workup was hydrolyzed with acetic acid/THF/water (20:10:3) at 40 °C for 4 h. The crude material was chromatographed on silica gel to give 0.210 g of **3d**: ultraviolet and CD spectra are given in Table I; ^{1}H NMR ($CDCl_3$) δ 8.03 (m, 2 H, ortho aromatic protons), 7.50 (m, 3 H, other aromatic protons), 5.72–5.12 (m, 5 H, olefinic protons, >CHOCO–), 4.30–3.70 (m, 2 H, C_{11} and C_{15} protons), 3.60 (s, 3 H, $COOCH_3$), 0.88 (t, 3 H, J = 5 Hz, CH_3); high-resolution mass spectrum (bis(trimethylsilyl) derivative), m/e 616.3592 (calcd for $C_{34}H_{56}Si_2O_6$ 616.3615), 601, 585, 545, 494, 455, 423, 404, 333, 263, and 173. Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 70.98; H, 8.91.

Prostaglandin $F_{2\alpha}$ 11-Benzoate Methyl Ester (3e). A solution of $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester[10] (482 mg) in pyridine (5 mL) was stirred at room temperature with benzoyl chloride (0.12 mL) for 1 h. After workup, the crude reaction product was stirred with acetic acid/THF/water (3:1:1) in order to remove the protecting group from the C-15 hydroxyl. The crude hydrolyzed product was chromatographed on silica gel to give pure **3e** (280 mg) as a viscous oil: NMR ($CDCl_3$) δ 8.01 (m, 2 H, ortho aromatic protons), 7.43 (m, 3 H, other aromatic protons), 5.57 (m, 2 H, CH=CH), 5.40 (m, 2 H, CH=CH), 5.10 (m, 1 H, >CHOCO–), 4.15 (m, 2 H, >CHOH), 3.64 (s, 3 H, $COOCH_3$), 0.83 (t, 3 H, J = 5 Hz, CH_3); for ultraviolet and CD spectra, see Table I; high-resolution mass spectrum (bis(trimethylsilyl) derivative), m/e 616.3605 (calcd for $C_{34}H_{56}Si_2O_6$ 616.3615), 494, 423, 333, and 199. Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 70.88; H, 8.53. The ultraviolet spectrum of **3e** is consistent with the introduction of one benzoyl group into the molecule. The other spectral properties of the molecule clearly differentiate **3e** from the isomeric 9-benzoate (**3d**); therefore **3e** must be the 11-benzoate.

Prostaglandin $F_{2\alpha}$ 9,11-Dibenzoate Methyl Ester (3f). A solution of $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester[10] (144 mg, 0.3 mmol) in pyridine (2 mL) was stirred with benzoyl chloride (169 mg, 1.2 mmol) at room temperature for 2 h. After workup, the *tert*-butyldimethylsilyl protecting group was removed by stirring the dibenzoate in acetic acid/THF/water (3:1:1) at room temperature overnight. There was obtained after workup 149 mg of an oil which was chromatographed (high-performance LC) on 34 g of analytical grade silica gel by using 30% ethyl acetate in hexane as eluant. Pure **3f** (127 mg, 0.2 mmol, 66%) was obtained in fractions (10 mL each) 16–24 as a colorless oil: IR (neat) ν_{OH} 3500, $\nu_{C=O}$ 1715, $\nu_{C=C}$ 1600, 1585, 1490 cm^{-1}; NMR ($CDCl_3$) δ 7.72 (m, 10 H, aromatic), 5.73 (m, 2 H, CH=CH), 5.42 (m, 4 H, CH=CH, 2>CH–OCO–), 4.16 (m, 1 H, >CHOH), 3.65 (s, 3 H, $COOCH_3$), 0.88 (t, 3 H, J = 5 Hz, CH_3); UV and CD, see Table I; mass spectrum, m/e 648.3475 (calcd for trimethylsilyl ether, $C_{38}H_{52}SiO_7$, 648.3482), 633, 617, 605, 577, 527, 526, 455, 404, 333, 314, 105. Anal. Calcd for $C_{33}H_{44}O_7$: C, 72.89; H, 7.69; Found: C, 72.54; H, 7.88.

Prostaglandin $F_{2\alpha}$ Tribenzoate Methyl Ester (3g). A solution of $PGF_{2\alpha}$ methyl ester (0.119 g) in pyridine (5 mL) was stirred with benzoyl chloride (0.25 mL) for 3 h. TLC indicated that complete benzoylation was slow, one of the hydroxyl groups being more resistant to esterification. After workup, the crude product was chromatographed on a silica gel column. The pure tribenzoate[13] (**3g**, 0.075 g) was obtained as a viscous oil: NMR ($CDCl_3$) δ 7.98 (m, 6 H, ortho aromatic protons), 7.41 (m, 9 H, other aromatic protons), 5.80 (m, 2 H, –CH=CH–), 5.40 (m, 5 H, CH=CH, >CHOCO–), 3.60 (s, 3 H, $COOCH_3$), 0.87 (t, 3 H, J = 5 Hz, CH_3); mass spectrum, m/e 680.3317 (calcd for $C_{42}H_{48}O_8$ 680.3349).

11-*epi*-Prostaglandin $F_{2\beta}$ 9,11-Dibenzoate Methyl Ester (4). The procedure of Mitsunobu and Yanaba[14] was used. $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester (1.21 g, 2.5 mmol) was dissolved in THF (125 mL). With stirring at 20 °C, triphenylphosphine (2.62 g, 10 mmol), benzoic acid (1.21 g, 10 mmol), and, slowly, diethylazodicarboxylate (1.74 g, 10 mol) were added sequentially to the solution. The starting material was consumed within 30 min as determined by TLC. Excess THF was removed under reduced pressure. Hexane–20% ethyl acetate (100 mL) was added to the residue. Crystals formed and after several hours these were removed by filtration. The filtrate was concentrated and the residue (3.7 g) was chromatographed (high-performance LC) on a Merck size C Lobar silica gel column by using 5% acetone in hexane. Appropriate fractions were combined and rechromatographed under the same conditions. In this way the intermediate 11-*epi*-$PGF_{2\beta}$ 9,11-dibenzoate 15-*tert*-butyldimethylsilyl ether methyl ester (0.580 g) was obtained. The latter was hydrolyzed in 10 mL of a solution made up of acetic acid (27 mL), THF (9 mL), water (9 mL), and 1 N aqueous HCl (24 drops) for 4 h at room temperature. After workup, the crude product (0.420 g) was chromatographed on a Merck size B Lobar silica gel column by using 15% acetone–hexane. The pure dibenzoate **4** (0.350 g) was a viscous oil: NMR ($CDCl_3$) δ 8.00 (m, 4 H, ortho aromatic protons), 7.43 (m, 6 H, other aromatic protons), 5.68 (m, 2 H, CH=CH), 5.45, 5.25 (m, 4 H, CH=CH, >CHOCO–), 4.02 (m, 1 H, >CH–O–), 3.63 (s, 3 H, $COOCH_3$), 0.84 (t, 3 H, J = 5 Hz, CH_3); mass spectrum, m/e 648, 635, 577.2642 (calcd for $M^+ - C_5H_{11}$, $C_{33}H_{42}SiO_7$; 577.2621), 404, 333, 314, 199, and 105.

Acknowledgment. We thank R. J. Wnuk for the mass spectral data reported herein and J. A. Woltersom for technical assistance. We also thank Professor A. Moscowitz for discussions of these results.

Registry No. 2a, 73070-13-0; **2a** *tert*-butyldimethylsilyl ether, 73078-82-7; **2a** trimethylsilyl ether, 73070-14-1; **2b**, 73089-63-1; **2b** trimethylsilyl ether, 73135-94-1; **2c**, 73070-15-2; **2d**, 73089-64-2; **2e**, 73070-16-3; **2f**, 73089-65-3; **3a**, 73070-17-4; **3a** bis(trimethylsilyl) ether, 73070-18-5; **3b**, 73070-19-6; **3b** bis(trimethylsilyl) ether, 73070-20-9; **3c**, 73070-21-0; **3c** trimethylsilyl ether, 73070-22-1; **3d**, 64982-03-2; **3d** bis(trimethylsilyl) ether, 73070-23-2; **3e**, 73070-24-3; **3e** bis(trimethylsilyl) ether, 73070-05-0; **3f**, 73070-06-1; **3f** trimethylsilyl ether, 73070-07-2; **3g**, 59895-13-5; **4**, 73070-08-3; 3α,5α-dihydroxy-2β-(3′-oxo-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether, 64072-25-9; 3α,5α-dihydroxy-2β-(3′-oxo-*trans*-1′-octenyl)cyclopentane-1-acetic acid γ-lactone, 60623-67-8; (3′*S*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether, 64072-30-6; (3′*R*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether, 64091-16-3; $PGF_{2\alpha}$ methyl ester, 33854-16-9; $PGF_{2\alpha}$ methyl ester 9,11-*n*-butylboronate ester, 73070-09-4; 15-*epi*-$PGF_{2\alpha}$ methyl ester, 13228-05-2; 15-*epi*-$PGF_{2\alpha}$ methyl ester 9,11-*n*-butylboronate ester, 73070-10-7; (3′*S*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone, 26054-67-1; (3′*R*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone, 39182-59-7; $PGF_{2\alpha}$ methyl ester 11,15-bis(ethoxyethyl) ether, 73070-11-8; $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester, 65147-38-8; 11-*epi*-$PGF_{2\beta}$ 9,11-bisbenzoate 15-*tert*-butyldimethylsilyl ether methyl ester, 73070-12-9.

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Synthesis of Natural Isocoumarins, Artemidin and 3-Propylisocoumarin

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It has been demonstrated, principally by Castro and co-workers, that a variety of heterocyclic compounds may be obtained by the interaction of cuprous acetylides with aryl halides bearing ortho nucleophilic substituents.[1] The claim made in 1963 that cuprous phenylacetylide reacted with *o*-iodobenzoic acid (**1**) to yield 3-phenylisocoumarin (**2**)[1a,b] led to the suggestion, in a review of the chemistry

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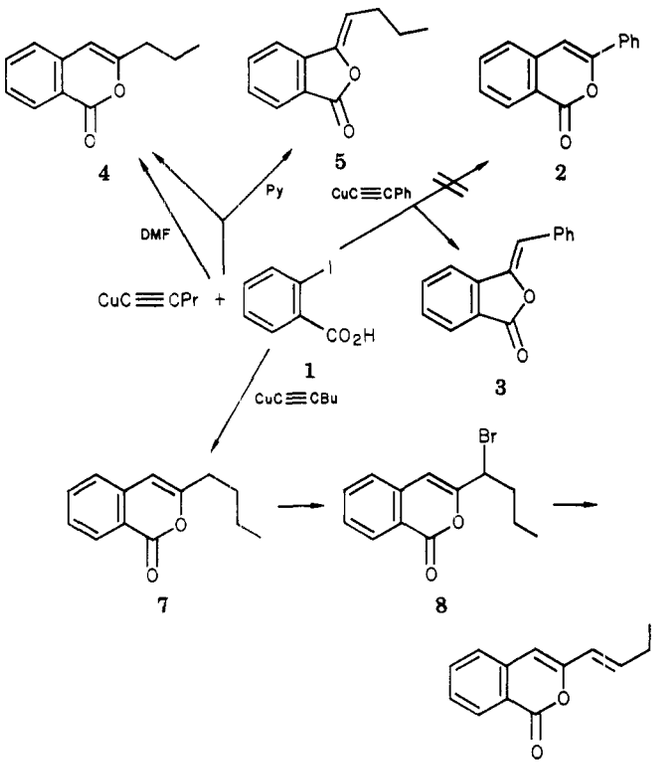
Scheme I



of isocoumarins,[2] that this may be regarded as a promising route to 3-substituted isocoumarins. This hope was apparently dashed a few years later,[1c] when the original workers reported that the product had been erroneously identified and was, in fact, 3-benzylidenephthalide (**3**) (see Scheme I). In an extended study of the scope of the reaction, they indicated that it provided instead the basis of a general preparation of phthalides. In only one case of nine examples studied, namely the reaction of **1** with cuprous *n*-propylacetylide, was an isocoumarin detected, and this yielded a mixture of 3-*n*-propylisocoumarin (**4**) and 3-*n*-butylidenephthalide (**5**) which could not be separated.

We considered it possibly significant that the formation of an isocoumarin resulted in the sole reported example in which a cuprous *alkyl*acetylide was employed and consequently that this simple procedure, with appropriate experimental modification, might yet provide an acceptable synthetic route to 3-alkylisocoumarins and dihydroisocoumarins, at least 30 of which have already been isolated as natural products. This has been realized, and the synthesis of two natural isocoumarins, 3-propylisocoumarin (**4**) and artemidin (**6**), are herein reported.

The product, $C_{12}H_{12}O_2$, obtained from the roots of *Felicia wrightii* Hilliard et Burtt., was assigned the structure 3-propylisocoumarin (**4**) on the basis of spectrometric data.[3] In a preliminary experiment, whereby *o*-iodobenzoic acid (**1**) was heated with cuprous *n*-propylacetylide in pyridine solution for 22 h, we reproduced the essential finding of Castro,[1c] i.e., the isocoumarin (**4**) and phthalide (**5**) were present in ca. 2:1 ratio as an inseparable mixture. We noted, however, that this ratio varied with reaction time, with longer periods resulting in greater 4:5 ratios. A further marked change resulted from conducting the reaction of dimethylformamide solution, when after 4 days no phthalide was detected in the ^1H NMR spectrum of the crude product. Under these conditions, the natural product, 3-propylisocoumarin (**4**), was readily isolated in 60% yield in a one-step synthesis. It was actually first synthesized[4] by a seven-step route described 16 years prior to the reported natural occurrence, and more recently by a shorter route involving a molecular rearrangement.[5]

This cuprous alkylacetylide–halobenzoic acid coupling reaction was then used as the key step in a short synthesis of artemidin (**6**), the isolation of which was reported independently and almost simultaneously from *Anthemis fuscata* Brot.[6] and *Artemisia dracunculus* L.[7] The 3-but-1′-*trans*-enylisocoumarin structure suggested for this product is well founded on spectroscopic[6,7] and chemical properties[8] and the cis isomer has also recently been isolated.[9] Treatment of the iodo acid **1** with cuprous *n*-butylacetylide cleanly afforded dihydroartemidin (**7**). This was readily converted to the natural product **6** in two steps. Allylic bromination of **7** with *N*-bromosuccinimide gave the 1′-bromo product **8** which underwent smooth elimination on treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene.

Experimental Section

NMR spectra were determined for solutions in [^2H]chloroform with tetramethylsilane as internal standard by using a Bruker FT 90-MHz instrument. Alumina (Fisher Adsorption, 80–200 mesh) and silica gel (Davison, Grade 12, 28–200 mesh) were used for chromatography.

Pent-1-yne and hex-1-yne, from which the cuprous salts were obtained as yellow solids (by standard treatment[1c,h] with copper sulfate pentahydrate and hydroxylamine hydrochloride in ammonium hydroxide), were used as commercially available (Farchan) without further purification.

Reaction of *o*-Iodobenzoic Acid (1) with Cuprous *n*-Propylacetylide in Pyridine Solution. The two reagents were added to pyridine and heated under reflux for 22 h. The presence of isocoumarin **4** and phthalide **5** in the crude product were indicated by infrared absorption (in CCl_4) at 1743 and 1790 cm^{-1}, respectively, and by the ^1H NMR spectrum showing vinyl proton absorption at δ 6.26 (s) and 5.65 (t), respectively. Integration of the vinyl proton absorption signals gave an isocoumarin:phthalide ratio of ca. 2:1. In another experiment (26 h reflux), a ratio of 2.6:1 was found. Attempts to separate **4** and **5** on a preparative scale were unsuccessful.

3-*n*-Propylisocoumarin (4). A solution of *o*-iodobenzoic acid (10 g) in dimethylformamide (150 mL) was added to a suspension of cuprous propylacetylide (5.22 g) in the same solvent (300 mL) and the mixture heated under reflux for 4 days (first 2 days under nitrogen atmosphere). It was then cooled, diluted with ether (500 mL), set aside at 0 °C overnight, and filtered. The filtrate was evaporated under reduced pressure, the residue dissolved in chloroform, and the solution filtered, washed successively with brine and water, dried ($MgSO_4$), and evaporated. A solution of this residue in benzene was filtered through a short column of alumina to yield 3-*n*-propylisocoumarin as a light yellow oil (6.97 g): IR (CCl_4) 1745 (CO) and 1660 (C=C) cm^{-1}; NMR δ 0.99 (t, J = 7 Hz, Me), 1.71 (m, 2′-CH_2), 2.52 (t, J = 7 Hz, 1′-CH_2), 6.26 (s, H-4), 7.34 (br d, J = 7.5 Hz, H-5), 7.44 (ddd, J = 7.5, 7.5, 1.5 Hz, H-7), 7.68 (ddd, J = 7.5, 7.5, 1.5 Hz, H-6), and 8.25 (br d, J

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= 7.5 Hz, H-8). This spectrum is in excellent agreement with that reported.[3]

3-*n*-Butylisocoumarin (Dihydroartemidin) (7). A solution of *o*-iodobenzoic acid (20 g) in dimethylformamide (250 mL) was added to a suspension of cuprous *n*-butylacetylide (12.73 g) in the same solvent (250 mL), and the mixture was refluxed and worked up as in the previous experiment to yield dihydroartemidin as an oil, which crystallized from ether–light petroleum as colorless cubes (7.14 g): mp 49.5–50.5 °C (lit.[8] mp 45–46 °C); NMR δ 0.94 (t, *J* = 7.5 Hz, H-4'), 1.19–2.05 (m, H-2' and 3'), 2.50 (t, *J* = 7.5 Hz, H-1'), 6.23 (s, H-4), 7.36 (br d, *J* = 8 Hz, H-5), 7.38 (ddd, *J* = 7.5, 7.5, 1.5 Hz, H-7), 7.66 (ddd, *J* = 7.5, 7.5, 1.5 Hz, H-6), and 8.21 (br d, *J* = 7.5 Hz, H-8). Saponification as described[8] gave the keto acid, mp 89–90 °C (lit.[8] 85–86 °C), which yielded the 2,4-dinitrophenylhydrazone, mp 179–180 °C (lit.[8] 174–175 °C).

1'-Bromo-3-*n*-butylisocoumarin (8). *N*-Bromosuccinimide (7.14 g) was added to a solution of dihydroartemidin (7.14 g) in carbon tetrachloride (150 mL) and the mixture heated under reflux for 10 h, then cooled, filtered, and evaporated. A solution of the residue was filtered first through a short column of alumina and then through silica gel. Crystallization of the eluted product from methanol or light petroleum gave 1'-bromo-3-*n*-butylisocoumarin as rectangular prisms (4.65 g): mp 69.5–70 °C; NMR δ 0.97 (t, *J* = 7 Hz, Me), 1.3–1.75 (m, H-3'), 2.21 (q, *J* = 7.5 Hz, H-2'), 4.71 (t, *J* = 7.5 Hz, H-1'), 6.55 (s, H-4), 7.42 (br d, *J* = 7.5 Hz, H-5), 7.52 (ddd, *J* = 7.5, 7.5, 1.5 Hz, H-7), 7.73 (ddd, *J* = 7.5, 7.5, 1.5 Hz, H-6), and 8.28 (dd, *J* = 7.5, 1.5 Hz, H-8). Anal. Calcd for $C_{13}H_{13}O_2Br$: C, 55.53; H, 4.66. Found: C, 55.84; H, 4.61.

Artemidin (6). A solution of 1,5-diazabicyclo[5.4.0]undec-5-ene (1.75 g) in benzene (75 mL) was added to a solution of the 1'-bromoartemidin (8) (3.23 g) in the same solvent (75 mL) and the mixture heated under reflux under nitrogen for 10 h. It was diluted with ether, washed with dilute sulfuric acid and water, and dried ($MgSO_4$). The residue obtained on evaporation was dissolved in benzene and filtered through a short column of alumina, and the product crystallized from light petroleum to give artemidin (3-but-1'-*trans*-enylisocoumarin) as prisms: mp 49.5–50.5 °C (lit.[8] mp 49–50 °C); NMR δ 1.09 (t, *J* = 7.5 Hz, Me), 2.25 (m, H-3'), 6.01 (dt, *J* = 15.5, 1.5 Hz, H-1'), 6.25 (s, H-4), 6.68 (dt, *J* = 15.5, 6.5 Hz, H-2'), 7.35 (br d, *J* = 8 Hz, H-5), 7.40 (ddd, *J* = 7.5, 7.5, 1.5 Hz, H-7), 7.65 (ddd, *J* = 7.5, 7.5, 1.5 Hz, H-6), and 8.22 (br d, *J* = 7.5 Hz, H-8).

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Registry No. 1, 88-67-5; 4, 13141-35-0; 5, 72917-31-8; 6, 29428-84-0; 7, 30531-69-2; 8, 72917-32-9; 2-(2-oxohexyl)benzoic acid, 30531-71-6; 2-(2-oxohexyl)benzoic acid 2,4-dinitrophenylhydrazone, 30650-58-9; CuC≡CPr, 19093-51-7; CuC≡CBu, 33589-44-5.

Communications

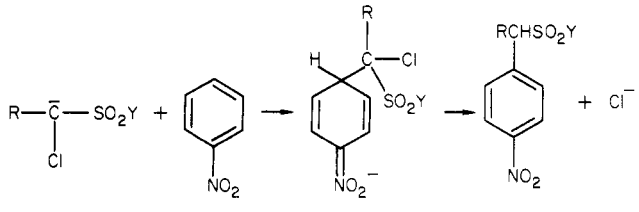
Vicarious Substitution of Hydrogen in Aromatic Nitro Compounds with Acetonitrile Derivatives[1]

Summary: Carbanions of α-phenoxy and thioalkoxy nitriles substitute hydrogen in the para or ortho position of aromatic nitro compounds, giving nitroarylacetonitriles in a process in which phenolate or thiolate anions are vicarious leaving groups.

Sir: In a preceding paper[2] we described the general principle of "vicarious" nucleophilic substitution of hydrogen in aromatic nitro compounds by carbanions derived from 1-haloalkylphenyl sulfones and *N,N*-dialkyl-1-haloalkanesulfonamides. The main feature of this process is that the α-halocarbanions attack an unsubstituted carbon atom of an aromatic nitro compound, giving an intermediate σ complex. The latter, upon loss of halide anion, gives rise to the product (Scheme I).

One could expect that this novel substitution could proceed with other C–H acids containing leaving groups in the α position. However, such C–H acids are usually active electrophiles. Therefore, the success of the vicarious substitution process would depend on the relative rates of the reactions of the carbanions with aromatic nitro compounds and with the starting C–H acid–carbanion precursors. α-Chloroalkanenitriles would be suitable reactants providing the rate of the reaction with aromatic nitro compounds is sufficiently high. Indeed, chloroacetonitrile in the presence of NaOH in Me_2SO reacts with 1-nitronaphthalene and 4-chloronitrobenzene, affording

Scheme I



Y = Ph, NR_2

the corresponding α-nitroarylacetonitriles in fair yields. With nitrobenzene or 4-nitrobiphenyl the substitution process does not occur; instead, chloroacetonitrile is completely destroyed, and the nitro compounds are essentially unaffected.

As is shown in Scheme I, vicarious substitution involves departure of the leaving group from an anionic σ complex. Hence, one could assume that α substituents such as phenoxy, alkoxy, and their corresponding thio analogues should also be able to serve as leaving groups in this process. This possibility would be of interest since these groups cannot be easily displaced via S_N2 type processes; yet they are good leaving groups from anionic intermediates, as, for example, in the case of transesterification or substitution of the methoxy group in *p*-nitroanisole.

Accordingly we investigated the reactions of aryloxy and alkoxy derivatives of acetonitrile and their thio analogues with aromatic nitro compounds in the presence of strong bases. In accord with our expectations, these nitriles indeed reacted with a variety of nitroarenes by vicarious substitution and yielded nitroarylated derivatives of acetonitrile or phenylacetonitrile, respectively.

The products of the substitution contain nitroaryl sub-

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