was treated with 1.6 g of NaH (40.3 mmol) at 23 °C for 30 min, at which time 0.74 g (2.0 mmol) of Bu_4NI and 3.6 mL (30.2 mmol) of BnBr were added.[32] After 60 min, the reaction was carefully quenched with water and saturated NH_4Cl and extracted with EtOAc (2×). The organic phase was washed with water (2×) and brine (1×), dried, filtered, and evaporated. The products were separated by MPLC with 95:5 EtOAc–EtOH to give **22** (1.88 g, 26%, R_f = 0.41) and **23** (1.76 g, 24%, R_f = 0.54).

22: oil; IR (film) 1672; ^{1}H NMR ($CDCl_3$) δ 2.4 (2, m), 2.49 (1, dd, J = 13.2, 7.4), 2.71 (1, dt, J = 13.5, 5.2), 3.24 (3, s), 3.25 (3, s), 3.45 (1, dd, J = 12.3, 5.2), 3.56 (1, d, J = 12.2), 3.66 (1, d, J = 12.2), 3.87 (1, dd, J = 12.3, 2.9), 4.2 (2, m), 4.32 (1, t, J = 8.4), 4.44 (1, d, J = 11.9), 4.54 (1, d, J = 11.8), 7.3 (5, m); ^{13}C NMR ($CDCl_3$) δ 32.0, 34.6, 48.9, 50.0, 50.3, 50.7, 57.7, 58.1, 70.2, 74.6, 105.6, 127.2, 127.3, 127.9, 137.2, 165.6, 165.8; CI MS 361 (trace), 360 (trace), 329, 222; FAB MS 361, 329; HR FAB calcd for $C_{19}H_{24}N_2O_5$ 361.1763, found 361.1707.

23: mp 92–94 °C; IR (KBr) 1667; ^{1}H NMR ($CDCl_3$) δ 2.14 (1, ddd, J = 13, 11, 4.4), 2.36 (1, dd, J = 13.2, 9.4), 2.45–2.65 (2, m), 3.26 (6, s), 3.57 (1, d, J = 12), 3.63 (2, m), 3.73 (1, d, J = 13), 4.22 (1, t, J = 4.2), 4.35 (1, t, J = 8.4), 4.45 (1, dd, J = 10.9, 6.5), 4.53 (2, s), 7.35 (5, m); ^{13}C NMR ($CDCl_3$) δ 33.8, 34.9, 49.2, 50.2, 51.0, 51.1, 58.3, 58.7, 70.6, 75.3, 105.9, 127.4, 127.7, 128.3, 137.2, 165.4, 166.4; CI MS 361 (trace), 360, 329. Anal. Calcd for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 62.88; H, 6.57; N, 7.46.

(2*S*,5a*S*,10a*S*)-Octahydro-2-hydroxy-1*H*,5*H*-dipyrrolo-[1,2-*a*:1′,2′-*d*]pyrazine-5,7,10-trione, *O*-Benzyl Ether (2g). A solution of 1.95 g (5.41 mmol) of **22** in 25 mL of THF was treated with 25 mL of water and two drops of concd H_2SO_4 and heated to reflux for 1 h. The solution was cooled and extracted with EtOAc (3×), and the organic layers were washed with saturated $NaHCO_3$ (3×) and brine (1×), dried, filtered, and evaporated to give 1.18 g (60%) of ketone **2g**: mp 166–167 °C; IR (KBr) 1768, 1675, 1656; ^{1}H NMR ($CDCl_3$) δ 2.42 (1, ddd, J = 18.6, 9.1, 5.0), 2.8 (1, m), 2.89 (1, dd, J = 19.7, 9.1), 3.16 (1, dd, J = 19.5, 9.2), 3.46 (1, dd, J = 12.4, 4.9), 3.79 (1, d, J = 19.7), 3.98 (1, bd, J = 12.4), 4.11 (1, d, J = 19.7), 4.18 (1, m), 4.29 (1, dd, J = 9.0, 5.3), 4.45 (1, d, J = 11.9), 4.55 (1, d, J = 11.9), 4.64 (1, t, J = 9.0), 7.3 (5, m); ^{13}C NMR ($CDCl_3$) δ 32.8, 39.2, 51.4, 52.2, 57.3, 58.1, 70.9, 74.8, 127.8, 127.9, 128.5, 137.5, 165.2, 166.4, 205.8; FAB MS 315 (MH^+); HR FAB calcd for $C_{17}H_{19}N_2O_4$ (MH^+) 315.1345, found 315.1338.

(2*S*,5a*R*,10a*R*)-Octahydro-2-hydroxy-1*H*,5*H*-dipyrrolo-[1,2-*a*:1′,2′-*d*]pyrazine-5,7,10-trione, *O*-Benzyl Ether (24). A solution of 0.88 g (2.44 mmol) of **23** in 15 mL of THF was treated with 15 mL of water and 1 drop of concd H_2SO_4 and heated to reflux for 1 h. The solution was cooled and extracted with EtOAc (3×), and the organic layers were washed with saturated $NaHCO_3$ (3×) and brine (1×), dried, filtered, and evaporated to give 0.60 g (68%) of ketone **24**: mp 148.0–149.5 °C; IR (KBr) 1773, 1652; ^{1}H NMR ($CDCl_3$) δ 2.12 (1, ddd, J = 13.6, 11.1, 4.3), 2.62 (1, dd, J = 13.7, 6.5), 2.88 (1, dd, J = 19.3, 8.8), 3.07 (1, dd, J = 19.1, 9.5), 3.66 (1, dd, J = 13.1, 4.3), 3.74 (1, dd, J = 19.9, 11.8), 4.11 (1, d, J = 19.7), 4.25 (1, t, J = 3.9), 4.5 (1, m), 4.54 (2, s), 4.65 (1, t, J = 9.0), 7.3 (5, m); ^{13}C NMR ($CDCl_3$) δ 34.2, 39.2, 51.5, 52.0, 57.4, 58.2, 70.9, 75.1, 127.6, 127.9, 128.5, 137.3, 164.5, 166.8, 205.8; CI MS 315 (MH^+); FAB MS 315; HR FAB calcd for $C_{17}H_{19}N_2O_4$ (MH^+) 315.1345, found 315.1355. Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 63.67; H, 5.60; N, 8.54.

Registry No. **2a**, 63667-06-1; **2b**, 142800-04-2; **2c**, 142800-05-3; **2f**, 142800-06-4; **2g**, 142800-07-5; **5**, 13504-85-3; **7**, 64187-47-9; **8**, 75776-54-4; **9**, 113490-85-0; **10**, 142800-08-6; **11**, 75776-77-1; **12**, 142800-09-7; **13**, 142800-10-0; **17**, 142800-11-1; **18**, 142800-12-2; **19**, 142865-29-0; **20**, 142800-13-3; **21**, 142800-14-4; **22**, 142800-15-5; **23**, 142865-31-4; **24**, 142865-30-3; BnBr, 100-39-0; 1,2-ethanedithiol, 540-63-6; (*R*)-(+)-1-methoxy-1-(trifluoromethyl)phenylacetyl chloride, 39637-99-5; (*S*)-(−)-1-methoxy-1-(trifluoromethyl)-phenylacetyl chloride, 20445-33-4.

Supplementary Material Available: X-ray data including an ORTEP plot for **20**, experimental procedures and spectral data for **7**, **8**, **9**, **18**, and **19**, ^{1}H NMR spectra for **2b**, **2e**, **2f**, **2g**, **13**, **17**, **18**, **19**, and **24**, and analytical HPLC chromatograms for **18** and **19** (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

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Convenient Method for the Synthesis of C-Alkylated Purine Nucleosides: Palladium-Catalyzed Cross-Coupling Reaction of Halogenopurine Nucleosides with Trialkylaluminums

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Received March 30, 1992

Introduction of various carbon chains onto the ring carbon of the naturally occurring purine nucleosides has been extensively investigated to synthesize biologically active analogs.[1] There have been ample precedents for the preparation method of 2- and 8-alkylpurine nucleosides, and the methods for the direct introduction of alkyl groups are mainly based on the application of radical reaction[2] and C-lithiation.[3] These methods, however, are not always satisfactory with respect to regioselectively, yield, and/or the scope of reactions. Although the cross-coupling of Grignard reagents with aryl halides has achieved great success in the field of synthetic organic chemistry,[4] application of such cross-coupling reactions to 8-bromoadenosine derivatives is far from satisfactory in view of its inefficiency.[5]

On the other hand, the cross-coupling using trialkylaluminums has not been widely investigated.[6] During the course of our studies on the palladium-catalyzed cross-coupling reaction with trialkylaluminums,[7] we have found that trialkylaluminums smoothly coupled with halogenopurine nucleosides. This paper describes a convenient method for the preparation of C-alkylated purine nucleosides.

Cross-coupling of 8-bromoadenosine (**1a**) itself with trimethylaluminum in the presence of palladium catalyst resulted in the recovery of the starting material. When 8-bromoadenosine was protected with a trimethylsilyl group in the coupling reaction, the expected 8-methyladenosine was successfully formed in high yield by the reaction with trimethylaluminum. Thus, treatment of 8-bromoadenosine (**1a**) (1 equiv) with excess hexamethyldisilazane (HMDS) gave quantitatively the corresponding trimethylsilylated 8-bromoadenosine, which was used in the next step without any purification. A mixture

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(2) (a) Maeda, M.; Nushi, K.; Kawazoe, Y. *Tetrahedron* **1974**, *30*, 2677. (b) Zady, M. F.; Wong, J. L. *J. Am. Chem. Soc.* **1977**, *99*, 5096. (c) Ikehara, M.; Linn, W.; Fukui, T. *Chem. Pharm. Bull.* **1977**, *25*, 2702. (d) Zady, M. F.; Wong, J. L. *J. Org. Chem.* **1979**, *44*, 1450. (e) Maki, Y.; Kameyama, K.; Suzuki, M.; Sako, M.; Hirota, K. *J. Chem. Res.* **1984**, 388.
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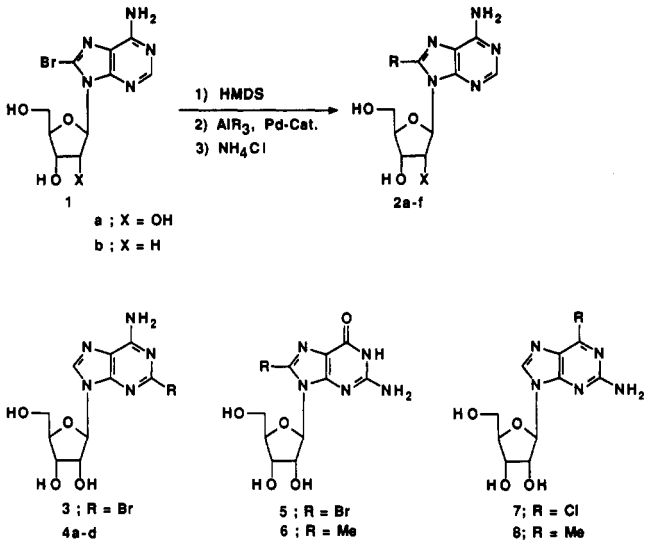
0022-3263/92/1957-5268$03.00/0

Scheme I



of the protected 8-bromoadenosine, $AlMe_3$ (2 equiv), $PdCl_2$ (0.05 equiv), and Ph_3P (0.1 equiv)[8] in dry THF was refluxed for 2 h under argon. The resulting cross-coupling product was deprotected by refluxing in methanol in the presence of ammonium chloride efficiently to give 8-methyladenosine (**2a**) in 95% yield. The structure of **2a** was confirmed by direct comparison of its spectral data with those reported previously.[2a]

Analogous reactions of 8-bromoadenosine (**1a**) with commercially available trialkylaluminums, such as $AlEt_3$, $AlPr_3$, and $Al(i\text{-}Bu)_3$, gave the corresponding 8-alkylpurine nucleosides **2b**,[10] **2c**,[10] and **2d** in 42%, 53%, and 13% yields, respectively. It is worthy of note that the coupling occurred even with a somewhat bulky alkylaluminum reagent possessing propyl and isobutyl groups, of which direct introduction into purine nucleosides is hitherto unknown. In the case of the reaction with trialkylaluminum reagents except for $AlMe_3$, debromination of bromopurine nucleosides, however, was observed as a side reaction and the debromination preferentially occurs rather than the cross-coupling in the reaction with $Al(i\text{-}Bu)_3$.

Reaction of 8-bromo-2′-deoxyadenosine (**1b**) with $AlMe_3$ and $AlEt_3$ resulted into the formation of the corresponding 8-alkyl-2′-deoxyadenosines **2e**[11] and **2f** in 84% and 62% yields, respectively. When treatment of 2-bromoadenosine (**3**), 8-bromoguanosine (**5**), and 2-amino-6-chloro-9-β-D-ribofuranosylpurine (**7**) with trialkylaluminums was carried out, the corresponding alkylated products **4a–d**,[12,13] **6**,[2a,14] and **8**[15] were obtained (see Table I).

The present coupling reaction is applicable to the introduction of an alkyl group into various purine nucleosides and could make further biochemical studies of biologically important nucleosides and nucleotides involving C-alkylated purine nucleosides feasible.

Table I. Formation of Alkylated Purine Nucleosides

product no.	R	X	reaction time (h)	yield (%)
2a	Me	OH	2	95
2b	Et	OH	8	42 (31)
2c	Pr	OH	24	53 (34)
2d	*i*-Bu	OH	72	13 (59)
2e	Me	H	8	84
2f	Et	H	12	62 (21)
4a	Me	–	1.5	76
4b	Et	–	10	72 (trace)
4c	Pr	–	56	67 (trace)
4d	*i*-Bu	–	72	34 (43)
6	Me	–	24	83
8	Me	–	40	70

[a] Values in parentheses are yield of the debrominated product.

Experimental Section

All melting points are uncorrected. Elemental analyses were carried out at the microanalytical laboratory of our university. Column chromatography was carried out on a silica gel (Wako gel D-300).

Preparation of C-Alkylated Purine Nucleosides. General Procedure. A mixture of purine nucleoside (1 equiv) with excess hexamethyldisilazane (HMDS) in the presence of a catalytic amount of ammonium sulfate was refluxed for 2–3 h under an Ar atmosphere, and the solvent was removed under reduced pressure to give the trimethylsilyl-protected nucleoside. A mixture of the protected nucleoside, $AlMe_3$ (2 equiv), $PdCl_2$ (0.05 equiv), and Ph_3P (0.1 equiv) in dry THF was refluxed for the appropriate time under Ar. The solvent was removed under reduced pressure, and the resulting residue was refluxed for 3 h in methanol in the presence of ammonium chloride. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column with chloroform–methanol (10:1) as eluant to give the corresponding alkylated nucleoside. In the case of the reaction with $AlEt_3$, $AlPr_3$, or $Al(i\text{-}Bu)_3$, the corresponding debrominated product was isolated as a later fraction (see Table I). Data for new compounds and known compounds having no ^1H NMR data in the literatures[2a,14,15] are listed below:

8-Isobutyladenosine (2d). Recrystallization from EtOH, mp 254–256 °C. ^1H NMR [270 MHz, $(CD_3)_2SO$]: δ 0.99 (6 H, d, J = 6.4 Hz, $CH_2CH(CH_3)_2$), 2.19 [1 H, m, $CH_2CH(CH_3)_2$], 2.78 (2 H, m, $-CH_2CH$), 3.42–3.75 (2 H, m, H-5′), 4.03 (1 H, br s, H-4′), 4.18 (1 H, br s, H-3′), 4.96 (1 H, m, H-2′), 5.25 (1 H, d, OH), 5.38 (1 H, d, OH), 5.78 (1 H, d, J = 7.3 Hz, H-1′), 5.99 (1 H, m, OH), 7.32 (2 H, br s, NH_2), 8.08 (1 H, s, H-2). MS (m/z): 323 (M^+). Anal. Calcd for $C_{14}H_{21}N_5O_4 \cdot 0.2EtOH$: C, 52.01; H, 6.73; N, 21.06. Found: C, 51.96, H, 6.68; N, 21.16.

2′-Deoxy-8-ethyladenosine (2f). Recrystallization from EtOH, mp 234–235 °C. ^1H NMR [270 MHz, $(CD_3)_2SO$]: δ 1.33 (3 H, t, J = 7.7 Hz, CH_2CH_3), 2.19 (1 H, m, H-2′), 2.95 (2 H, q, J = 7.7 Hz, $-CH_2CH_3$), 3.12 (1 H, m, H-2′), 3.50–3.71 (2 H, m, H-5′), 3.92 (1 H, br s, H-4′), 4.49 (1 H, br s, H-3′), 5.32 (1 H, d, OH), 5.60 (1 H, d, OH), 6.29 (1 H, d, J = 7.3 Hz, H-1′), 7.21 (2 H, br s, NH_2), 8.08 (1 H, s, H-2). MS (m/z): 279 (M^+). Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 51.61; H, 6.14; N, 25.07. Found: C, 51.77, H, 6.22; N, 25.08.

2-Propyladenosine (4c). Mp 220–221 °C. ^1H NMR [270 MHz, $(CD_3)_2SO$]: δ 0.93 (3 H, t, J = 7.3 Hz, CH_2CH_3), 1.74 (2 H, m, $CH_2CH_2CH_3$), 2.63 (2 H, t, J = 7.3 Hz, $CH_2CH_2CH_3$), 3.42–3.74 (2 H, m, H-5′), 4.00 (1 H, br s, H-4′), 4.18 (1 H, br s, H-3′), 4.69 (1 H, dd, J = 11.7 and 6.8 Hz, H-2′), 5.21 (1 H, d, OH), 5.43 (1 H, d, OH), 5.68 (1 H, m, OH), 5.87 (1 H, d, J = 6.8 Hz, H-1′), 7.27 (2 H, br s, NH_2), 8.27 (1 H, s, H-8). MS (m/z): 295 (M^+). Anal. Calcd for $C_{13}H_{19}N_5O_4 \cdot {}^1/_5H_2O$: C, 46.38; H, 5.45; N, 24.58. Found: C, 46.36, H, 5.32; N, 24.47.

2-Isobutyladenosine (4d). ^1H NMR [270 MHz, $(CD_3)_2SO$]: δ 0.90 [6 H, d, J = 6.4 Hz, $CH_2CH(CH_3)_2$], 2.17 [1 H, m, $CH_2CH(CH_3)_2$], 2.52 (2 H, m, $-CH_2CH$), 3.50–3.72 (2 H, m, H-5′), 4.00 (1 H, br s, H-4′), 4.16 (1 H, br s, H-3′), 4.69 (1 H, dd, J = 11.7 and 6.8 Hz, H-2′), 5.21 (1 H, d, OH), 5.43 (1 H, d, OH), 5.80 (1 H, m, OH), 5.86 (1 H, d, J = 6.8 Hz, H-1′), 7.27 (2 H, br s, NH_2), 8.26 (1 H, s, H-8). MS (m/z): 295 (M^+). Anal. Calcd for

(8) $PdCl_2$ and Ph_3P in the ratio 1:2 under reaction conditions would convert into $PdCl_2(Ph_3P)_2$.[9] Employment of $Pd(Ph_3P)_4$[7] instead of a combination of $PdCl_2$ and Ph_3P as a catalyst led to analogous results (**2a**, 90% yield).

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$C_{14}H_{21}N_5O_4 \cdot 1.1H_2O$: 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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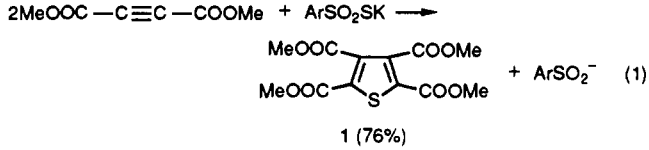
Received May 1, 1992

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

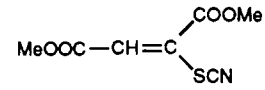


1 (76%)

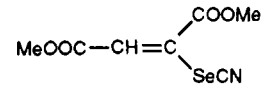
represents a route to 1 that is markedly superior in yield to those[2-6] previously published. It also employs much gentler reaction conditions and is now clearly the method of choice for the synthesis of 1.

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.)

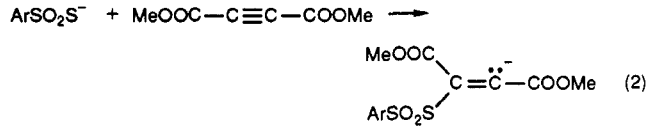


2



3

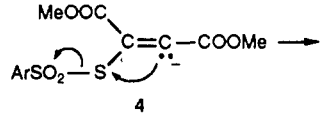
The formation of 2 and 3 suggests that the initial step in the formation of 1 in eq 1 is addition of the sulfur anion to the triple bond of MeOOC—C≡C—COOMe (eq 2).



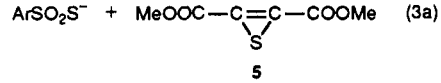
4

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.

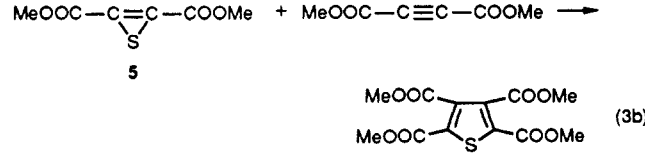
Why dose 4 go on to form 1 in high yield when the corresponding carbanion from the addition of SCN^- does not? We think this has its origin in the fact that $ArSO_2^-$ is a considerably better leaving group than CN^-, but we do not know at what stage of the reaction this feature becomes important. Thus, 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



5



5

(1) This research was supported at the University of Denver by the National Science Foundation, Grant CHE-9000175.

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