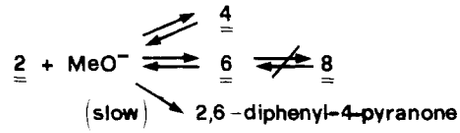
Scheme II



containing very dilute methoxide ion. Under this aspect, the tendency of pyrylium cations to undergo nucleophilic addition seems qualitatively higher than that of pyridinium cations under similar conditions.[21] Further work will be necessary in order to assess quantitatively this tendency.

The possibility of rapid interconversions between the reaction products (isomeric pyrans and/or dienones) has some implication on the chemistry of pyrylium and related heteroaromatic cations in the sense that the relative reactivities of different positions in these cations cannot be immediately related to the yield of the respective addition product. Under this view, an important role is also played by the nature of the medium, which can strongly affect the rate of return of the adducts to the starting reagents, allowing the easy detection of the less stable reaction products in the media containing minor amounts of the hydroxylic solvent.

Experimental Section

Published procedures were followed for the synthesis of the perchlorates of **1**[22] and **2**.[23] We found it convenient to purify these salts by dissolving them in the least amount of dry acetonitrile and precipitating with dry ethyl ether.

Electronic spectra were recorded on a Perkin-Elmer 402 instrument; molar absorption coefficients of **1** and **2** in methanol were recorded in the presence of $HClO_4$ in order to avoid the methanolysis reaction. NMR experiments at 60 MHz were done on a Jeol C60-HL instrument; the spin-tickling experiment at 90 MHz was done on an HX90 Bruker apparatus. Since the perchlorates of **1** and **2** are poorly soluble in methanol, the NMR spectra of the reaction products can be conveniently recorded upon addition of an equivalent amount of sodium methoxide to a suspension of the perchlorates in this solvent (20–30 mg in 0.5 mL of CD_3OD). This operation brings about the complete solubilization of the substrates. In order to avoid any interference of the signals of the products with those of any residual light methanol, the reagent was freed from CH_3OH by alternating several times vacuum pumping and addition of CD_3OD.

Isolation of Adducts. General Procedure. To a solution of the perchlorate of **1** or **2** in acetonitrile (ca. 5×10^{-2} M) was added an equivalent amount of potassium methoxide as a 2.8 M solution in methanol. The solvents were rapidly removed under reduced pressure at room temperature, and the organic materials were dissolved in CCl_4 or ethyl ether. The oily residue of evaporation was induced to crystallize by scratching or prolonged cooling. Attempted purification of these solids by recrystallization or chromatography led to decomposition.

Adduct from 1: mp 54–66 °C dec; MS, weak peak at *m/e* 264 corresponding to the molecular peak from a 1:1 adduct between **1** and CH_3O^-, intense peak (base peak) at *m/e* 233 $(M - OCH_3)^+$, and absence of peaks beyond *m/e* 264. The NMR spectrum (CCl_4) is in accordance with the formation of 4*H*-pyran **3** (Table I), except for the somewhat higher intensity of the phenyl region, presumably related to the overlapping with phenyl groups of otherwise undetected side products.

Adduct from 2: mp 65–75 °C dec; MS, weak peak at *m/e* 294 (M^+ of 1:1 adduct), intense peak at *m/e* 263 $(M - OCH_3)^+$, and absence of peaks beyond *m/e* 294. The NMR spectrum (CCl_4) shows the presence of 4*H*-pyran adduct **4** and a minor amount of 2,6-diphenyl-4-pyranone.

Acknowledgment. The authors are indebted to Professor G. Illuminati for helpful discussions. The assistance of Dr. Anna Maria Giuliani for the spin-tickling experiments and Mr. Giuseppe Frachey for the 60 MHz NMR measurements is also gratefully acknowledged.

Registry No.—**1**, 41044-52-4; **1** perchlorate, 3558-68-7; **2**, 47075-64-9; **2** perchlorate, 17539-77-4; **3**, 53856-27-2; **4**, 67069-64-1; **6**, 67069-65-2; **7**, 67069-66-3.

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Synthesis of 3-Aryl-5-bromo-2(5*H*)-furanones[1]

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A synthetic route to 3-aryl-5-bromo-2(5*H*)-furanones (**7**) based on treating a methyl 2-aryl-4-oxobutyrate (**5**) with bromine in acetic acid has been developed. The methyl 2-aryl-4-oxobutyrates were prepared in high yield by the following sequence: alkylation of an arylacetic acid using lithium diisopropylamide and allyl bromide, esterification with diazomethane to yield a methyl 2-aryl-4-pentenoate (**4**), and ozonolysis (**4** → **5**).

Continued interest in the synthesis of cardenolides[2] and isocardenolides[3] for biological evaluation led us to consider simpler 2(5*H*)-furanones[4,5] for antineoplastic and/or cytotoxicity studies. Semonsky and co-workers[6] have examined

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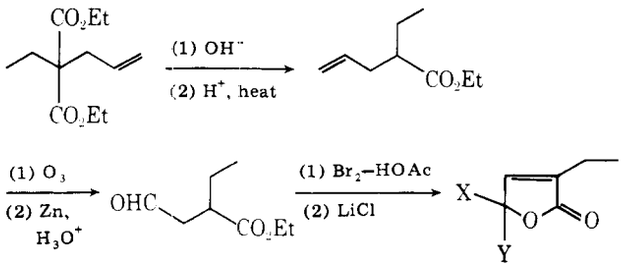
Scheme I



1a, X = Y = Cl
b, X = Cl; Y = Br
c, X = Y = Br
d, X = Br; Y = OEt
e, X = Br; Y = OAc

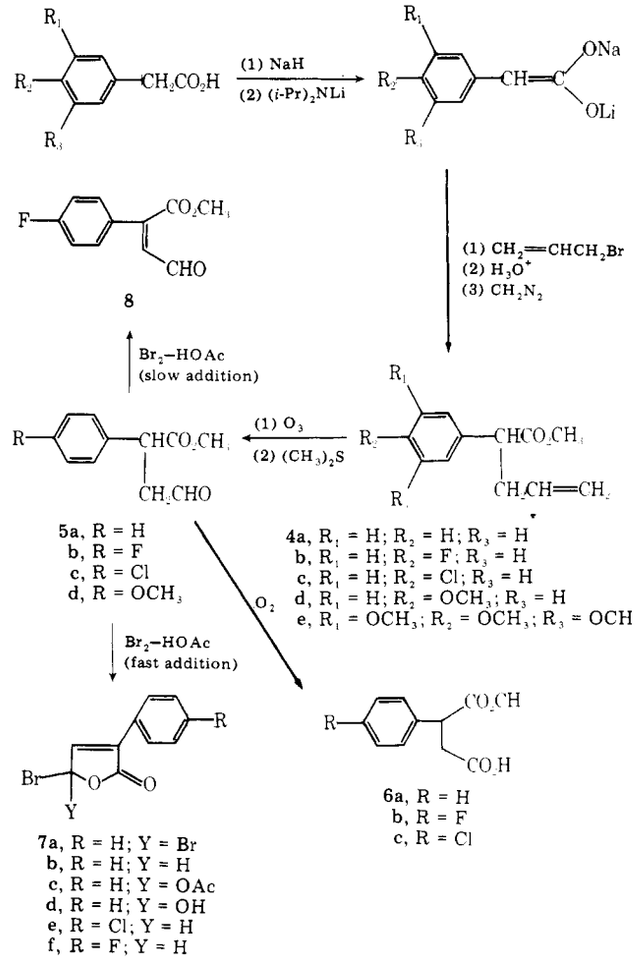
a series of 2(5*H*)-furanones of the 5-substituted mucohalic acid type for anticancer activity. Generally, the 5 substituent consisted of an aryl group or a side chain containing an aryl group. Among such lactones 3,4-dichloro-5-(*p*-methoxyphenyl)-2(5*H*)-furanone was found to display significant antineoplastic activity.

In the present study we explored the synthesis of the hitherto unknown 3-aryl-5-halo-2(5*H*)-furanones. A workable synthetic route was discovered[7] during an attempt to prepare ethyl 2-ethyl-4-oxo-2-butenoate by allowing bromine to react with ethyl 2-ethyl-4-oxobutyrate followed by addition of lithium chloride. Instead of the expected butenoate, a series (Scheme I) of 3-ethyl-5-halo-2(5*H*)-furanones (1) was isolated. Furanone **1c** was isolated from a reaction sequence where lithium chloride was not used. The furanones were obtained (silica gel chromatography) as oils and were only moderately stable at 0 °C. Consequently, the structures of these furanones were not confirmed by elemental analyses and biological evaluation was not pursued. Efforts to improve the yields of the 3-ethylfuranones by conducting the reactions at high dilution or in chloroform containing *p*-toluenesulfonic acid were not successful, and attention was focused on obtaining the presumably more stable 3-arylfuranones.

While ethyl 2-ethyl-4-pentenoate was readily available via a malonic ester synthesis,[8] the necessary alkyl 2-aryl-4-pentenoates required development of a convenient route.[9] The main step involved (Scheme II) alkylation of an arylacetic acid with allyl bromide based on a procedure outlined by Creger[10] for alkylating alkylacetic acids. The resulting acid was easily converted to the methyl ester **4** using diazomethane.[11]

Conversion of the methyl 2-aryl-4-pentenoates (**4**) to an aldehyde derivative (**5**) was originally accomplished employing ozone in an aprotic solvent followed by reduction of the ozonide with zinc and acetic acid. Reduction of the ozonide was found slow and somewhat unpredictable. Application of the Pappas[12] procedure by performing the ozonization in methanol and reduction of the resulting hydroperoxide with methyl sulfide afforded reasonable yields of the aldehyde. The methyl 2-aryl-4-oxobutyrates (see supplementary material) were stable at −11 °C for several months, but if exposed to air at 25 °C for several weeks they oxidized[13] to methyl esters of phenylsuccinic acids (**6**). Since the aldehydes were somewhat unstable, the 2,4-dinitrophenylhydrazone[14] derivatives were used to determine elemental composition. When bromine was rapidly added to methyl 2-phenyl-4-oxobutyrate in acetic acid, the deep red solution became yellow in about 1 h and the furanones were isolated as oils by silica gel chromatography to afford, in order of elution, 3-phenyl-5,5-dibromo-2(5*H*)-furanone (**7a**), 3-phenyl-5-bromo-2(5*H*)-furanone (**7b**), and 3-phenyl-5-acetoxy-5-bromo-2(5*H*)-furanone (**7c**). Rechromatography of a more polar fraction gave 3-phenyl-5-bromo-5-hydroxy-2(5*H*)-furanone (**7d**).[15]

Scheme II

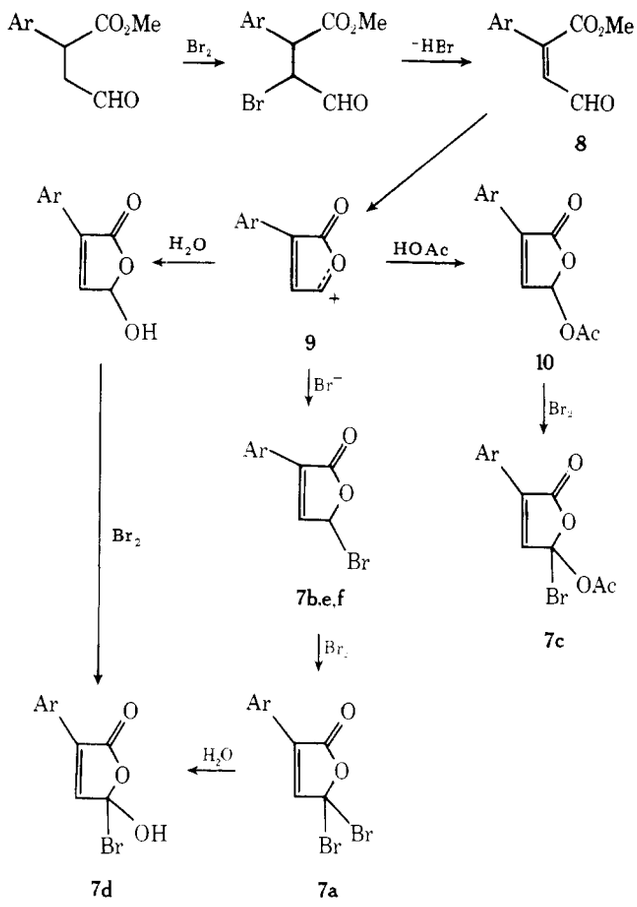


In a similar manner (Scheme II), methyl 2-(*p*-chlorophenyl)-4-oxobutyrate led to 3-(*p*-chlorophenyl)-5-bromo-2(5*H*)-furanone (**7e**) and methyl 2-(*p*-fluorophenyl)-4-oxobutyrate afforded methyl 3-(*p*-fluorophenyl)-5-bromo-2(5*H*)-furanone (**7f**).[16] Here lactones **7e** and **7f** were the major products isolated. In both reaction sequences other products were formed, but isolation proved to be too difficult for practical purposes. With the methyl 2-(*p*-fluorophenyl)-4-oxobutyrate bromination products, at least two or three additional compounds were produced during silica gel chromatography. However, once the 3-arylfuranone was isolated, decomposition was not observed. In fact, sublimation at 80 °C (under vacuum) was used to purify furanones **7a** and **7e.** A mechanism has been suggested (Scheme III) to account for the products observed from the bromination sequence.[17]

Slow addition of small aliquots of bromine to a solution of methyl 2-(*p*-fluorophenyl)-4-oxobutyrate in glacial acetic acid resulted in the formation of methyl 2-(*p*-fluorophenyl)-3-formylacrylate (**8**). The formylacrylate, isolated as long yellow needles, was of sufficient stability to allow full characterization but underwent slow decomposition. The bromination of methyl 2-(*p*-methoxyphenyl)-4-oxobutyrate (**5d**) was suspended when only complex mixtures were obtained, probably a result of phenyl ring bromination. Similarly, reactions with methyl 2-(3′,4′,5′-trimethoxyphenyl)-4-pentenoate were not pursued further.

The ^{1}H NMR spectra of the 5-disubstituted and 5-monosubstituted 3-arylfuranones showed the aromatic protons as complex multiplets. The 5-disubstituted furanones displayed one vinyl proton (C-4) at δ 6.81, 6.92, and 6.12 for lactones **7a, 7c,** and **7d,** respectively. These values compared well with those noted for 3-ethyl-5,5-dibromo-2(5*H*)-furanone (**1c,** δ 6.72), 3-ethyl-5-acetoxy-5-bromo-2(5*H*)-furanone (**1e,** δ 6.81),

Scheme III



and 3-ethyl-5-bromo-5-ethoxy-2(5*H*)-furanone (**1d**, δ 5.91). The apparent shielding effects of the 5-ethoxy and 5-hydroxy groups (**1d** and **7d**) on the C-4 hydrogen may be caused by a shift of the double bond π cloud toward C-4 due to the oxygen electronegativity. On the other hand, the 5-acetoxy derivative **7c** could deshield the C-4 hydrogen by an anisotropic effect. Interestingly, replacement of the 3-ethyl substituent with an aryl group only deshielded the C-4 hydrogen by about 0.1 ppm.

For the 5-monosubstituted furanones, 5-bromo-2(5*H*)-furanone[18] proved to be a good model system. The C-4 and C-5 hydrogens of 5-bromo-2(5*H*)-furanone have been reported to resonate at δ 7.80 and 7.08 with a coupling constant of 1.3 Hz. The δ 7.08 signal for the C-5 hydrogen of 5-bromo-2(5*H*)-furanone compared well with the values of δ 6.94, 7.08, and 7.08 observed for 3-phenyl-5-bromo-2(5*H*)-furanone (**7b**), 3-(*p*-chlorophenyl)-5-bromo-2(5*H*)-furanone (**7e**), and 3-(*p*-fluorophenyl)-5-bromo-2(5*H*)-furanone (**7f**), respectively. As observed earlier, the phenyl ring has only a minor effect on the vinyl hydrogen, and the more distant C-5 hydrogen should exhibit an even smaller shift. The vinyl hydrogen signals of furanones **7b, 7e,** and **7f** were located at δ 7.62, 7.69, and 7.64, respectively, and they relate fairly well to the vinyl hydrogen signal (δ 7.80) of 5-bromo-2(5*H*)-furanone. The vinyl protons for the 5-disubstituted furanones were decidely upfield from those of the 5-monosubstituted lactones. Again this would appear to be the consequence of π-cloud polarization. The two electronegative C-5 substituents should shift the π cloud more toward C-4, thereby further shielding the C-4 proton.

The 5-disubstituted furanone mass spectra were characterized by the initial loss of either C-5 substituent; however, elimination of a bromine radical was preferred. Following the loss of bromine, carbon monoxide was twice expelled and the remaining C-5 substituent was lost, producing an arylacetylene. The order of these steps differed for each type of compound. Arylacetylene formation was evident for each furanone and methyl 2-(*p*-fluorophenyl)-3-formylacrylate (**8**). With 3-phenyl-5-acetoxy-5-bromo-2(5*H*)-furanone (**7c**) the major fragmentation pathway encompassed initial loss of ketene followed by cleavage of a bromine radical, CO_2H, and carbon monoxide to produce phenylacetylene.

The monosubstituted furanones invariably lost the 5-bromo group from the molecular ion followed by two successive losses of carbon monoxide. Alternatively, the second carbon monoxide elimination can be superseded by loss of CHO. In addition, the molecular ion for the 5-monosubstituted furanones can expel carbon dioxide. The intensity of this very weak ion decreased in the order 3-phenyl > 3-(*p*-chlorophenyl) > 3-(*p*-fluorophenyl). These fragmentation pathways were comparable to those deduced for the 3-ethylfuranones.

Preliminary screening of the 3-arylfuranones (**7**) and their precursors for cytotoxicity was carried out by the National Cancer Institute using the P388 murine lymphocytic leukemia and KB (human nasopharynx carcinoma) in vitro cell lines, but no significant activity was found. Before any conclusion can be reached about antineoplastic activity, further evaluation of furanones **7** against several in vivo tumor lines will be necessary.

Experimental Section

Reagents and solvents (ligroin refers to a fraction boiling at approximately 60 °C) used in this study were obtained from J. T. Baker Chemical Co., Mallinckrodt, Inc., Aldrich Chemical Co., and MC/B Manufacturing Chemists, with the exception of *N*-methyl-*N*-nitrosourea and *n*-butyllithium which were provided by Fairfield Chemical Co. and Thiokol Corp. (Ventron Division), respectively. All solvents were redistilled, and solvent extracts were dried over magnesium sulfate. Tetrahydrofuran was distilled from sodium hydride or lithium aluminum hydride. Silica gel F-254 (0.25 mm E. Merck, Darmstadt) plates were used for thin-layer chromatography, and the plates were visualized with UV light or an anisaldehyde–sulfuric acid–glacial acetic acid (1:2:97) spray. Column chromatography employed silica gel (70–230 mesh) supplied by E. Merck. In each case the silica gel/substrate ratio was 50:1. Deuteriochloroform was used as solvent and tetramethylsilane as an internal standard for nuclear magnetic resonance measurements (by Dr. J. Witschel, Varian XL-100 and T-60A instruments). The mass spectra (70 eV) were recorded by Mr. E. Kelley employing Atlas CH-4B and SM-1B instruments. Melting points (uncorrected) were taken on a Kofler melting point apparatus. Elemental analyses were determined by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Ethyl 2-Ethyl-4-oxobutyrate. Ethyl 2-ethyl-4-pentenoate[8] (9.0 g, 0.058 mol) was placed in chloroform (100 mL) and treated with ozone (3%) at −40 °C for 1.5 h until a blue color appeared. Zinc (5 g) in glacial acetic acid (20 mL) was added, and the mixture was stirred at 0 °C for 1 h. The solution was filtered and poured into water (100 mL). The organic layer was separated, washed with 5% sodium bicarbonate, and dried. The solvent was removed to yield 8.4 g (93%) of ethyl 2-ethyl-4-oxobutyrate. The product was converted[14] to the 2,4-dinitrophenylhydrazone, mp 79–81 °C.

Anal. Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.32; N, 16.57. Found: C, 49.86; H, 5.42; N, 16.67.

Bromination–Dehydrobromination of Ethyl 2-Ethyl-4-oxobutyrate. Ethyl 2-ethyl-4-oxobutyrate (8.4 g, 0.053 mol) was dissolved in glacial acetic acid (30 mL). Bromine (8.5 g, 0.053 mol) was added over 30 min, and the solution was stirred at 24 °C for one day. The reaction mixture was poured into water (100 mL) and extracted with chloroform. The combined extract was washed with 10% sodium thiosulfate, water, and 5% sodium bicarbonate and dried. Solvent was removed, and the 12.3 g of pale yellow oil was placed in dimethylformamide (50 mL). Lithium chloride (10 g) was added, and the mixture was stirred under nitrogen at 100 °C for 1 h. The reaction mixture was poured into water (150 mL) and then extracted with ligroin. The extracts were combined and dried, and the solvent was removed to yield 2.30 g of a yellow liquid. Purification by silica gel chromatography (70 g; benzene) afforded the following products in order of their elution: 1.19 g of **3-ethyl-5-bromo-5-chloro-2(5*H*)-furanone** (**1b**) and **3-ethyl-5,5-dichloro-2(5*H*)-furanone**

(**1a**) as a 4:1 mixture [IR (neat) 1790, 1650, 1010, 940, 910, 800 cm^{-1}; ^1H NMR δ 1.14 (t, 3 H), 2.42 (q, 2 H), 6.41 (s, 1 H); mass spectrum, *m/e* (relative intensity) 228 (1), 226 (6), 224 (4), 195 (6), 189 (34), 180 (6), 161 (2), 151 (20), 145 (100), 117 (8), 109 (10), 81 (25), 65 (46)]; **3-ethyl-5-bromo-5-ethoxy-2(5*H*)-furanone (1d)** (0.313 g) [IR (neat) 1770, 1660, 1180, 960, 940, 860 cm^{-1}; ^1H NMR δ 1.0–1.5 (two sets of overlapping triplets, 6 H), 2.40 (q, 2 H), 3.86 (q, 2 H), 5.91 (s, 1 H); mass spectrum, *m/e* (relative intensity) 236 (59), 234 (56), 207 (91), 205 (81), 191 (100), 189 (90), 162 (35), 160 (39), 155 (81), 111 (81), 109 (38), 83 (60), 81 (64), 65 (55), 53 (66)]; and **3-ethyl-5-acetoxy-5-bromo-2(5*H*)-furanone (1e)** (0.246 g) [IR (neat) 1765, 1740 sh, 1660, 1210, 1000, 945, 875 cm^{-1}; ^1H NMR δ 1.18 (t, 3 H), 2.1–2.5 (m, 5 H), 2.20, 6.81 (s, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 247 (M − 1, 1), 206 (6), 205 (6), 189 (29), 188 (28), 169 (37), 161 (3), 160 (10), 127 (59), 109 (16), 99 (13), 81 (56), 65 (50), 43 (100), 29 (78)].

Bromination of Ethyl 2-Ethyl-4-oxobutyrate. Ethyl 2-ethyl-4-oxobutyrate (5 g, 0.032 mol) was placed in glacial acetic acid (25 mL). Bromine (5.5 g, 0.35 mol) was added over 20 min, and the solution was stirred at 24 °C for 6 h. The reaction mixture was poured into water (75 mL) and extracted with chloroform. The combined extract was washed with 5% sodium bicarbonate, water, 10% sodium thiosulfate, and water and dried. The solvent was removed to yield 6.5 g of pale yellow liquid. Isolation by silica gel chromatography (180 g; benzene) afforded the following: **3-ethyl-5,5-dibromo-2(5*H*)-furanone** ([**C**((49.2 mg) [IR (neat) 1780, 1640, 1000, 940, 880 cm^{-1}; ^1H NMR δ 1.14 (t, 3 H), 2.42 (q, 2 H), 6.72 (s, 1 H); mass spectrum, *m/e* (relative intensity) 192 (18), 191 (100), 190 (17), 189 (77), 123 (29), 121 (26), 111 (15), 82 (22), 81 (24), 66 (42), 65 (51), 53 (55)]; and **ethyl 2-ethyl-3,3-dibromo-4-oxobutyrate** (1.45 g) [^1H NMR δ 1.00 (t, 3 H), 1.24 (t, 3 H), 1.90 (2 H), 3.18 (t, 1 H), 4.22 (q, 2 H), 9.18 (s, 1 H)].

General Procedure 1. Synthesis of Methyl 2-Aryl-4-pentenoates. A four-neck round-bottom flask (1000 mL) was equipped with a reflux condenser, mechanical stirrer, thermometer (held in contact with the flask contents by a ground glass joint), addition funnel, and nitrogen source. To the flask was added tetrahydrofuran (350 mL), diisopropylamine (11.0 mL, 0.15 mol), and sodium hydride (9.6 g of a 50% oil dispersion, 0.20 mol). The arylacetic acid (0.15 mol) in tetrahydrofuran (50 mL) was added with stirring over a 20-min period. The resulting gelatinous slurry was heated at reflux for 20 min to complete metalation of the arylacetic acid. At this time the addition funnel was replaced by a septum and the white slurry was cooled, under a brisk nitrogen flow, to 10 °C. Injection of *n*-butyllithium (2 M in heptane, 75 mL, 0.15 mol) into the flask was done at a rate that maintained the temperature at 10 °C or less. After stirring for 10 min at 10 °C, allyl bromide (25.4 mL, 0.15 mol) was added while maintaining the temperature at or below 10 °C. The reaction mixture was stirred at 10 °C for 15 min and then at 25 °C for 1 h. Water (200 mL) was slowly added to the reaction flask. The organic layer was removed, and the remaining aqueous layer was washed with ether, acidified to pH 2 with 6 N HCl, and extracted with ether. The combined ether extract was washed with a saturated sodium chloride solution, dried, and concentrated to leave the 2-aryl-4-pentenoic acid as an oil. Diazomethane[11] was slowly added to a solution of the crude 2-aryl-4-pentenoic acid in 1,2-dimethoxyethane (50 mL) at 10 °C until an excess of diazomethane was present. The solvent was removed in vacuo, leaving an oily residue which was purified by vacuum distillation.

Methyl 2-Phenyl-4-pentenoate (4a). Application of general procedure 1 to phenylacetic acid (20.4 g, 0.15 mol) provided an oil which distilled at 98–104 °C (0.5 mm) to provide 24.7 g (86.6%) of ester **4a** as a colorless liquid.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.46. Found: C, 75.41; H, 7.30.

Methyl 2-(*p*-Fluorophenyl)-4-pentenoate (4b). Extension of general procedure 1 to *p*-fluorophenylacetic acid (95% pure; 25.0 g, 0.15 mol) furnished a dark brown oil. Distillation at 76–79 °C (0.3 mm) gave 29.7 g (95%) of ester **4b** as a colorless oil.

Anal. Calcd for $C_{12}H_{13}FO_2$: C, 69.25; H, 6.25; F, 9.13. Found: C, 69.24; H, 6.30; F, 9.28.

Methyl 2-(*p*-Chlorophenyl)-4-pentenoate (4c). Use of general procedure 1 with *p*-chlorophenylacetic acid (26.4 g, 0.15 mol) produced a clear brown oil. Distillation at 84–86 °C (0.20 mm) gave 23.9 g (70.9%) of ester **4c** as a slightly yellow oil.

Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.09; H, 5.86; Cl, 15.67.

Methyl 2-(*p*-Methoxyphenyl)-4-pentenoate (4d). Using procedure 1, *p*-methoxyphenylacetic acid (24.9 g, 0.15 mol) afforded, after distillation at 90–92 °C (0.1 mm), 24.6 g (74.4%) of ester **4d** as a colorless oil.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 69.85; H, 6.97.[19]

Methyl 2-(3′,4′,5′-Trimethoxyphenyl)-4-pentenoate (4e). By means of general procedure 1, 3,4,5-trimethoxyphenylacetic acid (8.20 g, 0.034 mol) was alkylated and esterified to give a yellow oil. Distillation at 174–176 °C (3 mm) gave 5.8 g (61%) of ester **4e** as a pale yellow oil.

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.24; H, 7.25.

General Procedure 2. Synthesis of Methyl 2-Aryl-4-oxobutyrates. An excess of ozone was bubbled through a solution of the methyl 2-aryl-4-pentenoate in methanol at −78 °C. After excess ozone was removed by passing nitrogen through the solution, methyl sulfide (30% excess) was introduced and the cold solution was allowed to warm to 25 °C. After stirring for 3–5 h at 25 °C, the solvent was removed to give an oil. Vacuum distillation of this oil afforded dimethyl sulfoxide and the methyl 2-aryl-4-oxobutyrate.

Methyl 2-Phenyl-4-oxobutyrate (5a). Application of general procedure 2 to methyl 2-phenyl-4-pentenoate (28.1 g, 0.15 mol) in methanol (500 mL) furnished a colorless oil which was distilled to give dimethyl sulfoxide at 50–60 °C (0.7 mm) and aldehyde **5a** (22.6 g, 78.5%) at 104–105 °C (0.7 mm) as a colorless oil.

The 2,4-dinitrophenylhydrazone derivative of aldehyde **5a** was synthesized in the usual manner to yield, upon recrystallization from ethanol (100%), orange needles, mp 135–136 °C.

Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.84; H, 4.33; N, 15.05. Found: C, 54.83; H, 4.26; N, 15.03.

Methyl 2-(*p*-Fluorophenyl)-4-oxobutyrate (5b). Adoption of general procedure 2 to methyl 2-(*p*-fluorophenyl)-4-pentenoate (10.0 g, 0.048 mol) in methanol (275 mL) resulted in a colorless oil. Distillation of this oil afforded dimethyl sulfoxide at 50 °C (0.17 mm) and aldehyde **5b** (7.30 g, 72.4%) at 100–103 °C (0.17 mm) as a colorless oil.

Elemental microanalysis was performed on the 2,4-dinitrophenylhydrazone derivative of aldehyde **5b**, which was recrystallized (5 times) from ethanol (100%), resulting in orange needles, mp 158–159 °C.

Anal. Calcd for $C_{17}H_{15}FN_4O_6$: C, 52.31; H, 3.87; F, 4.87; N, 14.35. Found: C, 52.36; H, 3.85; F, 4.92; N, 14.37.

Methyl 2-(*p*-Chlorophenyl)-4-oxobutyrate (5c). Utilization of general procedure 2 with methyl 2-(*p*-chlorophenyl)-4-pentenoate (20.0 g, 0.089 mol) in methanol (200 mL) gave a brown oil which was distilled to yield dimethyl sulfoxide (42 °C, 0.3 mm) and aldehyde **5c** (15.9 g, 78.7%) at 108–110 °C (0.06 mm) as a colorless oil.

The 2,4-dinitrophenylhydrazone derivative of aldehyde **5c** was synthesized and recrystallized several times from ethanol (100%) to produce orange needles, mp 164.5–165.5 °C.

Anal. Calcd for $C_{17}H_{15}ClN_4O_6$: C, 50.20; H, 3.72; Cl, 8.72; N, 13.77. Found: C, 50.38; H, 3.51; Cl, 8.71; N, 13.79.

Methyl 2-(*p*-Methoxyphenyl)-4-oxobutyrate (5d). Employing general procedure 2 with methyl 2-(*p*-methoxyphenyl)-4-pentenoate (22.0 g, 0.10 mol) in methanol (500 mL) gave a light yellow oil which slowly darkened at 25 °C. Distillation of this oil gave dimethyl sulfoxide (50 °C at 1.4 mm) and aldehyde **5d** (16.2 g, 73%) at 159–163 °C (1.3 mm) as a colorless oil.

Elemental analytical data was obtained for the 2,4-dinitrophenylhydrazone derivative of aldehyde **5d**. Three recrystallizations from ethanol (100%) gave orange needles, mp 159–160 °C.

Anal. Calcd for $C_{18}H_{18}N_4O_7$: C, 53.73; H, 4.51; N, 13.93. Found: C, 53.74; H, 4.58; N, 14.04.

Methyl Ester of Phenylsuccinic Acid (6a). Carboxylic acid **6a** was produced by exposing methyl 2-phenyl-4-oxobutyrate to air for about 3 weeks. During this time the liquid aldehyde began to solidify, yielding a colorless solid. Recrystallization (several times) from chloroform–ligroin yielded colorless prisms of acid **6a** (yield ca. 50%), mp 100–101 °C.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.80. Found: C, 63.40; H, 5.75.

Methyl Ester of *p*-Fluorophenylsuccinic Acid (6b). When methyl 2-(*p*-fluorophenyl)-4-oxobutyrate (2.2 g) was exposed to air at 25 °C for more than 2 months, only an oil resulted (in contrast to aldehyde **5a**). However, the oil solidified upon seeding with a few small crystals of acid **6b** from a previous experiment. A solution of the solid in hot chloroform was mixed with hexane until turbidity was observed. Slow cooling to 25 °C produced colorless crystals. The process was repeated three times to afford needles (0.81 g), mp 103–105 °C.

Anal. Calcd for $C_{11}H_{11}FO_4$: C, 58.40; H, 4.91; F, 8.40. Found: C, 58.42; H, 4.87; F, 8.42.

Methyl Ester of *p*-Chlorophenylsuccinic Acid (6c). As noted for aldehyde **5a**, methyl 2-(*p*-chlorophenyl)-4-oxobutyrate solidified

after exposure to air (25 °C) for several weeks. The solid recrystallized from chloroform–ligroin, furnishing acid **6c** as colorless crystals, mp 129–130 °C.

Anal. Calcd for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57; Cl, 14.61. Found: C, 54.25; H, 4.54; Cl. 14.77.

Bromination of Methyl 2-Phenyl-4-oxobutyrate (5a). Bromine (1.3 g, 8.4 mmol) was quickly added to a stirred solution of aldehyde **5a** (1.6 g, 8.4 mmol) in glacial acetic acid (13 mL). In approximately 1 h the deep red solution turned light yellow. Stirring was continued for 20 h at 25 °C. The reaction mixture was diluted with water (20 mL) and extracted with chloroform, and the combined extract was washed with 10% sodium bicarbonate, water, and 10% sodium thiosulfate. Removal of solvent led to 1.21 g of a yellow oil. Silica gel chromatography (chloroform) afforded the following products in order of elution. The first product, **3-phenyl-5,5-dibromo-2(5*H*)-furanone (7a;** 0.233 g), was purified by a single sublimation (72 °C at 0.15 mm) that resulted in colorless crystals: mp 65–65.5 °C; IR (KBr) 3000, 1765, 1620, 1485, 1435, 1290, 1265, 1178, 1080, 1020, 1000, 990, 943, 878, 775, 748, 734, 690, 680 cm^{-1}; ^1H NMR δ 6.81 (s, 1 H, vinyl CH), 7.40–7.86 (m, 5 H, aromatic); mass spectrum, *m/e* (relative intensity) 320 (6), 318 (13), 316 (6), 240 (19), 239 (100), 238 (19), 237 (99), 211 (16), 209 (17), 183 (16), 181 (17), 129 (8), 102 (53); UV λ_{max} (EtOH, 100%) 264 nm (ϵ 10 200).

Anal. Calcd for $C_{10}H_6Br_2O_2$: C, 37.77; H, 1.90; Br, 50.26. Found: C, 37.78; H, 1.87; Br. 50.22.

The second product, **3-phenyl-5-bromo-2(5*H*)-furanone (7b;** 0.103 g), was crystallized from hexane to give colorless crystals: mp 82.5–83.5 °C; IR (KBr) 3000, 1775, 1620, 1495, 1440, 1315, 1255, 1182, 1090, 1062, 980, 930, 858, 785, 743 cm^{-1}; ^1H NMR δ 6.94 (d, 1 H, J = 2 Hz, CH), 7.38–7.49 (m, 3 H, aromatic), 7.62 (d, 1 H, J = 2 Hz, vinyl CH), 7.79–7.89 (m, 2 H, aromatic); mass spectrum, *m/e* (relative intensity) 240 (3), 238 (3), 196 (2), 194 (11), 160 (36), 159 (100), 139 (2), 137 (9), 131 (29), 103 (66), 102 (44); UV λ_{max} (EtOH, 100%) 273 nm (ϵ 9900). High-resolution mass spectrum: calcd for $C_{10}H_7{}^{79}BrO_2$, 237.9630; found, 237.9628; calcd for $C_{10}H_7{}^{81}BrO_2$, 239.9610; found, 239.9642.

The third product, **3-phenyl-5-acetoxy-5-bromo-2(5*H*)-furanone (7c;** 0.081 g), was recrystallized from pentane and resulted in colorless plates: mp 80.5–81.0 °C; IR (KBr) 3100, 3000, 1770 br, 1660, 1600, 1495, 1440, 1420, 1378, 1340, 1298, 1198, 1165, 1118, 1047, 984, 952, 915, 870, 785, 765, 752, 697 cm^{-1}; ^1H NMR δ 2.18 (s, 3 H, CH_3CO_2), 6.92 (s, 1 H, vinyl CH), 7.40–7.52 (m, 3 H aromatic), 7.74–7.88 (m, 2 H, aromatic); mass spectrum, *m/e* (relative intensity) 298 (15), 296 (15), 256 (29), 254 (31), 239 (12), 237 (12), 217 (<1), 183 (14), 181 (14), 176 (14), 175 (59), 174 (100), 145 (77), 131 (22), 130 (27), 129 (42), 102 (65); UV λ_{max} (EtOH, 100%) 272 nm (ϵ 10 500).

Anal. Calcd for $C_{12}H_9BrO_4$: C, 48.52; H, 3.05; Br, 26.89. Found: C, 48.64; H, 3.05; Br, 26.91.

Finally, the column was washed with chloroform–methanol (10:1), furnishing a fraction (ca. 0.330 g) composed of two components. Silica gel chromatography (ethyl acetate) of this mixture led to a tan tar (0.215 g) and a minor compound (0.013 g) not further identified. The major product, **3-phenyl-5-bromo-5-hydroxy-2(5*H*)-furanone (7d)**, crystallized from chloroform–hexane as colorless crystals: mp 100–101 °C; IR (KBr) 3400 br, 1760, 1640, 1600, 1490, 1440, 1325, 1295, 1125, 1000, 975, 863, 770, 743, 688 cm^{-1}; ^1H NMR δ 5.50 (broad s, 1 H, exchanges with D_2O, OH), 6.12 (s, 1 H, vinyl CH), 7.20–7.91 (m, 5 H, aromatic); mass spectrum, *m/e* (relative intensity) 256 (9), 254 (11), 240 (5), 238 (5), 175 (21), 159 (9), 148 (14), 147 (20), 131 (43), 130 (100), 129 (96), 102 (86); UV λ_{max} (EtOH, 100%) 286 nm (ϵ 15 000).

Anal. Calcd for $C_{10}H_7BrO_3$: C, 47.09; H, 2.77; Br, 31.32. Found: C, 46.86; H, 3.13; Br, 31.24.

Bromination of Methyl 2-(*p*-Chlorophenyl)-4-oxobutyrate (5c). To a solution of methyl 2-(*p*-chlorophenyl)-4-oxobutyrate (8.0 g, 0.035 mol) in glacial acetic acid (100 mL) was added bromine (5.6 g, 0.035 mol) in glacial acetic acid (80 mL). The deep red solution turned light yellow in 30 min. After stirring for 7 h, the reaction mixture was diluted with water (500 mL) and extracted with chloroform. The combined chloroform extract was washed with water, 10% sodium bicarbonate, and 10% sodium thiosulfate. Subsequent drying and solvent removal led to a yellow oil (9.6 g) comprised of four compounds (TLC: ligroin–acetone, 4:1). The oil was dry-loaded on a column of silica gel. Elution with ligroin–acetone (4:1) yielded a yellow oil (2.2 g) as the major component (also highest R_f). This compound was found to be **3-(*p*-chlorophenyl)-5-bromo-2(5*H*)-furanone (7e)** and was further purified by crystallization from ether–pentane followed by sublimation of the resulting yellow solid at 80 °C (0.01 mm). Finally, recrystallization of the colorless powder from ether–pentane resulted in colorless plates: mp 115–116 °C; IR (KBr) 3078, 2973, 1761, 1608, 1580, 1488, 1405, 1307, 1295, 1243, 1170, 1087, 1060, 1010, 970, 918, 880, 830, 756, 665 cm^{-1}; ^1H NMR δ 7.08 (d, 1 H, J = 2 Hz, CH), 7.38–7.56 (m, 2 H, aromatic), 7.69 (d, 1 H, J = 2 Hz, vinyl CH), 7.82–7.99 (m, 2 H, aromatic); mass spectrum, *m/e* (relative intensity) 276 (4), 274 (2), 272 (2), 230 (1), 228 (2), 222 (3), 221 (17), 220 (16), 215 (5), 214 (6), 206 (5), 196 (7), 195 (40), 194 (22), 193 (100), 180 (18), 165 (12), 139 (19), 138 (14), 137 (49), 136 (27); UV λ_{max} (EtOH, 100%) 283 nm (ϵ 12 300).

Anal. Calcd for $C_{10}H_6BrClO_2$: C, 43.91; H, 2.21; Br, 29.22; Cl, 12.96. Found: C, 43.85; H, 2.16; Br, 29.20; Cl, 12.96.

Bromination of Methyl 2-(*p*-Fluorophenyl)-4-oxobutyrate (5b). Bromine (4.00 g, 0.025 mol) in glacial acetic acid (10 mL) was rapidly introduced into a solution of methyl 2-(*p*-fluorophenyl)-4-oxobutyrate (5.25 g, 0.025 mol) in glacial acetic acid (90 mL). After 1 h the deep red solution began to lighten. Continued stirring for 17 h at 25 °C produced a pale yellow solution. The crude product was isolated as described for lactone **7e.** Solvent removal provided a light yellow oil (4.58 g) which solidified at −10 °C. Purification by silica gel chromatography (dry-loaded; ligroin–acetone, 4:1) furnished a yellow solid (ca. 1.74 g) that proved to be 3-(*p*-fluorophenyl)-5-bromo-2(5*H*)-furanone (**7f**). The lactone was decolorized with activated charcoal and recrystallized from acetone–hexane to provide colorless plates: mp 97–98 °C; IR (KBr) 3100, 1760, 1620, 1601, 1510, 1310, 1293, 1245, 1175, 1160, 1115, 1063, 974, 953, 885, 838, 670 cm^{-1}; ^1H NMR δ 7.08 (d, 1 H, J = 2 Hz, CH), 7.20–7.33 (m, 2 H, aromatic), 7.64 (d, 1 H, J = 2 Hz, vinyl CH), 7.84–8.10 (m, 2 H, aromatic); mass spectrum, *m/e* (relative intensity) 258 (2), 256 (2), 178 (29), 177 (100), 159 (2), 150 (3), 149 (37), 122 (12), 121 (69), 120 (54), 101 (38); UV λ_{max} (EtOH, 100%) 282 nm (ϵ 9100).

Anal. Calcd for $C_{10}H_6BrFO_2$: C, 46.72; H, 2.35; Br, 31.08; F, 7.39. Found: C, 46.83; H, 2.32; Br, 31.14; F, 7.50.

Methyl 2-(*p*-Fluorophenyl)-3-formylacrylate (8). To a stirred solution of methyl 2-(*p*-fluorophenyl)-4-oxobutyrate (6.12 g, 0.029 mol) in glacial acetic acid (50 mL) was added bromine (4.63 g, 0.029 mol) in glacial acetic acid (50 mL) in 10-mL increments over a 2.3-h period. Additional bromine–acetic acid solution was not added to the reaction mixture until the color (deep red) from the previous addition became light yellow. Immediately after the color had disappeared from the last bromine–acetic acid addition, water (200 mL) was added and the resulting solution extracted with chloroform. The combined extract was washed with water, saturated sodium bicarbonate solution, 10% sodium thiosulfate, and water. The chloroform solution was dried (sodium sulfate), and the solvent was removed to afford a yellow oil (2.28 g) that was subjected to silica gel chromatography (hexane–ethyl acetate, 9:1). The first compound eluted was identified as olefin 8 (0.434 g). Recrystallization from pentane afforded yellow needles: mp 64–65 °C; IR (KBr) 3100, 2850 sh, 2750 sh, 1725, 1675, 1600, 1510, 1430, 1395, 1250, 1160, 1108, 1025, 910, 838, 767, 737 cm^{-1}; ^1H NMR δ 3.86 (s, 3 H, OCH_3), 7.00 (d, 1 H, J = 8 Hz, vinyl CH), 7.19–7.51 (m, 4 H, aromatic), 9.66 (d, 1 H, J = 8 Hz, CHO); mass spectrum, *m/e* (relative intensity) 208 (13), 181 (6), 180 (73), 179 (11), 177 (10), 160 (7), 149 (21), 136 (6), 135 (23), 133 (8), 122 (14), 121 (100), 120 (43); UV λ_{max} (EtOH, 100%) 288 nm (ϵ 7200).

Anal. Calcd for $C_{11}H_9FO_3$: C, 63.46; H, 4.36; F, 9.13. Found: C, 63.43; H, 4.34; F, 9.14.

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Registry No.—**1a,** 67031-03-2; **1b,** 67031-02-1; **1c,** 67031-04-3; **1d,** 67031-05-4; **1e,** 67031-06-5; **4a,** 14815-73-7; **4b,** 67031-08-7; **4c,** 67031-09-8; **4d,** 67031-10-1; **4e,** 67031-11-2; **5a,** 67031-12-3; **5a** DNP, 67031-13-4; **5b,** 67031-14-5; **5b** DNP, 67031-15-6; **5c,** 67031-16-7; **5c** DNP, 67031-17-8; **5d,** 67031-18-9; **5d** DNP, 67031-19-0; **6a,** 54897-85-7; **6b,** 67031-20-3; **6c,** 67031-21-4; **7a,** 67031-07-6; **7b,** 67030-93-7; **7c,** 67030-92-6; **7d,** 67030-91-5; **7e,** 67030-90-4; **7f,** 67030-98-2; **8,** 67030-97-1; ethyl 2-ethyl-4-oxobutyrate, 67030-96-0; ethyl 2-ethyl-4-pentenoate, 67030-95-9; ethyl 2-ethyl-4-oxobutyrate DNP, 3601-51-2; ethyl 2-ethyl-3,3-dibromo-4-oxobutyrate, 67030-94-8; phenylacetic acid, 103-82-2; *p*-fluorophenylacetic acid, 405-50-5; *p*-chlorophenylacetic acid, 1878-66-6; *p*-methoxyphenylacetic acid, 104-01-8; 3,4,5-trimethoxyphenylacetic acid, 951-82-6.

Supplementary Material Available: Complete IR, NMR, and mass spectral data are available for compounds **4–6** (4 pages). Ordering information is given on any current masthead page.

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(16) The pseudomixed anhydride **10** (Scheme III) was also detected by ^{1}H NMR spectroscopy.
(17) Ethyl 2-ethyl-3,3-dibromo-4-oxobutyrate was isolated in 7% yield (see Experimental Section) and was found to decompose upon standing at 10 °C for 72 h. Only a ^{1}H NMR spectrum was obtained. Ethyl 2-ethyl-3-bromo-4-oxobutyrate was probably present as a reaction intermediate but was not isolated.
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Alkyl Nitrite–Metal Halide Deamination Reactions. 5. In Situ Generation of Nitrosyl Halides. Effective Product Control from Nitrosyl Chloride Diazotization of Primary Aliphatic Amines in *N,N*-Dimethylformamide[1]

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Nitrosyl chloride and nitrosyl bromide are formed by an efficient halide/alkoxide exchange between titanium tetrahalides and alkyl nitrites. Complete replacement of halide by alkoxide occurs and results in the formation of titanium tetraalkoxides. Reactions of primary aliphatic amines with in situ generated nitrosyl halides in *N,N*-dimethylformamide effectively minimizes elimination, rearrangement, and oxidation processes normally encountered in alternate diazotization procedures and facilitates product recovery in high yield. Comparative results for the diazotization of benzylamine by nitrosyl chloride generated from selected metal halides and *tert*-butyl nitrite are reported; the generality of chloride/alkoxide exchange for the early transition metal halides is indicated. Diazotization of primary aliphatic amines by in situ generated nitrosyl chloride in dimethylformamide produces unrearranged alkyl chlorides, alcohols, and formate esters.

Methods for deaminaton of aliphatic amines by nitrosyl halides have received considerably less attention than corresponding processes that employ nitrous acid or dinitrogen tetroxide.[3] The gaseous nitrosyl halide reagents require special handling techniques and, as is characteristic in diazotization reactions of primary aliphatic amines, generally effect the production of complex reaction mixtures in moderate yields.[4-6] In chemical operations that employ nitrosyl halides in aprotic media, these reagents are generated externally and then passed into the reaction solution from a collection vessel employed to measure the volume of the nitrosyl halide. Methods for in situ generation of nitrosyl halides, based on known reactions of hydrogen halides with sodium nitrite,[7] dinitrogen tetroxide,[8] or alkyl nitrites,[9] have not been advanced for use in deaminaton or addition procedures due to their production of potentially interfering byproducts;[10] in addition, excess amounts of hydrogen halides are often used to facilitate nitrosyl halide formation or to avoid the normally complex stoichiometric measurement of the gaseous acid. In this paper we report general methods for in situ generation of nitrosyl chloride and nitrosyl bromide that avoid the complexities usually observed with the use of hydrogen halides.

In his recent thorough examinations of deamination reactions of aliphatic amines by nitrosyl chloride at low temperatures in aprotic media, Bakke[11] identified five principal reaction pathways of the intermediate alkyldiazonium chlorides: chloride substitution, elimination, rearrangement, displacement by solvent, and diazoalkane formation (eq 1–5).

$$RCH_2CH_2N_2^+Cl^- \rightarrow RCH_2CH_2Cl + N_2 \quad (1)$$

$$RCH_2CH_2N_2^+Cl^- \rightarrow RCH{=}CH_2 + HCl + N_2 \quad (2)$$

$$RCH_2CH_2N_2^+Cl^- \rightarrow RCHClCH_3 + N_2 \quad (3)$$

$$RCH_2CH_2N_2^+Cl^- + Sol: \rightarrow RCH_2CH_2\text{-}Sol^+Cl^- + N_2 \quad (4)$$

$$RCH_2CH_2N_2^+Cl^- \rightarrow RCH_2CH{=}N_2 + HCl \quad (5)$$

Reactions were performed at −70 °C in ether solvents to minimize rearrangement and, under these conditions, the process represented by eq 1 was dominant (88% of products from eq 1–4).[11a] In hydrocarbon and chlorocarbon solvents, however, the production of both aldehydes and oximes, presumed formed from the corresponding nitrosoalkane, was dominant.[11c] These and prior reports of diazotization efficiency in reactions of aliphatic amines with nitrosyl chloride

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