Experimental Section

Mass spectra or satisfactory elemental analysis was obtained for all compounds. Melting points were obtained on a Fisher-Johns hot stage melting point apparatus and are uncorrected. All boiling points reported are for bulb to bulb distillations and are the oven temperature recorded unless otherwise indicated. Coupling constants (J) are reported in Hz.

Methyl 2-Cyano-5-methoxy-2,5-pentadienoate (6). A mixture of tetramethoxypropane (12.3 g), acetic anhydride (25 ml), and $ZnCl_2$ (68 mg) was heated under reflux and methyl cyanoacetate (4.95 g, 0.5 mol) was added dropwise. Reflux was maintained for 18 hr after which the volatiles were distilled out until the distillation temperature reached 122°. The residue was cooled and filtered. The filtrate solidified on standing. The solid was distilled (Kugelrohr oven, 0.1 m) affording a yellow oil (bp 90°), acetate of diacetal 4 and a yellow solid (**6**, 7.5 g, 90%) 110–140° (partial decomposition): pmr $\delta_{TMS}(CDCl_3)$ 7.92 (d, J = 13, 1 H, C_3H), 7.42 (d, J = 13, 1 H, C_5H), 6.11 (t, J = 13, 1 H, C_4H) 3.95 and 3.89 (s and s, 6 H's, $-OCH_3$'s); ir (CH_2Cl_2) 2250, 1720, 1615 cm^{-1}; cmr (relative TMS, CH_2Cl_2 ppm) 117.03 (labeled CN); 167.3 (C_5), 164.1 (C_1), 156.2 (C_5), 117.0 (C_6), 104.0 (C_4), 99.0 (C_2), 59.7 (C_8), 53.5 (C_7); ir (C_7); ir (CH_2Cl_2) 2235, 1720, 1620, 1560 cm^{-1}.

Methyl 5-(*N*-Methylanilino)-2-cyano-2,4-pentadienoate. Enol ether (**6**, 5.0 g, 0.03 mol) was dissolved in methanol (400 ml) and *N*-methylaniline (4.8 g, 0.045 mol) added. The stirred mixture was heated under reflux for 6 hr, then cooled and volatiles were removed at reduced pressure. The darkened residue was titurated with ether–hexane (1:1) resulting in a solid that was recrystallized from CH_2Cl_2–ether and afford 6.35 g of **12** (88%, mp 145–146°); pmr δ_{CDCl_3}(TMS) 7.92 (d, J = 13, 1 H, C_3H), 7.5 (d, J = 13, 1 H, C_5H), 7.27 (m, 5 H, Ph-), 5.85 (t, J = 13, 1 H, C_4H), 3.74 (s, 3 H, OCH_3), 3.41 (s, 3 H, NCH_3); ir (CH_2Cl_2) 2230, 1700, 1615, 1560 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 118.09 (labeled nitrile), 164.3 (C_1),[11] 158.4 (C_5), 154.2 (C_3), 146.9 ($C_{1'}$), 130.8 ($C_{3',3'}$ or C_m), 127.0 ($C_{4'}$ or C_p) 121.6 ($C_{2',2'}$ or C_o), 118.1 (C_6), 101.1 (C_4), ~91 (C_2),[11] 52.9 (C_7 or $-OCH_3$), 38.7 (C_8 or NCH_3).

Methyl 2-Bromonicotinate (7) from Enamine 12. Enamine **12** (1 g, 0.004 mol) was dissolved in 5 ml of acetic acid and warmed to 40°. An acetic acid solution (10 ml) saturated with HBr (sat. at 0°) was added dropwise while maintaining the reaction mixture at 40–45°. After addition was complete the temperature was raised to 55° for 30 min. The darkened solution was cooled, poured into water, and neutralized by careful addition of Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3 × 125 ml). The organic extracts were combined, washed with water, and dried (Na_2SO_4). Evaporation of the volatiles at reduced pressure left a residue that was distilled (Kugelrohr oven at 0.1 m) affording a colorless liquid at 60° (*N*-methylaniline) and a viscous oil at 90–120° (**7**, 0.77 g, 87%): pmr δ_{CDCl_3}(TMS) 8.47 (dd, $J_{6,4}$ = 2, $J_{6,5}$ = 5, 1 H, C_6H), 8.07 (dd, $J_{4,5}$ = 8.5, $J_{4,6}$ = 2, 1 H, C_4H), 7.40 (dd, $J_{4\text{-}5}$ = 8.5, $J_{5,6}$ = 5, 1 H, C_5H), 3.95 (s, 3 H, OCH_3); ir = 1735 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 170.2 (C_7), 153.1 (C_6), 141.2 (C_2), 140.6 (C_4), 133.0 (C_3), 123.6 (C_5), 53.9 (C_8); cmr (relative to TMS, CH_2Cl_2 ppm) (C_2 label) 141.11, ir (CH_2Cl_2) 1735, 1580 cm^{-1}; pmr (labeled **7**) δ_{CDCl_3}(TMS) 8.47 (ddd, $J_{6,5}$ = 5, $J_{6,4}$ = 2, $J_{C_2,6}$ = 16, 1 H, C_6H), 8.07 (ddd, $J_{4,5}$ = 8.5, $J_{4,6}$ = 2, $J_{C_2,4}$ = 8, 1 H, C_4H), 7.40 (ddd, $J_{5,4}$ = 8.5, $J_{4,6}$ = 2, $J_{C_2,5}$ = 3, 1 H, C_5H).

Methyl 2-Bromonicotinate (7) from Vinyl Ether 6. Vinyl ether **6** (1.20 g, 0.007 mol) was treated with HBr in the exact manner described above for enamine **12** affording **7** (1.46 g, 97%, bp 105–120° (35 mm)); ir (film) 1735, 1580, 1560 cm^{-1}.

Methyl Nicotinate (8). At room temperature methyl 2-bromonicotinate (**7**, 1.65 g, 0.008 mol) was added to a vigorously stirred suspension of 1% Pd/$BaCO_3$ (10 g) in ethanol (150 ml) under hydrogen at atmospheric pressure. After 171 ml of H_2 was absorbed, the suspended catalyst was filtered and the volatiles were removed at reduced pressure. The resulting oil was distilled (bp 110–125° (~25 mm)) affording **8** (0.98 g, 93%, mp 42–43°); pmr δ_{CDCl_3}(TMS) 9.31 (dd, $J_{2,6}$ = 2 = $J_{2,4}$, 1 H, C_2H), 8.82 (dd, $J_{2,6}$ = 2, $J_{6,5}$ = 5), 8.43 (dt, $J_{4,5}$ = 8, $J_{2,4}$ = 2 = $J_{4,6}$, 1 H, C_4H), 7.40 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 5, 1 H, C_5H), 3.95 (s, 3 H, OCH_3), ir (CH_2Cl_2) 1725 and 1580 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 166.0 (C_7 or $-CO-$), 153.9 (C_6), 151.0 (C_2), 137.3 (C_4), 126.5 (C_3), 123.9 (C_5), 52.8 (C_8 or OCH_3); cmr (relative to TMS, CH_2Cl_2 ppm) (C_2 label) 151.16; ir (CH_2Cl_2) 1730 cm^{-1}.

Nicotinamide (1) was prepared from methyl nicotinate (**8**) as described earlier (approximately 75% from **8**):[1] ir (KBr) 3450, 1665, 1620 cm^{-1}; mp 130–131°.

1,1-Dicyano-4-methoxy-1,3-butadiene (10). Malononitrile (1.00 g, 0.015 mol) was converted to butadiene **10** following the procedure used to prepare vinyl ether **6** (1.23 g, 60%, bp 100–130° (10.01 mm)): ir (CH_2Cl_2) 2250, 1620 cm^{-1}; pmr δ_{CDCl_3}(TMS) 7.48 (d, J = 13, 1 H, C_3H), 7.40 (d, J = 13, 1 H, C_5H), 6.07 (t, J = 13, 1 H, C_4H), 3.92 (s, 3 H, OCH_3); cmr (relative to TMS, $CDCL_3$ ppm) 167.7 (C_4), 160.1 (C_2), 114.4 and 112.5 (C_5, C_6), 103.7 (C_3), 76.4 (C_1), 59.3 (C_7 or OCH_3).

Bromonicotinonitrile (11). Butadiene **10** (1.34 g, 0.01 mol) was converted to bromonicotinonitrile **11** following the procedure used to prepare methyl bromonicotinate (**7**, 1.59 g, 87%): ir (CH_2Cl_2) 2250 and 1580 cm^{-1}; pmr δ_{CDCl_3}(TMS) 7.49 (dd, $J_{4,5}$ = 8, $J_{6,5}$ = 5, 1 H, C_5), 8.03 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 2, 1 H, C_4), 8.70 (dd, $J_{6,5}$ = 5, $J_{6,4}$ = 2, 1 H, C_6H); cmr (relative to TMS, $CDCl_3$ ppm) 153.0 (C_6), 143.8 (C_2), 142.4 (C_4), 122.5 (C_5), 115.7 (C_3), 114.4 (C_7 or C ≡N).

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Registry No.—**1**, 98-92-0; **4**, 105-34-0; **5**, 102-52-3; **6**, 52718-94-2; **7**, 52718-95-3; **8**, 93-60-7; **10**, 52718-96-4; **11**, 20577-26-8; **12**, 26932-71-8; *N*-methylaniline, 100-61-8; malononitrile, 109-77-3.

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Site of N-Amination of Adenine and Alkyladenines[1]

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In contrast to the many examples of heterocyclic *N*-oxides,[2] which are useful as synthetic intermediates and interesting because some, especially in the purine series,[3] have shown biological activity, there are fewer recorded examples of the isoelectronic *N*-imines and their corresponding *N*-amino salts.[4] The *N*-amino derivatives of the nucleic acid bases are of particular interest as intermediates and with respect to their possible biological activity. We wish to report the synthesis of 1-aminoadeninium salts and the effect of alkyl substituents on adenine upon the position of N-amination.[5]

Amination of a heterocyclic nitrogen is the most direct route to *N*-amino salts. Chloramine and hydroxylamine-*O*-sulfonic acid (HSA) are the traditional reagents used for N-amination,[4,6] while *O*-mesitylenesulfonylhydroxylamine (MSH)[7] and *O*-dinitrophenoxyamine[8] are enjoying increasing favor. Adenine (**1**) failed to aminate with HSA but with MSH in methanol yielded (≥65%) an *N*-aminoadeninium

mesitylenesulfonate (**2a**), convertible to the *N*-aminoadeninium chloride (**2b**) on ion exchange resin. Of the five conceivable sites of N-amination of adenine, attack at N^6 was readily ruled out by comparison of the uv spectra of **2** with those reported for 6-hydrazinopurine.[9] Positions N-1 and N-3 were the likely targets: N-1 is the site of oxidation by H_2O_2/HOAc to form the *N*-oxide[10] while N-3 is the site of alkylation on adenine under neutral conditions.[11,12,19]

We attempted to direct the N-amination separately to the 1 and 3 positions by analogy with the reciprocal directivity observed for 1- and 9-alkyl-substituted adenines *vs.* 3- and 7-substituted derivatives.[13,14] If N-amination were similar to alkylation, a 7-alkyladenine would yield a 7-alkyl-3-aminoadeninium salt while a 9-alkyladenine would give a 9-alkyl-1-aminoadeninium salt. Employment of a labile alkyl group would permit us to remove the alkyl group and thus obtain the corresponding *N*-aminoadeninium salts. We used 9- and 7-pivaloyloxymethyladenines (**3, 5**) since the pivaloyloxymethyl (Pom) group can be removed easily by treatment with methanolic ammonia.[15] Amination of **3** and **5** and subsequent removal of the Pom group from each product resulted in the isolation, in very good yield, of the *identical N-aminoadeninium mesitylenesulfonate* originally obtained by direct amination of adenine. This result showed that 7- or 9-alkyl substituents do not direct the course of N-amination in the same way that they control the course of N-alkylation. The problem remained to establish the structure of **2a** arrived at by the three routes. Adjacency of the two NH_2 groups was shown by treatment of compound **2a** with triethyl orthoformate in dimethylformamide, which produced the known *s*-triazolo[5,1-*i*]purine (**7**)[16] in 95% yield. Accordingly, the product of amination of adenine and of representative 7- and 9-alkyladenines with *O*-mesitylenesulfonylhydroxylamine is 1-aminoadeninium mesitylenesulfonate. The locus of N-amination is not a function of the anionic portion of the MSH reagent being used, since, when the analogous alkylating agent methyl mesitylenesulfonate was employed with adenine, methylation occurred at N-3 as indicated by the uv spectrum of the product.[14] When 7-Pom-adenine (**5**) was oxidized with *m*-chloroperbenzoic acid, followed by removal of the Pom group with methanolic ammonia, the product was adenine 1-oxide as indicated by uv and tlc comparison with an authentic sample.

Analogy of the N-amination reaction is thus better drawn with N-oxidation than with N-alkylation. Theoretical predictions have not yet provided the basis for differentiation between the N-oxidation (or, now, N-amination) and N-alkylation processes,[17-20] so that further examination of the N-amination process will be necessary. The mild conditions used in the amination of adenine and alkyladenines with the reagent MSH of Tamura, *et al.*,[7] *i.e.*, 30 min at 25° in various solvents, recommend its use in sensitive or more complex systems.

Experimental Section

Melting points are uncorrected. The nmr spectra were recorded on a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard and $(CD_3)_2SO$ as the solvent unless otherwise noted. The ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer, and the infrared spectra were obtained on a Perkin-Elmer Model 337 infrared spectrophotometer in KBr pellets. Microanalyses were performed by Mr. Josef Nemeth and associates, who also weighed samples for the quantitative electronic absorption spectra. Low resolution mass spectra were obtained on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and STATOS recorder.

1-Aminoadeninium Mesitylenesulfonate (2a) and Chloride (2b). Freshly prepared *O*-mesitylenesulfonylhydroxylamine[7] (MSH) (0.63 g, 3 mmol) was added to a solution of adenine (135 mg, 1 mmol) in methanol. The solution was stirred at 25° for ~30 min and then immersed in a Dry Ice/isopropyl alcohol bath. The precipitate (200 mg) was collected from the cold mixture, and a second crop (27 mg) was collected from the cooled filtrate, for a total yield of 65%:[21] mp 244°; λ_{max} (MeOH) 263 nm; nmr δ 2.18 (s, 3, *p*-CH_3), 2.52 (s, *o*-CH_3's superimposed on solvent), 6.50 (br, 1, exchanges with D_2O, NH), 6.73 (s, 2, *m*-H's), 8.43 and 8.52 (ss, 2, purine H's); mass spectrum (70 eV) *m/e* (rel intensity) 200 (52, M − 150), 150 (76, M − 200), 135 (25), 120 (97), 118 (100).

The chloride salt **2b** (88% recovery) was obtained by passing **2a** through a Dowex-1 (Cl^-) column. One recrystallization from water afforded an analytical sample: mp 252°; λ_{max} (H_2O) ($\epsilon \times 10^{-3}$) at pH 1 256 (10.3), at pH 7 263 (11.1), at pH 12 269 (13.7); mass spectrum (70 eV) *m/e* (rel intensity) 150 (100, M − HCl), 123 (15, 150 − HCN).

Anal. Calcd for $C_5H_7ClN_6$: C, 32.18; H, 3.78; N, 45.01. Found: C, 31.89; H, 3.84; N, 44.78.

***N*-Amino-9-pivaloyloxymethyladeninium Mesitylenesulfonate (4).** Freshly prepared MSH[7] (0.6 g) was added to a solution of 9-pivaloyloxymethyladenine[15] (100 mg, 0.4 mmol) in 50 ml of acetone. The solution was stirred at 25° for 30 min, and a white precipitate of **4** was collected: 174 mg (94% yield); darkening at 254° and mp 261° (sealed tube); λ_{max} (H_2O) ($\epsilon \times 10^{-3}$), at pH 1 256 (12.0), at pH 7 256 (11.9), at pH 12 268–269 (13.9); nmr δ 1.11 (s, 9, Pom CH_3's), 2.15 (s, 3, *p*-CH_3), 2.49 (s, *o*-CH_3's superimposed on solvent), 6.18 (s, 2, Pom CH_2), 6.57 (s, 1, exchanges with D_2O, NH), 6.70 (s, 2, *m*-H's), 8.55 and 8.63 (ss, 2, purine H's); mass spectrum (70 eV) *m/e* (rel intensity), 264 (34, M − 200), 200 (24, M − 264), 150 (78), 135 (23), 57 (100).

Anal. Calcd for $C_{20}H_{28}N_6O_5S$: C, 51.71; H, 6.08; N, 18.09. Found: C, 51.46; H, 5.94; N, 17.85.

Cleavage of the 9-Pom Group of 4. A solution of 120 mg of the *N*-amino-9-Pom-adeninium mesitylenesulfonate (**4**) in methanol saturated with ammonia was allowed to stand overnight at 25°. The solution was then evaporated to dryness *in vacuo*, the residue was washed with ether, and the solid was collected by centrifugation. Recrystallization from methanol gave 57 mg (62%) of chromatographically (tlc) pure **2a:** mp 241–242°; λ_{max} (H_2O) at pH 1 258, at pH 7 264, at pH 12 269; nmr δ 2.18 (s, 3, *p*-CH_3), 2.49 (s, *o*-CH_3's superimposed on solvent), 6.50 (br, 1, exchanges with D_2O, NH), 6.72 (s, 2, *m*-H's), 8.43 and 8.52 (ss, 2, purine H's); mass spectrum (70 eV), *m/e* (rel intensity), 200 (50, M − 150), 150 (100,

M − 200), 135 (73), 118 (93); the ir spectrum was superimposable on that of the product of the direct amination of adenine.

***N*-Amino-7-pivaloyloxymethyladeninium Mesitylenesulfonate (6).** In a procedure similar to that used for the preparation of **4**, 0.5 g of MSH and 150 mg of 7-Pom-adenine[15] gave 185 mg (67%) of compound **6**: mp 230–231°; λ_{max} (H_2O) ($\epsilon \times 10^{-3}$) at pH 1 266 (8.76), at pH 7 261 (10.3), at pH 12 269 (12.5); nmr δ 1.10 (s, 9, Pom CH_3's), 2.17 (s, 3, *p*-CH_3), 2.50 (s, *o*-CH_3's superimposed on solvent), 6.38 (s, 3, 1 H exchanges with D_2O, Pom CH_2, and NH), 6.72 (s, 2, *m*-H's), 8.38 and 8.55 (ss, 2, purine H's); mass spectrum (70 eV), *m/e* (rel intensity), 264 (21, M − 200), 200 (26, M − 264), 179 (24), 150 (30), 135 (20), 57 (100).

Anal. Calcd for $C_{20}H_{28}N_6O_5S \cdot \frac{1}{2}H_2O$: C, 50.73; H, 6.17; N, 17.75. Found: C, 50.60; H, 5.99; N, 17.65.

Cleavage of the 7-Pom Group of 6. A solution of 120 mg of the *N*-amino-7-Pom-adeninium mesitylenesulfonate in methanol saturated with ammonia was allowed to stand at 25° for 6 hr. The solution was evaporated to dryness *in vacuo*, the residue was washed with ether, and the solid was collected by centrifugation. Recrystallization from methanol gave **2a** in chromatographic purity (tlc): yield, 66%; mp 243–244°, λ_{max} (H_2O) at pH 1 257, at pH 7 265, at pH 12 270; nmr δ 2.18 (s, 3, *p*-CH_3), 2.50 (s, *o*-CH_3's superimposed on solvent), 6.51 (s, 1, exchanged with D_2O, NH), 6.72 (s, 2, *m*-H's), 8.43 and 8.52 (ss, 2, purine H's); mass spectrum (70 eV), *m/e* (rel intensity), 200 (43, M − 150), 150 (65, M − 200), 135 (17), 118 (100); the ir spectrum was superimposable on that of the product of direct amination of adenine and on the spectrum of the 9-Pom (4) cleavage product.

***s*-Triazolo[5,1-*i*]purine (7).** Triethyl orthoformate (5 ml) was added to a suspension of **2a** (680 mg, 1.95 mmol) in 25 ml of dry dimethylformamide. The mixture was heated at reflux for 5 min, allowed to cool, and the volatile material was removed *in vacuo*. The resulting solid was suspended in methanol and filtered to afford **7**: 226 mg (95% yield); mp >300°; the uv spectra were identical with reported spectra;[16] λ_{max} (H_2O) at pH 1 261, 273, at pH 7 262 and 277, at pH 12 290; nmr δ 8.48 (s, 1), 8.60 (s, 1), 9.58 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity), 160 (100, M). This compound is weakly fluorescent, showing an emission maximum of 349 nm upon excitation at 291 nm.

Registry No.—**2a**, 52500-49-9; **2b**, 52500-50-2; **4**, 52500-52-4; **6**, 52500-54-6; **7**, 4022-94-0; *O*-mesitylenesulfonylhydroxylamine, 36016-40-7; adenine, 73-24-5; 9-pivaloyloxymethyladenine, 18997-21-2; 7-pivaloyloxymethyladenine, 18997-22-3; triethyl orthoformate, 122-51-0.

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Synthesis of 2-Cyano, 2-Acyl, and 2-Carboxamido Derivatives of 3-Aminobenzo[*b*]thiophene Involving Nitro Displacement

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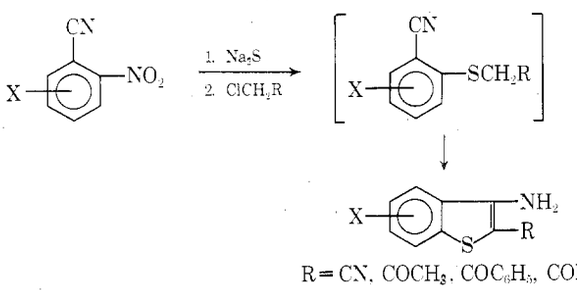
Until recently, 3-aminobenzo[*b*]thiophenes, substituted at the 2 position with cyano or acyl functions, were inaccessible. Clarke and coworkers[1] reported the synthesis of 3-aminobenzo[*b*]thiophene-2-carbonitrile by the reaction of *o*-mercaptobenzonitrile[2] with chloroacetonitrile in aqueous alkali. Similarly prepared were 3-aminobenzo[*b*]thien-2-yl methyl and phenyl ketones using chloroacetone and phenacyl chloride, respectively. The same authors[3] also described the preparation of the methyl ketone from 3-chloro-1,2-benzisothiazole[4] and pentane-2,4-dione in the presence of sodium ethoxide. A facile synthesis of N-substituted 3-aminobenzo[*b*]thien-2-yl ketones from 3-chloro-1,2-benzisothiazolium chlorides[5] and methyl ketones has been reported by Böshagen and Geiger.[6] In an earlier paper,[7] we described the preparation of methyl 3-aminobenzo[*b*]thiophene-2-carboxylate esters from *o*-nitrobenzonitriles and methyl thioglycolate in the presence of base. The reaction involved displacement of the activated nitro group by thioglycolate anion and subsequent base-catalyzed ring closure. Attempts to extend the scope of this procedure for the synthesis of the analogous 2-cyano and 2-acyl derivatives were frustrated by the instability or inaccessibility of the required mercaptan reagents.

We now wish to report two related processes, both involving nitro displacement, for the preparation of these compounds. In the first, an *o*-nitrobenzonitrile was allowed to react with sodium sulfide in aqueous DMF. The nitro group was readily displaced at ice bath temperature, and the anion of the corresponding *o*-mercaptobenzonitrile was formed (Scheme I). *In situ* alkylation with chloroacetonitrile, chloroacetone, or phenacyl chloride, with subsequent sulfide-catalyzed cyclization, yielded the corresponding 3-aminobenzo[*b*]thiophene-2-carbonitriles, 3-aminobenzo[*b*]thien-2-yl methyl ketones, or phenyl ketones, respectively. The procedure was also used as an alternate method of synthesis for 3-aminobenzo[*b*]thiophene-2-carboxamides[8] when chloroacetamide was utilized as the alkylating agent. The derivatives prepared and the yields obtained are summarized in Table I. When the starting nitrile was 2-chloro-5-nitrobenzonitrile, the 2-cyano (**10**) and 2-benzoyl (**11**) derivatives of 3-amino-5-nitrobenzo[*b*]thiophene were readily formed by a process involving active chlorine displacement.

Scheme I



R = CN, $COCH_3$, COC_6H_5, $CONH_2$

When *o*-nitrobenzonitrile or 6-nitro-*o*-anisonitrile was subjected to the initial reaction conditions, sulfide displacement did not occur even at 100° during an extended