$CDCl_3$) δ 8.15 (C-8a), 19.14 (C-3a), 21.63 (C-1a), 36.33 (C-4), 69.39 (C-3), 68.34 (C-1), 111.80 (C-9a), 119.77 (C-5), 126.99 (C-8), 137.19 (C-10a), 144.19 (C-4a), 153.58 (C-7), and 157.82 (C-10) (other signals were too weak); MS, m/z 288 (16) $(M)^+$, 273 (100). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.61; H, 5.73.

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Registry No. **1a**, 124917-66-4; **1a** (10-methyl ester), 124821-11-0; **1b**, 124917-67-5; **2**, 124917-65-3; **3**, 124854-79-1; **4**, 124821-02-9; **5**, 124821-03-0; **6**, 124821-04-1; **7**, 124821-05-2; **8**, 6971-52-4; **9**, 88010-47-3; **10**, 54490-80-1; **11**, 24605-23-0; **12**, 1123-64-4; **13**, 30839-34-0; **14**, 84568-08-1; **15**, 124821-06-3; **16**, 124821-07-4; **17**, 124821-08-5; **18**, 124917-64-2; **19a**, 124821-09-6; **20**, 124821-10-9; $MeO_2CCH_2COCH_3$, 105-45-3; $CH_3CH{=}CHCOCl$, 10487-71-5; 2-methylresorcinol, 608-25-3.

Preparation of Novel 4-Substituted 6-Methoxy-, 6,7-Dimethoxy-, and 6,7-(Methylenedioxy)isochroman-3-ones. 2

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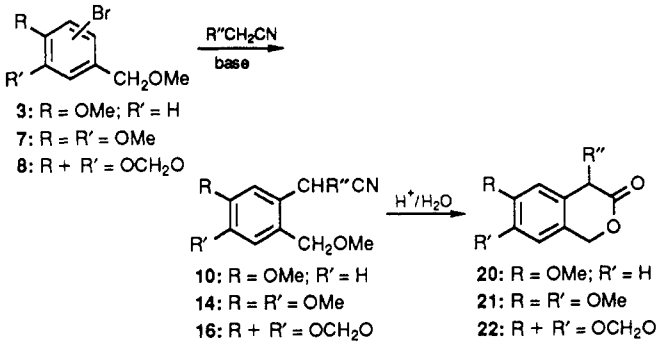
The titled compounds **20**, **21**, and **22** have been prepared in modest yields by a two-step reaction involving first the reaction of bromoarenes **3**, **7**, and **8** with lithioalkyl- and lithioarylacetonitriles under aryne-forming conditions. The cyano products **10**, **14**, and **16** so formed were then converted to the corresponding isochroman-3-ones by acidic hydrolysis.

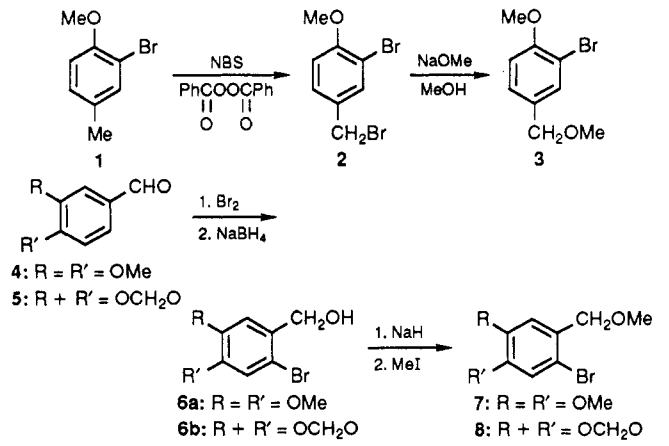
Introduction

Spangler[1] has shown that gas-phase pyrolysis of isochroman-3-ones furnishes synthetically useful *o*-quinodimethanes, several of which have served as valuable intermediates in natural product synthesis.[2] For example, the key step in the synthesis of deoxyisosikkimotoxin involves trapping the *o*-quinodimethane, obtained by the pyrolysis of the corresponding 6,7-dimethoxyisochroman-3-one, with *N*-phenylmaleimide.[3] 3-Isochromanones have also been converted by nonpyrolytic means to derivatives of isoquinoline,[4] thioisoquinoline,[5] and epoxyethanophenanthrene.[6]

Scheme I



Scheme II



We recently described[7] an efficient, two-step synthesis of novel 4-alkyl and 4-aryl derivatives of 6-(acetoxymethyl)isochroman-3-ones in which the key step involves the addition of a nitrile anion to 3,6-bis(methoxy-

(1) Spangler, R. J.; Beckmann, B. G.; Kim, J. H. *J. Org. Chem.* **1977**, *42*, 2989.

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0022-3263/90/1955-1471$02.50/0

Table I

entry	haloarene	nitrile	base	nitrile product, % yield[d]	isochromanones, % yield
1	3	CH_3CN	a	**10a**, 30[e]	**20a**, 30
2	3	CH_3CH_2CN	a	**10b**, 45[e]	**20b**, 31
3	3	$CH_3CH_2CH_2CN$	a	**10c**, 42[e]	**20c**, 35
4	3	$C_6H_5CH_2CN$	a	**10d**, 25[e]	**20d**, 33
5	3	3-MeO-$C_6H_4CH_2CN$	a	**10e**, 25[e]	**20e**, 35
6	3	4-MeO-$C_6H_4CH_2CN$	a	**10f**, 27[e]	**20f**, 37
7	3	3,4-$(MeO)_2$-$C_6H_3CH_2CN$	a	**10g**, 20[e]	**20g**, 60
8	3	3,4,5-$(MeO)_3$-$C_6H_2CH_2CN$	a	**10h**, 15[e]	**20h**, 35
9	7	CH_3CN	b	**14a**, 42	**21a**, 20
10	7	CH_3CH_2CN	b	**14b**, 66	**21b**, 53
11	8	CH_3CN	b	**16a**, 35	**22a**, 27
12		CH_3CN	c	**16a**, 66	
13	8	CH_3CH_2CN	b	**16b**, 40	**22b**, 55
14		CH_3CH_2CN	c	**16b**, 68	
15	8	4-MeO-$C_6H_4CH_2CN$	b	**16c**, 47	**22c**, 37
16	8	3-MeO-$C_6H_4CH_2CN$	b	**16d**, 45	**22d**, 35
17	8	3,4-$(MeO)_2$-$C_6H_3CH_2CN$	b	**16e**, 25	**22e**, 48
18	8	3,4,5-$(MeO)_3$-$C_6H_2CH_2CN$	b	**16f**, 28	**22f**, 44
19	8	3,4,5-$(MeO)_3$-$C_6H_2CH_2CN$	c	**16f**, 27	
20	8	4-F-$C_6H_4CH_2CN$	b	**16g**, 57	**22g**, 74
21	8	3-F-$C_6H_4CH_2CN$	b	**16h**, 58	**22h**, 55
22	8	2-F-$C_6H_4CH_2CN$	b	**16i**, 61	**22i**, 51
23	8	3,4-(methylenedioxy)-$C_6H_3CH_2CN$	b	**16j**, 30	**22j**, 53
24	8	3,4-(methylenedioxy)-$C_6H_3CH_2CN$	c	**16j**, 22	

[a] $NaNH_2/NH_3$. [b] LDA. [c] LiTMP. [d] Chromatographically isolated pure product. [e] Minor amount of other isomer was also obtained in approximate ratio of 9:1.

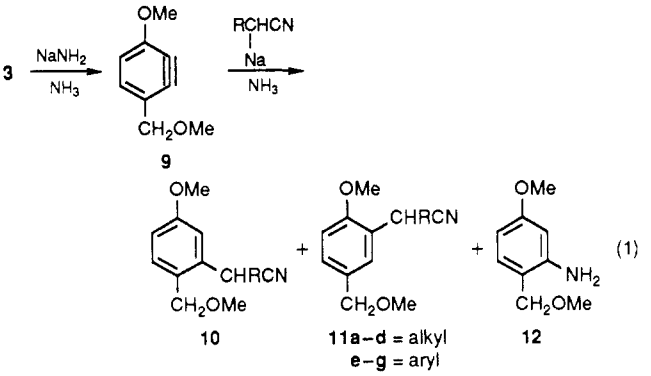
methyl)benzyne forming an *o*-(methoxymethyl)-α-cyano adduct. Subsequent acidic hydrolysis of the ortho adduct affords the corresponding isochroman-3-one. Prior to this study, 4-arylisochroman-3-ones were unknown, and the few 4-alkyl derivatives that had been reported were prepared by the alkylation of the corresponding isochromanon-3-one enolate.[8] However, these alkylations were frequently accompanied by dialkylation-yielding mixtures that occasionally were difficult to separate.

Herein, we report the extension of the arynic isochroman-3-one synthesis to the preparation of 4-alkyl and 4-aryl derivatives of 6-methoxy-, 6,7-dimethoxy-, and 6,7-(methylenedioxy)isochroman-3-ones (**20–22**). The methoxy and methylenedioxy groups were chosen for study since they are incorporated in many natural products. As shown in Scheme I, the synthetic methodology consists of first treating bromo (methoxymethyl)arenes **3**, **7**, and **8** with lithioalkyl- or lithioarylacetonitriles under aryne-forming conditions (LDA/THF). Hydrolysis of the ortho α-cyano(methoxymethyl)arenes **10**, **14**, and **16**, respectively, gives the corresponding isochroman-3-ones, **20**, **21**, and **22**.

Results and Discussion

The starting bromoarenes were prepared in straightforward manners from readily available arenes as outlined in Scheme II. 2-Bromo-4-(methoxymethyl)anisole (**3**) was prepared by treating 2-bromo-4-methylanisole (**1**) with NBS and benzoyl peroxide in the presence of light and then reacting the dibromoanisole (**2**) so formed with sodium methoxide in methanol. 4-Bromo-5-(methoxymethyl)veratrole (**7**) and 4-bromo-5-(methoxymethyl)piperonal (**8**) were synthesized by the successive bromination and reduction ($NaBH_4$) of veratraldehyde (**4**) and piperonal (**5**) to the respective bromobenzyl alcohol **6a** and **6b**, which upon treatment with sodium hydride followed by methyl iodide gave **7** and **8**, respectively.

The results of the reaction of bromoarenes **3**, **7**, and **8** with various aliphatic and aromatic nitriles in the presence of base (sodamide in liquid ammonia, LDA or LiTMP in THF) to yield α-substituted alkyl- and arylacetonitriles **10**, **14**, and **16** respectively, are shown in Table I. We initially carried out these arynic reactions with 2-bromo-4-(methoxymethyl)anisole (**3**) using sodamide as the base in liquid ammonia to generate aryne **9** (eq 1). The data



in Table I show that the α-alkyl nitriles **10a–c** were obtained in higher yields (30–45%) than those (15–25%) of the α-aryl nitriles **10d–h** under these conditions. In addition, small amounts of (~5–10%) the other aryne addition isomers, i.e. α-alkyl- or α-aryl-2-(methoxy)-5-(methoxymethyl)phenylacetonitrile (**11a–h**), were obtained. The major product, however, in every case was 2-(methoxymethyl)-5-methoxyaniline (**12**) formed by the amination of aryne **9** by the liquid ammonia solvent. The greater preference for the less reactive but more abundant ammonia solvent over the more reactive but less abundant nitrile anions by aryne **9** is consistent with that of other monomethoxy-substituted arynes.[9] Since the selectivity of the dimethoxy- and (methylenedioxy)arynes generated from the corresponding bromoarenes **7** and **8**[10] would be expected to be even lower than that observed for aryne **9**, the use of sterically hindered lithium amide bases in the

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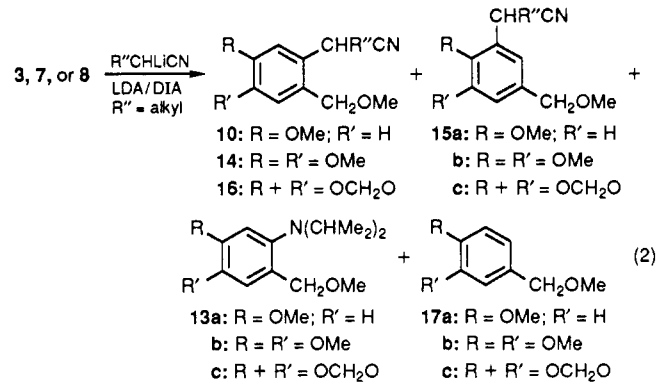
(9) Biehl, E. R.; Nieh, E. *J. Org. Chem.* **1970**, *34*, 3595.

(10) For specific examples on the increased reactivity (decreased selectivity) of polymethoxyarynes, see: Razzuk, A.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 2619 and references therein.

nonnucleophilic solvent THF for generating arynes was explored.

In all cases, the reaction of bromoarenes **3**, **7**, and **8** with aliphatic nitriles and LDA (eq 2) gave the corresponding α-alkyl nitriles **10a–c**, **14a,b**, and **16a,b**, respectively, in modest yields (35–50%). Minor amounts (10–15%) of the



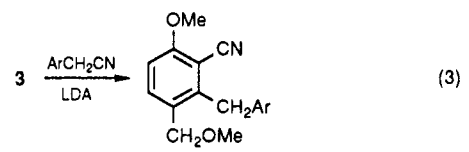
(2)

other aryne nitrile addition products (**15a–c**) were also obtained. The amination of the corresponding arynes by LDA and/or diisopropylamine, although significantly less than that observed in the sodamide/liquid ammonia mediated reactions, was still a pesky side reaction yielding *N,N*-diisopropylamine products (**13**) in 10–20% yields. Additionally, small amounts (10–15%) of debrominated arenes (**17**) were obtained.

By replacing LDA with LiTMP, the aryne-amination side reaction was essentially eliminated, resulting in modest increases (ca. 10–15%) of nitrile product yields in most cases, with the exception of **16a** (66% vs 35%) and **16b** (68% vs 40%), which were significantly improved by using LiTMP instead of LDA.

The reaction of bromoarenes **3**, **7**, and **8** with aromatic nitriles with LDA gave mixed results. For example, only **8** gave desired simple nitrile anion addition products **16** (25–61%). The use of LiTMP was explored only briefly since early experiments showed that LiTMP-mediated reactions gave nitrile products in lower yields than those conducted with LDA since the anions of starting aromatic nitriles appeared to decompose in the presence of LiTMP.

In contrast, the reaction of **3** and **7** with arylacetonitriles and LDA did not yield the expected simple anion addition products, but rather gave the rearranged nitriles **18** and **19**, respectively (eqs 3 and 4). These rearranged products most likely arise via the tandem-addition rearrangement mechanism previously suggested by Meyers[11] and Biehl.[12]



(3)

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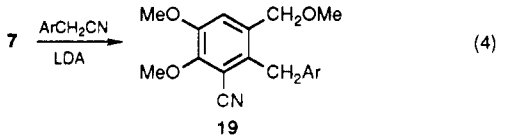

(4)

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These rearranged nitriles obviously are not suitably configured for cyclization to isochroman-3-ones; but because of the highly functionalized aromatic ring, they should serve as valuable intermediates in organic synthesis. The synthetic utility of these rearranged nitriles is currently under study, and the results will be reported in due course.

The structures of the desired nitrile products **10**, **14**, and **16** were assigned on the basis of ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and mass spectrometry. For example, each showed the characteristic nitrile IR absorption stretch at 2240–2250 cm^{-1}. Further, the mass spectrum of each nitrile exhibited a M – 32 base peak corresponding to the cyano-*o*-quinodimethane ion resulting from the loss of methanol from the parent ion and a M – 31 peak for the benzyl ion arising from the α-cleavage of the methoxymethyl group. Further, in the ^{1}H NMR spectrum of each major nitrile product, the CH_2 hydrogens in the methoxymethyl side chain exhibited an AB splitting pattern having $\Delta\nu/J$ values between 1 and 3. One factor contributing to the nonequivalency of these geminal hydrogen atoms is undoubtedly due to the presence of the adjacent chiral center in the nitrile functionality. The nonequivalency of the methylene hydrogens may also result in part from slow rotation about the CH_2–O bond caused by the bulky ortho nitrile substituent. For example, the methylene signals in the ^{1}H NMR spectra of the minor aryne nitrile products, in which these two groups are meta with respect to each other, are unsplit, appearing as singlets.

With the nitriles **10a–h**, **14a,b**, and **16a–j** on hand, they were then hydrolyzed to the respective isochroman-3-ones **20a–h**, **21a,b**, and **22a–j** in modest yields by a refluxing 1:1 mixture of 12 N HCl and glacial acetic acid. The results are listed in Table I. During the hydrolysis, the minor isomeric nitrile addition products were hydrolyzed to hydroxy acids and were easily separated from isochroman-3-ones by basic extraction. The structures assigned to these isochroman-3-ones were consistent with their IR, MS, and NMR spectra. Thus, the IR spectra of each exhibited a strong carbonyl stretching vibration at 1720–1740 cm^{-1}. Their mass spectra also revealed a strong *o*-quinodimethane ion P – 44 peak (usually the base peak) resulting from the loss of carbon dioxide from the parent ion. Generally, the geminal C_4 hydrogen atoms of the isochroman-3-ones **20–22** and the hydrogen atoms of the methylenedioxy group in isochroman-3-ones **22** exhibited typical AB splitting patterns in the ^{1}H NMR spectra. However, in a few cases (e.g. the 4′-fluoro derivative **22g**) these geminal hydrogen pairs were unsplit and appeared as singlets. We presently are investigating the influence on 4-substituents on the AB splitting patterns of isochroman-3-ones.

We also are exploring both pyrolytic and nonpyrolytic methods for converting these isochroman-3-ones to natural products, and the results will be reported in due course.

Experimental Section

General. Melting points were determined on an electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 grating spectrometer. High-field (200-MHz) proton and carbon-13-spectra were taken on an IBM-Bruker WP200-SY spectrometer. NMR spectra were run in $CDCl_3$ solution, and chemical shifts were related to Me_4Si. Gas chromatographic analyses and mass spectra (70 eV) were obtained on a Hewlett-Packard Model 5988A spectrometer using a 0.2 mm × 12 m capillary column containing cross-linked methylsilicone of 0.33 μm film thickness. Data reported are m/z values for the most abundant peaks. Microanalyses were performed on a Carlo ERBA instrument. E. Merck silica gel 9385 (230–400 mesh) was used for flash column chromatography. Tetrahydrofuran (THF) and diisopropylamine were dried and distilled prior to use. Haloarenes and arylacetonitriles were either obtained from Aldrich

(11) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1984**, *25*, 2941. Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178.

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Chemical Co. or prepared by standard procedures. *n*-Butyllithium was obtained from Aldrich Chemical Co. All reactions were carried out in an oven-dried flask under nitrogen atmosphere.

2-Bromo-4-(methoxymethyl)anisole (3). *N*-Bromosuccinimide (106 g, 0.5 mol) was added to a solution of 2-bromo-4-methylanisole (199 g, 0.5 mol) in dry carbon tetrachloride (800 mL) containing 2 g of benzoyl peroxide under nitrogen atmosphere, in the presence of light (photolamp). After the addition of NBS, the resulting slurry was refluxed for 3 h, cooled, and filtered to remove the solid material. The filtrate was concentrated under reduced pressure to give 4-(bromomethyl)-2-bromoanisole (**2**), which, without further purification, was dissolved in benzene (500 mL), and the solution was added to a stirred solution of sodium methoxide prepared from sodium (18 g, 0.78 mol) in methanol (300 mL). The reaction mixture was refluxed with stirring for 2 h, cooled, and filtered to remove any solid material, and the filtrate was concentrated under reduced pressure. The residue was acidified with dilute HCl and extracted with methylene chloride. The methylene chloride extract was washed with water and brine, dried (Na_2SO_4), and evaporated to give an oil that upon vacuum distillation yielded 103 g (89%) of pure **3** (104–105 °C (0.4 Torr)); ^1H NMR ($CDCl_3$) δ 3.36 (s, 3 H), 3.87 (s, 3 H), 4.35 (s, 2 H), 6.86 (d, J = 8.5 Hz, 1 H), 7.21 (dd, J = 8.5, 1.9 Hz, 1 H), 7.53 (d, J = 1.9 Hz, 1 H); MS m/z 230 (M^+), 232 ($M^+ + 2$), 191, 189.

4-Bromo-5-(methoxymethyl)veratrole (7). To a solution of veratraldehyde (40 g) in acetic acid (500 mL) and bromine (40 mL) was added a solution (50 mL) of carbon disulfide containing a catalytic amount of iodine. After the reaction mixture was stirred for 2 days at ambient temperature, the acetic acid was removed at reduced pressure to give 40 g of crude 6-bromoveratraldehyde as a yellow solid, which was purified by washing with very cold ethanol. The resulting white powder (35 g) and sodium borohydride (7.4 g) were dissolved in ethanol (200 mL), and the resulting solution was stirred for 1 h. The usual workup gave 2-bromo-4,5-dimethoxybenzyl alcohol (**6a**) as a white solid (36 g) in nearly quantitative yield: mp 94–95 °C; ^1H NMR ($CDCl_3$) δ 3.82 (s, 6 H), 4.6 (s, 2 H), 6.95 (s, 2 H). Anal. Calcd for $C_9H_{11}O_3Br$: C, 43.74; H, 4.48. Found: C, 43.99; H, 4.56. The alcohol **5** was treated without purification with 1.2 equiv of sodium hydride in THF (200 mL) at room temperature for 1 h. Methyl iodide (14 mL) was then added, and solution was stirred at room temperature overnight. After the usual workup followed by vacuum distillation, pure **7** (37 g) was obtained as white solid, mp 45–46 °C, in 95% yield: ^1H NMR ($CDCl_3$) δ 3.43 (s, 3 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 4.44 (s, 2 H), 6.97 (s, 1 H), 6.99 (s, 1 H). Anal. Calcd for $C_{10}H_{13}O_3Br$: C, 45.99; H, 5.12. Found: C, 46.04; H, 5.12.

4-Bromo-5-(methoxymethyl)-1,2-(methylenedioxy)benzene (8). Treatment of piperonal (**4**) (40 g) with bromine (40 mL) in acetic acid (500 mL) and carbon disulfide (50 mL) containing a catalytic amount of iodine gave 6-bromopiperonal (**6b**) (46 g, 70% yield, mp 128–130 °C). Treatment of **6b** (46 g) with sodium borohydride (1.5 equiv, 11 g) in the same manner as described above for **7** gave the brominated piperonyl alcohol (**6b**) (46 g) as white crystals (EtOAc/hexane): mp 87–88 °C; ^1H NMR ($CDCl_3$) δ 2.38 (s, 1 H), 4.62 (s, 2 H), 5.98 (s, 2 H), 6.95 (s, 1 H), 6.98 (s, 1 H). Anal. Calcd for $C_8H_7O_3Br$: C, 41.58; H, 3.05. Found: C, 41.65; H, 3.05. Alcohol **6b** (46 g) upon successive treatment with sodium hydride (10 g of 60% dispersion) followed by methyl iodide (15 mL) gave 4-bromo-5-(methoxymethyl)piperonal (**8**) (41 g) in overall yields of 60% from **4**, bp 82–85 °C (0.3 mm); ^1H NMR ($CDCl_3$) δ 3.44 (s, 3 H), 4.44 (s, 2 H), 5.98 (s, 2 H), 6.96 (s, 1 H), 7.0 (s, 1 H).

General Procedure for the Aryne Reactions: a. Using Sodamide as Base. Sodamide (0.2 mol) was prepared from 4.6 g (0.2 mol) of sodium in liquid ammonia (150 mL) containing 0.01 g of ferric nitrate. After the discharge of the initial blue solution to gray, indicating the conversion of sodium to sodium amide, the appropriate nitrile was added slowly over a period of 5 min. After the addition was complete, the mixture was stirred for 2 h and quenched with ammonium chloride and the ammonia was evaporated. The residue was extracted with methylene chloride (3 × 50 mL), and the combined extracts were washed with 6 N HCl (to remove 4-(methoxymethyl)-3-methoxyaniline) and then brine, dried (Na_2SO_4), and concentrated under reduced pressure to provide an oil that consisted of a mixture of nitrile products. Purification of the products was accomplished by flash column chromatography using a mixture of hexane/EtOAc [9:1 or 4:1, depending on the polarity of the nitrile product] as an eluent. The yields are given in Table I.

b. Using LDA or LiTMP as Base. In a flame-dried flask flushed with nitrogen, LDA (30 mmol) was prepared by adding diisopropylamine (36 mmol) into a solution of *n*-BuLi (30 mmol, 2.5 M in hexane) in THF (50 mL) at −78 °C under a nitrogen atmosphere (using septum cap technique). After the solution was stirred for 10 min at −78 °C, the appropriate alkyl- or arylacetonitrile (10 mmol) in THF (50 mL) was added dropwise over 20 min. The reaction mixture was stirred at −78 °C for 10 min and then allowed to warm to −40 °C at which point a solution of haloarene (10 mmol) in THF (50 mL) was added dropwise at −40 °C, and the solution was allowed to warm to room temperature slowly over a period of 2 h. The resulting dark reddish brown solution was then quenched with absolute ethanol, the THF was evaporated under reduced pressure, and the residue was extracted with methylene chloride (2 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated (rotary evaporator) to provide an oil, which was purified by flash column chromatography using a mixture of hexane/EtOAc (19:1 or 9:1), depending on the polarity of the nitrile product) as eluent. The characterization of **10g** and **16f** are given below as typical examples.

α-(3′,4′-Dimethoxyphenyl)-5-methoxy-2-(methoxymethyl)phenylacetonitrile (10g): white needles (hexane); mp 78–79 °C; ^1H NMR ($CDCl_3$) δ 3.34 (s, 3 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 4.42 (s, 2 H), 5.64 (s, 1 H), 6.81–7.25 (m, 6 H); IR (neat) 2235 (CN), 1605, 1490 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 37.85, 55.31, 55.89 (2 OMe), 57.80, 72.57, 111.03, 111.28, 112.87, 119.86, 120.14, 127.40, 127.58, 131.92, 136.65, 148.50, 151.10, 160.05; MS m/z 327 (M^+), 296 (M − OMe), 295 (M − MeOH). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.46; N, 4.27. Found: C, 70.08; H, 6.63; N, 4.18.

α-(3′,4′,5′-Trimethoxyphenyl)-2-(methoxymethyl)-4,5-(methylenedioxy)phenylacetonitrile (16f): white crystals (EtOAc); mp 138–139 °C; ^1H NMR ($CDCl_3$) δ 3.32 (s, 3 H), 3.78 (s, 6 H), 3.79 (s, 3 H), 4.32 (d, J = 11.4 Hz, 1 H), 4.40 (d, J = 11.4 Hz, 1 H), 5.58 (s, 1 H), 5.90 (d, J = 10.0 Hz, 1 H), 5.93 (d, J = 10.0 Hz, 1 H), 6.54 (s, 2 H), 6.76 (s, 1 H), 6.79 (s, 1 H); IR (neat) 2240 (CN), 1605 cm^{-1}; MS m/z 341 (M^+), 310 (M − OMe), 309 (M − MeOH). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.72; H, 5.68; N, 3.86.

Preparation of Isochroman-3-ones 20, 21, and 22. General Procedure for the Preparation of 4-Alkyl- or 4-Aryl-Substituted Derivatives of Isochroman-3-ones. A solution of the appropriate cyano compound (5 mmol) in acetic acid (15 mL) and hydrochloric acid (15 mL) was refluxed for 1 h. The reaction mixture was then cooled, diluted with water (100 mL), and extracted with methylene chloride (2 × 100 mL). The combined methylene chloride extracts were successively washed with water (2 × 100 mL), saturated aqueous sodium bicarbonate solution (2 × 75 mL), and brine (2 × 75 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the corresponding lactone product. All lactone products were purified by flash column chromatography (EtOAc/hexane, 1:9) to give pure isochroman-3-ones. The yields are given in Table I. Characterization of selected isochroman-3-ones follow.

6-Methoxyisochroman-3-one (20a): colorless solid (EtOH); mp 75–78 °C (lit.[13] mp 74–78 °C).

4-Methyl-6-methoxyisochroman-3-one (20b): colorless thick liquid; ^1H NMR ($CDCl_3$) δ 1.59 (d, J = 8.5 Hz, 3 H), 3.83 (s, 3 H), 4.1 (q, J = 8.5 Hz, 1 H), 5.34 (d, J = 13.8 Hz, 1 H), 5.44 (d, J = 13.8 Hz, 1 H), 6.86–7.15 (m, 3 H); IR ($CHCl_3$) 1740 (C=O), 1610 cm^{-1}; MS m/z 192 (M^+), 148 (M − CO_2). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.82; H, 6.36.

6,7-Dimethoxyisochroman-3-one (21a): white needles, mp 105–107 °C (lit.[13] mp 106–108 °C).

4-Methyl-6,7-dimethoxyisochroman-3-one (21b): white needles (EtOAc), mp 118–119 °C; ^1H NMR ($CDCl_3$) δ 1.53 (d, J = 7.1 Hz, 3 H), 3.51 (q, J = 7.1 Hz, 1 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 5.14 (d, J = 12.0 Hz, 1 H), 5.22 (d, J = 12.0 Hz, 1 H), 6.71

(13) Finkelstein, J.; Brossi, A. *Org. Synth.* **1976**, *55*, 45.

(s, 2 H); IR ($CHCl_3$) 1740 (C=O), 1600 cm^{-1}; MS m/z 222 (M^+), 178 (M – CO_2). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.01; H, 6.30.

6,7-(Methylenedioxy)isochroman-3-one (22a): white needles (EtOH); mp 131–133 (lit.[2b] mp 130.5–132 °C).

4-Methyl-6,7-(methylenedioxy)isochroman-3-one (22b): white needles (EtOAc); mp 158–160 °C; ^1H NMR ($CDCl_3$) δ 1.55 (d, J = 7.0 Hz, 3 H), 3.52 (q, J = 7.0 Hz, 1 H), 5.11 (d, J = 12.0 Hz, 1 H), 5.19 (d, J = 12.0 Hz, 1 H), 5.96 (s, 2 H), 6.69 (s, 1 H), 6.74 (s, 1 H); IR ($CHCl_3$) 1740 (C=O), 1605 cm^{-1}; MS m/z 206 (M^+), 162 (M – CO_2). Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.94. Found: C, 63.98; H, 5.00.

4-(3′,4′-Dimethoxyphenyl)-6,7-(methylenedioxy)isochroman-3-one (22e): white needles (EtOAc/hexane); mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 3.85 (s, 6 H), 4.88 (s, 1 H), 5.07 (d, J = 12.0 Hz, 1 H), 5.15 (d, J = 12.0 Hz, 1 H), 5.98 (s, 2 H), 6.56 (s, 2 H), 6.72 (s, 1 H), 6.75 (s, 1 H), 6.80 (s, 1 H), 6.81 (s, 1 H); ^{13}C δ 51.02, 55.91 (2 MeO), 69.21, 101.50, 105.43, 108.41, 111.26, 111.53, 120.14, 125.40, 126.63, 127.70, 147.32, 148.27, 148.86, 149.44, 171.09; IR ($CHCl_3$) 1740 (C=O), 1605 cm^{-1}; MS m/z 328 (M^+), 284 (M – CO_2). Anal. Calcd for $C_{18}H_{16}O_6$; C, 65.85; H, 4.91. Found: C, 65.80; H, 5.01.

4-(4′-Fluorophenyl)-6,7-(methylenedioxy)isochroman-3-one (22g): white needles (EtOH); mp 119–121 °C; ^1H NMR ($CDCl_3$) δ 4.80 (s, 1 H), 5.07 (s, 2 H), 5.93 (s, 2 H), 6.46 (s, 1 H), 6.69 (s, 1 H), 7.05 (d, J = 8.0 Hz, 2 H), 7.11 (d, J = 8.0 2 H); IR ($CHCl_3$) 1730 (C=O), 1600, 1500 cm^{-1}; MS m/z 286 (M^+), 242 (M – CO_2). Anal. Calcd for $C_{16}H_{11}O_4F$; C, 67.13; H, 3.87. Found: C, 67.11; H, 3.89.

4-(3′-Fluorophenyl)-6,7-(methylenedioxy)isochroman-3-one (22h): white needles (EtOH); mp 81–82 °C; ^1H NMR ($CDCl_3$) δ 4.96 (s, 1 H), 5.24 (d, J = 12.0 Hz, 1 H), 5.32 (d, J = 12.0 Hz, 1 H), 5.91 (s, 2 H), 6.27 (s, 1 H), 6.71 (s, 1 H), 7.17–7.35 (m, 4 H); IR ($CHCl_3$) 1730 (C=O), 1600, 1590, 1490 cm^{-1}; MS m/z 286 (M^+), 242 (M – CO_2). Anal. Calcd for $C_{16}H_{11}O_4F$; C 67.13; H, 3.87. Found: C, 67.22; H, 3.92.

4-(2′-Fluorophenyl)-6,7-(methylenedioxy)isochroman-3-one (22i): white needles (EtOH); mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 4.91 (s, 1 H), 5.22 (d, J = 12.0 Hz, 1 H), 5.33 (d, J = 12.0 Hz, 1 H), 5.92 (s, 2 H), 6.33 (s, 1 H), 6.59 (s, 1 H), 7.15–7.36 (m, 4 H); IR ($CHCl_3$) 1730 (C=O), 1600, 1590, 1490 cm^{-1}; MS m/z 286 (M^+), 242 (M – CO_2). Anal. Calcd for $C_{16}H_{11}O_4F$; C, 67.13; H, 3.87. Found: C, 67.25; H, 3.97.

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Registry No. 1, 22002-45-5; **3**, 111210-24-3; **4**, 120-14-9; **5**, 120-57-0; **6a**, 54370-00-2; **6b**, 6642-34-8; **7**, 124618-99-1; **8**, 34679-09-9; **10a**, 124619-00-7; **10b**, 124619-01-8; **10c**, 124619-02-9; **10d**, 124619-03-0; **10e**, 124619-04-1; **10f**, 124619-05-2; **10g**, 124619-06-3; **10h**, 124619-07-4; **11a**, 124619-08-5; **11b**, 124619-09-6; **11c**, 124619-10-9; **11d**, 124619-11-0; **11e**, 124619-12-1; **11f**, 124619-13-2; **11g**, 124619-14-3; **11h**, 124619-15-4; **12**, 124619-44-9; **13b**, 124619-45-0; **13c**, 124619-46-1; **14a**, 124619-16-5; **14b**, 124619-17-6; **15b** (R″ = Me), 124619-47-2; **15b** (R″ = Et), 124619-48-3; **15c** (R″ = Me), 124619-49-4; **15c** (R″ = Et), 124650-72-2; **16a**, 124619-18-7; **16b**, 124619-19-8; **16c**, 124619-20-1; **16d**, 124619-21-2; **16e**, 124619-22-3; **16f**, 124619-23-4; **16g**, 124619-24-5; **16h**, 124619-25-6; **16i**, 124619-26-7; **16j**, 124650-71-1; **17b**, 3840-28-6; **17c**, 86633-25-2; **20a**, 43088-72-8; **20b**, 124619-27-8; **20c**, 124619-28-9; **20d**, 124619-29-0; **20e**, 124619-30-3; **20f**, 124619-31-4; **20g**, 124619-32-5; **20h**, 124619-33-6; **21a**, 16135-41-4; **21b**, 124619-34-7; **22a**, 34140-20-0; **22b**, 124619-35-8; **22c**, 124619-36-9; **22d**, 124619-37-0; **22e**, 124619-38-1; **22f**, 124619-39-2; **22g**, 124619-40-5; **22h**, 124619-41-6; **22i**, 124619-42-7; **22j**, 124619-43-8; CH_3CH_2CN, 107-12-0; $CH_3(CH_2)_2CN$, 109-74-0; $C_6H_5CH_2CN$, 140-29-4; 3-$MeOC_6H_4CH_2CN$, 19924-43-7; 4-$MeOC_6H_4CH_2CN$, 104-47-2; 3,4-$(MeO)_2C_6H_3CH_2CN$, 93-17-4; 3,4,5-$(MeO)_3C_6H_2CH_2CN$, 13338-63-1; 4-$FC_6H_4CH_2CN$, 459-22-3; 3-$FC_6H_4CH_2CN$, 501-00-8; 2-$FC_6H_4CH_2CN$, 326-62-5; 3,4-(methylenedioxy)$C_6H_3CH_2CN$, 4439-02-5; 6-bromopiperonal, 15930-53-7.

Supplementary Material Available: Full characterization data for **10a–f,h**, **14a,b**, **16a–e,g–i**, **20c–f,h**, **22c,d,f,j** (7 pages). Ordering information is given on any current masthead page.

Synthesis and Characterization of (Methoxy(thiocarbonyl))sulfenyl Chloride

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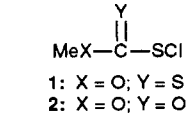
(Methoxy(thiocarbonyl))sulfenyl chloride (**1**), a previously elusive compound, has now been generated by cleavage of methoxy(thiocarbonyl) *N*-methyl-*N*-phenylamino sulfide (**7**) with gaseous hydrogen chloride. The sulfenyl chloride **1** had limited stability and was characterized by trapping with *O,O′*-dimethyl thiocarbonate or with methanethiol to yield (methoxycarbonyl)(methoxy(thiocarbonyl))disulfane (**8**) or (methoxy(thiocarbonyl))-methyldisulfane (**9**), respectively. Chlorination of acetyl methoxy(thiocarbonyl) sulfide (**6**) could be arrested at 1 plus acetyl chloride, and further chlorination of 1 provided (methoxydichloromethyl)disulfanyl chloride (**5**).

(Methoxy(thiocarbonyl))sulfenyl chloride (**1**) is the thio analogue of the valuable reagent (methoxycarbonyl)-sulfenyl chloride (**2**),[2,3] a distillable compound (bp 31–32 °C/12 mm) which is indefinitely stable upon storage at −20 °C, and it is the isomer of our recently reported ((methylthio)carbonyl)sulfenyl chloride (**3**),[4] which was shown to rearrange cleanly ($t_{1/2} \approx 75$ min at 25 °C) to (methyldithio)carbonyl chloride, MeSS(C=O)Cl. This paper describes two routes to the preparation of **1**, which has



1: X = O; Y = S
2: X = O; Y = O
3: X = S; Y = O

(1) (a) Taken in part from the Ph.D. Thesis of A. L. Schroll, University of Minnesota, 1986. (b) Present address: Department of Chemistry, St. Michael's College, Winooski Park, Colchester, VT 05404.

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