv max (95% ethanol) 207 (ϵ 2200) and 263 nm (ϵ 14,500); ir (CCl_4) 3175, 1318, 1125, 1065, and 864 cm^{-1}; *m/e* (rel abundance) 102 (m^+, 100%) 60 (5.3%), 51 (3.3%), 45 (13.3%), 44 (6.7%), 42 (40%), and 41 (4%).

The acetal **5** (mp 69–71°) was prepared in 96% yield from **2** by treatment with benzaldehyde (and a trace of *p*-toluenesulfonic acid) in toluene heated under reflux for 1 hr. Thermolysis of **5** at 170° (nitrogen atmosphere) afforded only a 15% yield of **6** (*ca.* 90% purity) as an unstable clear white liquid:[10] bp >170°; nmr (CCl_4–Me_4Si) δ 6.46 (s, *ca.* 1.6 H), 6.65 (s, 1 H), and 7.51 (m, *ca.* 5.6 H).

Vinylene thionocarbonate (**4**) and 2-phenyl-1,3-dioxol-4-ene (**6**; generated *in situ* from **5**) were each treated with anthracene in benzene at 170° for 16 hr to give adducts **7** (60% yield) and **8** (65% yield), respectively.

In order to confirm the structures of the adducts, **7**

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(4) Examples of the use of acetylene synthons in Diels–Alder reactions are quite rare. For other examples, see: (a) B. M. Trost and F. Chen, *Tetrahedron Lett.*, 2603 (1971); (b) H. E. Zimmerman, G. L. Grunewald, R. M. Paufler, and M. A. Sherwin, *J. Amer. Chem. Soc.*, **91**, 2330 (1969); (c) S. Masamune, H. Cuts, and M. G. Hogben, *Tetrahedron Lett.*, 1017 (1966).

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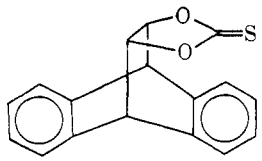
(9) Although the yield in this reaction is low, quantities of **1** can be readily prepared since *ca.* 90% of the vinylene carbonate can be recovered and recycled.

(10) The pot residue, following the initial distillation, contained a significant quantity of polymer. Attempted purification of **6** (which polymerized completely in *ca.* 10 hr at room temperature) either by careful distillation or chromatography resulted in extensive polymerization. Consequently, the stable adduct **5** was used in subsequent reactions to generate **6** *in situ*.



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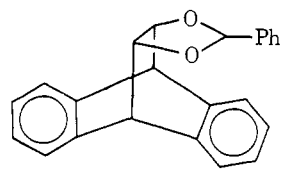

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and **8** were synthesized by an alternate route from anthracene. The known thionocarbonate,[5b] **7**, and **8** were prepared by treatment of 9,10-dihydro-9,10-ethanoanthracene-11,12-diol[6a] with *N*,*N*-thionocarbonyldiimidazole and benzaldehyde, respectively. In both instances the compounds prepared by the alternate route were identical with the adducts obtained directly from the Diels–Alder route.

2-Phenyl-1,3-dioxol-4-ene (**6**), in addition to its utility as an acetylene equivalent, will also be of value in the synthesis of 1,2-diols by the Diels–Alder route. The adduct obtained with **6** can be readily converted to the diol upon mild acid treatment. In this regard the use of **6** complements the use of vinylene carbonate; the adduct formed using this latter dienophile is converted to the diol upon base treatment.

Further work is underway to more completely define the dienophilicity of **4** and **6** and to use this general route to prepare other potentially useful dienophiles (*e.g.*, 2-methyl-2-carboxy-1,3-dioxol-4-ene, an oxirene equivalent[11]) *via* the intermediacy of **2**.

Acknowledgment. This work was supported in part by General Research Support Grant No. G002-B from the National Institutes of Health.

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Determination of the Amino Acid Sequence of the C-Terminal Cyanogen Bromide Fragment of Actin by Computer-Assisted Gas Chromatography–Mass Spectrometry

Sir:

Recently we have described a general method aimed at the determination of the amino acid sequence of proteins by computer-assisted gas chromatography–mass spectrometry (GC–MS–computer) of complex mixtures of oligopeptides.[1] Conditions for the generation of optimally suited mixtures from primary degradation peptides of proteins, by acid or enzymatic hydrolysis, were evaluated. Esterification, acetylation, and reduction by $LiAlD_4$ converted these oligopeptides to the corresponding polyamino alcohols[2,3] which were then *O*-trimethylsilylated. These derivatives, now well suited for gas chromatographic separation, also produce mass spectra with abundant sequence determining ions.[1] This simplicity of the mass spectra, which are easily interpretable even if due to minor components of the mixture, and the general applicability (Arg, His, Trp, and sulfur containing amino acids can be handled without modification) certainly outweigh the more involved derivatization procedure, compared with unreduced derivatives. A detailed account of the chemical steps involved as well as the gas chromatographic and mass spectrometric properties of the resulting derivatives is in preparation.[4,5] Although no report on the handling of such complex mixtures by other mass spectrometric techniques is available in the literature, the gas chromatographic properties of the silylated polyamino alcohols make them the most promising candidates for a highly automated, generally applicable sequencing technique.

We have used this approach to determine the amino acid sequence of the C-terminal cyanogen bromide fragment of rabbit skeletal muscle actin. This peptide contains 20 amino acid residues and has the following amino acid composition:[6] Lys 2, His 1, Arg 1, Asp 1, Thr 1, Ser 1, Glu 2, Gln 1, Pro 1, Gly 1, Ala 1, Val 1, Ile 2, Tyr 1, Phe 1, Trp 1, AEtCys (aminoethylcysteine) 1.

The peptide (0.75 μmol) was hydrolyzed with 6 *N* HCl at 110° for 20 min. The resulting mixture of oligopeptides was then derivatized as outlined above and the resulting mixture of *O*-trimethylsilylated polyamino alcohols[7] was analyzed by a GC–MS–computer system.[8,9] The total ionization plot (*i.e.*, computer-generated gas chromatogram) obtained in this experiment is shown in Figure 1 together with the results of the interpretation of the data in terms of the sequences of the oligopeptides present in the mixture prior to derivatization.

The identification of the *O*-trimethylsilylated polyamino alcohols was based on three sets of data generated by the computer in the course of this GC–MS experiment. (1) Mass spectra. As in the free polyamino alcohols[2,3] cleavage of the carbon–carbon bonds of the ethylenediamine backbone units leads to abundant sequence determining ions from which the sequence of the side chains and thus that of the amino acids in the original oligopeptide can easily be deduced. *O*-Silylation not only overcomes the previous obstacle encountered with polyfunctional amino acids[3] but also enhances the abundance of the C-terminal fragment ions.[1,10] (2) Mass chromatograms[11] (plots of ions *vs.* time). Coincidence of maxima of mass chromatograms of the various sequence determining ions may be used efficiently to locate peptide derivatives as well as to resolve gas chromatographic fractions of incompletely separated peptide derivatives. (3) Retention indices[12] were automatically assigned to all gas chro-

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(7) It should be noted that the notoriously troublesome amino acids arginine, histidine, and tryptophan do not require special treatment in this reductive technique; arginine is merely converted to *N*-methylornithine and the side chains of the other two remain unchanged.
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