$C_{14}H_{21}N_5O_4 \cdot 1.1H_2O$: C, 41.67; H, 5.47; N, 22.09. Found: C, 41.43; H, 5.18; N, 21.79.

8-Methylguanosine (6).[2a,14] 254 mg (86%). Mp 194–196 °C. ^{1}H NMR [270 MHz, $(CD_3)_2SO$]: δ 2.42 (3 H, s, $-CH_3$), 3.42–3.71 (2 H, m, H-5′), 3.87 (1 H, br s, H-4′), 4.11 (1 H, br s, H-3′), 4.71 (1 H, dd, J = 11.2 and 6.8 Hz, H-2′), 5.13 (2 H, m, 2 × OH), 5.35 (1 H,d, OH), 5.69 (1 H, d, J = 6.8 Hz, H-1′), 6.31 (2 H, br s, NH_2), 10.61 (1 H, s, NH).

2-Amino-6-methylpurine 9-β-D-Ribonucleoside (8).[15] Recrystallization from H_2O, mp 155–156 °C. ^{1}H NMR [270 MHz, $(CD_3)_2SO$]: δ 2.51 (3 H, s, CH_3), 3.52–3.71 (2 H, m, H-5′), 3.93 (1 H, br s, H-4′), 4.14 (1 H, br s, H-3′), 4.52 (1 H, dd, J = 11.2 and 5.9 Hz, H-2′), 5.08–5.17 (2 H, m, 2 × OH), 5.43 (1 H, d, OH), 5.83 (1 H, d, J = 5.9 Hz, H-1′), 6.43 (2 H, br s, NH_2), 8.24 (1 H, s, H-8). MS (m/z): 281 (M^+).

A Facile Synthesis of Tetramethyl Thiophenetetracarboxylate: Reaction of Dimethyl Acetylenedicarboxylate with Potassium *p*-Toluenethiosulfonate[1]

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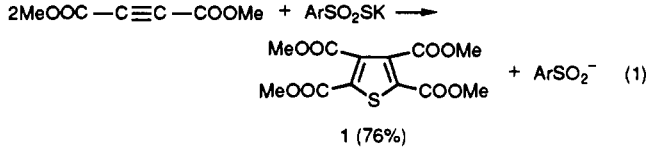
Earlier syntheses[2-6] of tetramethyl thiophenetetracarboxylate (1) have afforded the compound in relatively low (20–38%) yield and have generally involved elevated reaction temperatures (140–215 °C). In following up an investigation[7] of certain aspects of the chemistry of potassium *p*-toluenethiosulfonate ($ArSO_2SK$, Ar = *p*-$CH_3C_6H_4$), we have now unexpectedly discovered that this salt reacts readily with 2 mol of dimethyl acetylenedicarboxylate in 2 h at room temperature in acetonitrile to produce 1 in 76% yield (eq 1). The reaction in eq 1

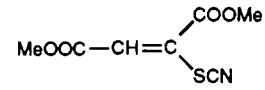


1 (76%)

represents a route to 1 that is markedly superior in yield to those[2-6] previously published. It also employs much gentler reaction conditions and is now clearly the method of choice for the synthesis of 1.

Initially we hoped that reaction of $ArSO_2SK$ with other alkynes in acetonitrile might lead to other thiophenes, but this has proved not to be the case. Thus, treatment of either phenylacetylene or diphenylacetylene with $ArSO_2SK$ (either 24 h at room temperature or 8 h at reflux) led only to recovery of starting materials. With ethyl 3-phenyl-2-propynoate (PhC≡C—COOEt) a reaction did take place very slowly; after 14 days at reflux this gave an adduct, $ArSO_2C(Ph)$=CH—COOEt (76%). This product presumably arises from the addition of $ArSO_2^-$ (formed by slow reversion of the *p*-toluenethiosulfonate,[8] $ArSO_2S^- \rightleftarrows ArSO_2^- + S$), *not* $ArSO_2S^-$, to the triple bond, since the same adduct was obtained (73%) in a much shorter reaction time (40 h) when PhC≡C—COOEt was reacted directly with sodium *p*-toluenesulfinate in refluxing acetonitrile. Reaction to form the thiophene therefore occurs only when two strong electron-withdrawing groups are attached to the carbons of the triple bond.

We also explored whether sulfur anions other than $ArSO_2S^-$ would react with MeOOC—C≡C—COOMe. While no reaction was observed with sodium thiosulfate (Na_2SSO_3), reaction of potassium thiocyanate (KSCN) with dimethyl acetylenedicarboxylate at room temperature for 5 h in acetonitrile did give 1 in low yield (19%); the main product was 2. A similar adduct, 3, was obtained in the reaction of potassium selenocyanate (KSeCN) with 1. (In the KSeCN case no selenophene was isolated as a minor product.)



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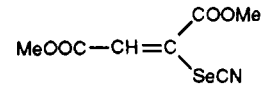
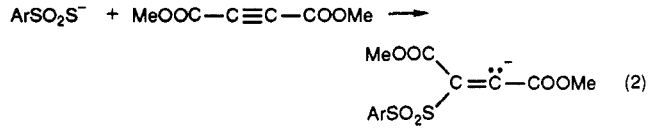


3

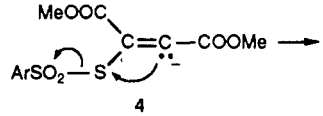
The formation of 2 and 3 suggests that the initial step in the formation of 1 in eq 1 is addition of the sulfur anion to the triple bond of MeOOC—C≡C—COOMe (eq 2).



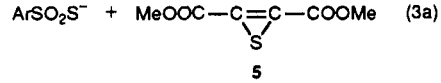
4

The failure of the reaction with PhC≡CCOOMe and PhC≡CPh indicates that two electron-withdrawing groups must be attached to the C≡C in order for the equilibrium for this addition to be sufficiently favorable.

Why dose 4 go on to form 1 in high yield when the corresponding carbanion from the addition of SCN^- does not? We think this has its origin in the fact that $ArSO_2^-$ is a considerably better leaving group than CN^-, but we do not know at what stage of the reaction this feature becomes important. Thus, one route for formation of 1 would have 4 undergo facile intramolecular displacement of $ArSO_2^-$ to form thiirene 5 (eq 3a). Thiirenes have been



4



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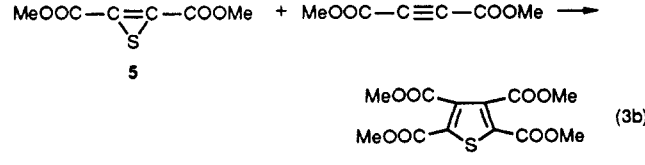

5

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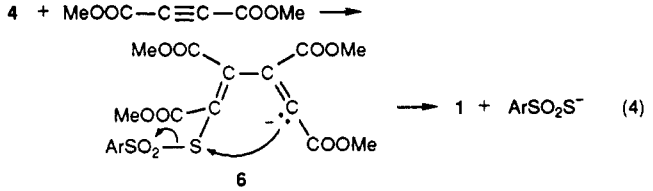
postulated[9] to under go 1,3-dipolar addition to acetylenes to form thiophenes (eq 3b).[10] Another option (eq 4) would have 4 react reversibly with a second alkyne to give 6, which would then cyclize to the thiophene.



Experimental Section

Reactions with Dimethyl Acetylenedicarboxylate. Potassium *p*-toluenethiosulfonate (1.13 g, 5 mmol) was added slowly to a stirred solution of 1.42 g (10 mmol) of dimethyl acetylenedicarboxylate (Aldrich) in 20 mL of acetonitrile. The reaction mixture was stirred at room temperature for 2 h and then poured into water. The product was extracted with methylene chloride. The methylene chloride extracts were dried ($MgSO_4$), and the organic solvent was removed by evaporation. The residue was purified by chromatography on silica gel using 1:2 CH_2Cl_2–hexane as eluant. Recrystallization from methanol gave 1.20 g (76%) of tetramethyl thiophenetetracarboxylate (1), mp 124–125 °C (lit.[2] mp 125 °C); ^1H NMR ($CDCl_3$) δ 3.92; IR (KBr) 2960, 1720, 1540, 1440, 1270, 1220, and 1000 cm^{-1}.

Potassium thiocyanate (0.97 g) was added to a stirred solution of 1.42 g of dimethyl acetylenedicarboxylate in 20 mL of acetonitrile, and the reaction mixture was stirred at room temperature for 5 h. It was then worked up in the same manner as in the reaction with p-$CH_3C_6H_4SO_2SK$. The products were separated by column chromatography on silica gel using 1:1 CH_2Cl_2–hexane as the eluant. After recrystallization from methanol there was obtained 0.30 g (19%) of 1, mp 124–125 °C, and 0.88 g (44%) of thiocyanate 2: mp 34–35 °C; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 3.97 (s, 3 H), 6.88 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.66, 53.83, 108.29, 125.97, 137.82, 161.54, 164.57. Anal. Calcd for $C_7H_7NO_4S$: C, 41.79; H, 3.51; N, 6.96. Found: C, 41.86; H, 3.59; N, 6.83.

Potassium Selenocyanate. Reaction of KSeCN (0.72 g, 5 mmol) with dimethyl acetylenedicarboxylate (1.42 g, 10 mmol) was carried out in the same manner as with KSCN. After workup and chromatography on silica gel using 1:2 CH_2Cl_2–hexane as eluant there was obtained 0.86 g (49%) of selenocyanate 3: mp 40–41 °C; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3 H), 3.96 (s, 3 H), 6.95 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 53.89, 53.92, 120.55, 122.78, 143.39, 163.44, 167.54. Anal. Calcd for $C_7H_7NO_4Se$: C, 33.89; H, 2.84. Found: C, 33.47, H, 2.88.

Reactions with Ethyl 3-Phenyl-2-propynoate. Potassium *p*-Toluenethiosulfonate. Ethyl 3-phenyl-2-propynoate (1.74 g, 10 mmol) and p-$CH_3C_6H_4SO_2SK$ (1.13 g, 5 mmol) were added to 20 mL of acetonitrile, and the reaction mixture was stirred at reflux for 14 days. It was then worked up in the same manner as in the other reactions. The residue remaining after the removal of the methylene chloride was recrystallized from methanol giving 1.26 g (76%) of ethyl 3-(*p*-tolylsulfonyl)-3-phenyl-2-propenoate: mp 83–84 °C; ^1H NMR ($CDCl_3$) δ 1.03 (t, 3 H), 2.40 (s, 3 H), 4.00 (q, 2 H), 7.01–7.48 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 13.62, 21.59, 61.19, 126.77, 127.72, 129.04, 129.31, 129.52, 129.62, 129.89, 134.16, 145.03, 154.54, 163.77; IR (KBr) 3000, 1730, 1600, 1315 (SO_2), 1210, 1145 (SO_2) cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49. Found: C, 65.04; H, 5.46.

Sodium *p*-Toluenesulfinate. Stirring a mixture of 0.45 g (2.5 mmol) of sodium p-toluenesulfinate and 0.41 g (2.5 mmol) of ethyl 3-phenyl-2-propynoate in 20 mL of acetonitrile under reflux for 40 h gave upon workup 0.60 g (73%) of ethyl 3-(*p*-tolylsulfonyl)-3-phenyl-2-propenoate, mp 83–84 °C.

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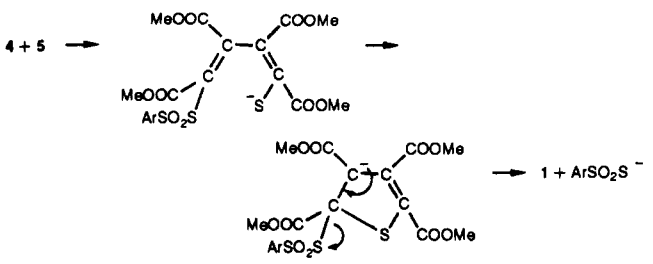
(10) It is also possible that 5 might give 1 by reacting with a second 4 via the sequence shown below:



Development of Novel Phenolic Antioxidants. Synthesis, Structure Determination, and Analysis of Spiro[2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuran-2,1′-cyclopropane]

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Introduction

Sterically hindered phenols form an important class of peroxyl trapping antioxidants. Indeed, α-tocopherol (**1a**), a component of vitamin E, is the major lipid-soluble antioxidant in human blood,[1] and its biological function, as well as that of analogs of it, continues to be of considerable interest.[2] Ingold and co-workers have published a number of papers defining the structural features that are responsible for the high antioxidant activity of 1 and its analogs, at least as measured in homogeneous solution,[3] and they and others[4] have determined rate constants, k_1, for the reaction of the phenols with peroxyl radicals (eq 1). Complementary studies have been reported in micellar

$$ArOH + ROO^{\bullet} \rightarrow ArO^{\bullet} + ROOH \qquad (1)$$

systems[5] and more recently in environments designed to model biological membranes.[2]

The relative efficacies of the phenolic antioxidants, as reflected in k_1, as well as the absolute values of these rate constants are found to be media dependent.[6] It is clear that the major factor defining the free radical chain terminating activity of the phenols is the nature of the substitution on the aromatic ring, as shown by the data compiled in Table I. Ortho, meta, and para alkyl, para alkoxy, and alkylthio groups are seen to augment the reactivity of the phenols toward radicals, owing to stabilization of the incipient phenoxyl radical character of the transition state for hydrogen atom transfer.[3d,e,4] EPR studies have

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