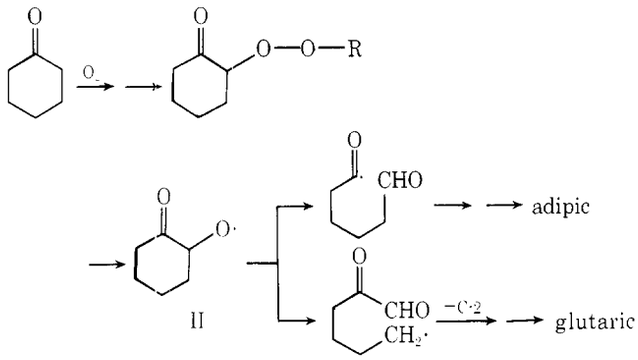
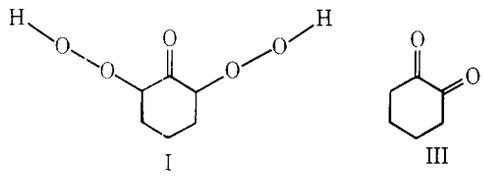


loss of C-1 from an intermediate 2,6-dihydroperoxycyclohexanone compound (I).[5] A more recent proposal that glutaric acid is formed by loss of C-2 from an α-ketooxy radical (II) is consistent with the observed high retention of the labeled carbonyl carbon.[3]

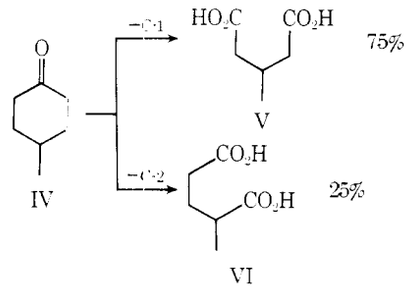
It has been reported that α-ketooxy radicals undergo thermolysis or metal-catalyzed cleavage to generate carboxylic acids in which the carboxyl group is derived from the keto group.[6] It has been proposed that 1,2-cyclohexanedione (III)



is formed during oxidation of cyclohexanone and gives rise to most of the CO and CO_2 evolved.[7] Although 1,2-cyclohexanedione may account for CO and CO_2 generation, it is not a viable intermediate for glutaric or succinic acid formation. Loss of a carbonyl carbon from III would decrease the isotopic enrichment by a factor of 2.

Significant glutaric acid formation from decarboxylation of adipic acid is not consistent with the observed high degree of retention of C-1 from labeled cyclohexanone or with reported carboxylic acid decarboxylation studies.[8,9] The extent to which succinic acid is derived from solvent acetic acid was examined using [1-^{14}C]acetic acid under the oxidation conditions used for labeled cyclohexanone. The conversion of cyclohexanone was 44% with a yield to adipic acid of 27%. Radiometric analysis of isolated succinic acid showed the presence of 0.04 mol of [1-^{14}C]carboxyl groups per mole of succinic acid. Assuming all HO_2C–CH_2· radicals were derived from acetic acid, about 2% of the succinic acid was derived from acetic acid.

The effect of methyl substitution on the extent of loss of C-1 was found to be substantial. Whereas unsubstituted (labeled) cyclohexanone gave glutaric acid with >90% retention of C-1, 4-methylcyclohexanone (IV) gave a 3-methylglutaric (V)/2-methylglutaric (VI) acid ratio of 3:1. The stability of diacid products V and VI to reaction conditions was checked by replacing half of the cyclohexanone in a typical oxidation experiment with equal molar amounts of V and VI. Of the cyclohexanone charged, 34% was converted to adipic acid. The ratio of V/VI in the product was 1.0 within experimental error



based on ^{1}H NMR integrals for the methyl resonances for V (δ 1.05) and VI (δ 1.15). The preponderance of loss of C-1 with methyl substitution may be largely a steric effect.

Experimental Section

All oxidation reactions were carried out in 10-cm^3 stainless steel shaker tubes at 100 °C with 200 psi of O_2 for 10–16 h. A typical starting solution consisted of 5.5 g (91.7 mmol) of acetic acid, 1.05 g (10.7 mmol) of [1-^{14}C]cyclohexanone, and 0.10 g (0.42 mmol) of $Co(OAc)_3$. Gas chromatographic analyses for adipic, glutaric, and succinic acids were carried out on a 12 ft × 0.12 in. stainless steel column of OV-1 at 190 °C following treatment with BSTFA to form trimethylsilyl diesters. [1-^{14}C]Cyclohexanone was commercially available.[10] [1-^{13}C]Cyclohexanone was prepared by carbonylation of bisborinane with ^{13}CO.[11] Products containing ^{14}C were analyzed with a Packard liquid scintillation spectrometer using standard dilution techniques. Each sample was crystallized repeatedly to obtain constant specific activity. Products containing ^{13}C were analyzed by gas chromatography/mass spectroscopic techniques.[12]

Acknowledgment. We thank Drs. B. A. Carlson, U. Klabunde, E. J. Lukosius, and J. B. Sieja for helpful discussions.

Registry No.—$Co(OAc)_3$, 917-69-1; cyclohexanone, 108-94-1; glutaric acid, 110-94-1; succinic acid, 110-15-6.

References and Notes

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(2) A. Onopchenko and J. G. D. Schulz, *J. Org. Chem.*, **38**, 3729 (1973); **40**, 3338 (1975).
(3) D. G. Hendry, C. W. Gould, D. Schuetzle, M. G. Syz, and F. R. Mayo, *J. Org. Chem.*, **41**, 1 (1976).
(4) K. Tanaka, *Prepr. Div. Pet. Chem. Am. Chem. Soc.*, **19**, 103 (1974).
(5) G. N. Koshel et al., *Neftekhimiya*, **14** (2), 263 (1974).
(6) Y. Sawaki and Y. Ogata, *J. Org. Chem.*, **41**, 2340 (1976).
(7) I. I. Korsak and V. E. Agabekov, *Dokl. Akad. Nauk B. SSR*, **19** (8), 711 (1975).
(8) (a) H. B. Tinker, *J. Catal.*, **19**, 237 (1970); (b) S. S. Lande and J. K. Kochi, *J. Am. Chem. Soc.*, **90**, 5196 (1968).
(9) Reaction product vapors contained too little CO and CO_2 for quantitative isotopic measurements. At 100 °C decarboxylation of solvent acetic acid could account for a significant fraction of the total CO and CO_2. It is reported that, at 150 °C, "about 30% of the total carbon oxides results from its (acetic acid) decomposition." [8a]
(10) [1-^{14}C]Cyclohexanone was obtained from Amersham/Searle Corp. That the ^{14}C was contained only in C-1 was shown by oxidizing [1-^{14}C]cyclohexanone to adipic acid and then converting the adipic acid to cyclopentanone by BaO-catalyzed decarboxylation. The specific activity of the cyclopentanone was exactly half that of the starting [1-^{14}C[cyclohexanone.
(11) H. C. Brown, "Organic Syntheses Via Boranes", Wiley, New York, N.Y., 1975, p 158.
(12) GC/MS was done using chemical ionization by T. A. Blazer, Central Research and Development Department.

Synthesis of *N*-(4-Azido-2-nitrophenyl)amino-1-alkyl-β-D-glucopyranosides: Photoaffinity Labeling Derivatives of Glucose

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During the course of studies of the mechanism of glucose transport in human erythrocytes, the need arose for derivatives of glucose which could serve as photoaffinity labeling agents.[1,2] Since an integral part of these studies involved the evaluation of reagents in which the distance between the sugar moiety and the photolabile grouping was varied systemati-

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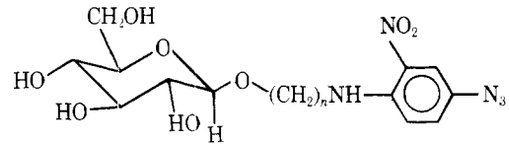
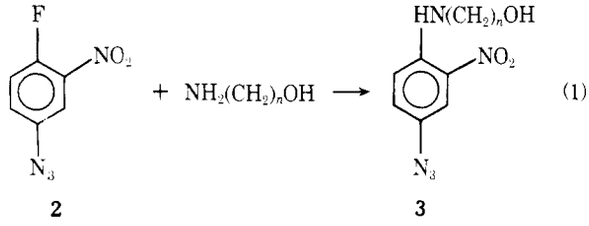


1

cally, we designed a synthetic scheme for the preparation of glucosides **1** of ω-(arylazido)alkanols.

The key step in this synthesis involves the highly selective *N*-arylation of an α,ω-amino alcohol by 4-fluoro-3-nitrophenyl azide[1b] (**2**) (eq 1) to form substituted anilines (**3**). The structural assignments for the anilines are based on the appearance of quartets at ca. δ 3.4 in their NMR spectra.

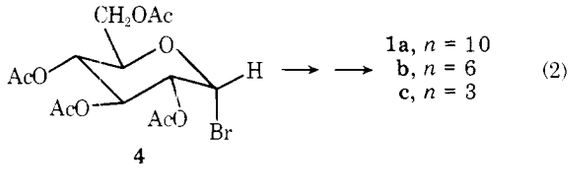


(1)

2 **3**

a, $n = 10$
b, $n = 6$
c, $n = 3$

Glucosylation (eq 2) was accomplished by a modified[3] Koenigs–Knorr reaction using silver oxide and tetraacetyl-α-D-glucosyl bromide. Deacetylation yielded the free sugar derivatives **1a–c**.



(2)

4

These reactions should be generally applicable to the synthesis of photoaffinity labeling agents of other sugar derivatives provided the glycosylation step is carried out under mild conditions.

Experimental Section

Nuclear magnetic resonance (NMR) data were obtained from a Varian Model T-60 spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrometer. The mass spectrum was determined on a Hitachi Perkin-Elmer Model RMU-7 mass spectrometer at 80 eV.

4-Fluoro-3-nitrophenyl Azide (2). This material is commercially available from ICN Pharmaceuticals, Inc., Cleveland, Ohio, or from Pierce Chemicals, Rockford, Ill. Alternatively, it can be synthesized from 4-fluoro-3-nitroaniline by the following procedure.[4] A slurry of 1.561 g (0.010 mol) of 3-nitro-4-fluoraniline in 100 mL of 1.1 M sulfuric acid was cooled to −20 °C. A solution of 1.38 g (0.020 mol) of sodium nitrite in 10 mL of water was added over 5 min to the stirred mixture. The slurry was allowed to warm to −10 °C over 20 min at which time 100 mL of ether was added. Potassium azide (1.622 g, 0.020 mol) in 10 mL of water was added over 5 min at −10 °C. After 10 min of stirring, the layers were separated and the aqueous phase was extracted twice with ether. The extracts were dried ($MgSO_4$) and evaporated to yield 0.896 g of crude product. Recrystallization from petroleum ether (20–40 °C) gave 0.778 g (43%) of orange needles: mp 53–55 °C (lit.[1b] mp 52 °C); NMR δ 7.75 (m, 1 H), 7.35 (m, 2 H); mass spectrum (*m/e*) 182 (molecular ion), 154 ($M^+ - N_2$) and 108 ($M^+ - N_2 - NO_2$, base peak).

10-*N*-(4-Azido-2-nitrophenyl)amino-1-decanol (3a). A solution of 570 mg (2.5 mmol) of **2** and 865 mg (5.0 m mol) of 10-amino-1-decanol in 2.5 mL of dioxane was kept at 25 °C for 2.5 h. The solvent was evaporated at a temperature not exceeding 70 °C.[5] The residue was dissolved in chloroform and chromatographed on a silica gel column (1 × 50 cm) using chloroform as an eluant. The product **3a** was obtained as red crystals: mp 58–59 °C; yield 857 mg (83%); IR (melt) 4.72 μm (N_3); ^1H NMR δ 8.2 (broad, 1 H), 6.7–7.9 (m, 3 H), 3.7 (t, 2 H), 3.3 (q, 2 H, $J = 6$ Hz), 2.3–1.15 (m, 16 H).

Anal. Calcd for $C_{16}H_{25}N_5O_3$: C, 57.29; H, 7.51; N, 20.88. Found: C, 57.53; H, 7.63; N, 20.65.

3-*N*-(4-Azido-2-nitrophenyl)amino-1-propanol (3c). By the above procedure there was obtained a 68% yield[6] of **3c**: mp 86–86.5 °C; IR (Nujol) 4.68 μm (N_3); ^1H NMR δ 8.2 (broad, 1 H), 6.8–7.9 (m, 3 H), 3.84 (t, 2 H), 3.46 (q, 2 H, $J = 6$ Hz), 2.16–1.66 (m, 3 H).

Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.58; H, 4.63; N, 29.53. Found: C, 45.61; H, 4.56; N, 29.75.

6-*N*-(4-Azido-2-nitrophenyl)amino-1-hexanol (3b). Similarly, compound **3b** was obtained as a red oil in 70% yield; IR (film) 4.78 μm (N_3); NMR δ 8.0 (b 1 H), 7.8–6.7 (m, 3 H), 3.65 (t, 1 H), 3.30 (q, 1 H), 2.0–1.2 (m, 9 H). The oil could not be induced to crystallize.

10-*N*-(4-Azido-2-nitrophenyl)amino-1-decyl-β-D-glucopyranoside (1a). The following mixture was stirred at 25 °C for 22 h: 586 mg (1.75 mmol) of **3a**, 720 mg (1.75 mmol) of tetra-*O*-acetyl-α-D-glucopyranosyl bromide,[7] 410 mg (1.75 mmol) of freshly prepared silver oxide,[8] 270 mg (2.0 mmol) of anhydrous calcium sulfate, and 4.0 mL of benzene. The slurry was filtered and the filtrate was washed thoroughly with a solution of 100 mg of silver nitrate in 25 mL of water, twice with water, and once with brine. The organic phase was dried (Na_2SO_4), filtered through celite, and evaporated. The crude product mixture (1.12 g) was acetylated to aid the chromatographic separation. This was accomplished by treatment with 0.25 mL of acetic anhydride in 1.0 mL of pyridine for 1 h at 25 °C. Benzene (25 mL) was added and the solution was washed once with water, three times with cold HCl, twice with water, and once with brine. The organic layer was dried (Na_2SO_4) and evaporated. Chromatographic separation ($CHCl_3$) on a 3 × 50 cm column of silica gel gave two major fractions: the acetate of **3a** (32%) and the acetate of **1a**[9] which was contaminated with some pentaacetyl glucose. Evaporation of the solvent from the second fraction gave a residue which was dissolved in 40 mL of methanol. This solution was saturated with ammonia gas and kept at 25 °C for 24 h after which the volatile materials were removed by evaporation. The residue was triturated with benzene to remove acetamide and then dissolved in 100 mL of $CHCl_3$. The glucose was removed by washing with water (5×). The dried $CHCl_3$ was evaporated and the residue was crystallized from 2 mL of methanol to give 266 mg of **1a** (46%): mp 105–106.5 °C; IR (Nujol) 4.73 μm (N_3).

Anal. Calcd. for $C_{22}H_{35}N_5O_8$: C, 53.13; H, 7.03; N, 14.08. Found: C, 53.37; H, 7.29; N, 13.85.

Similar results were obtained more conveniently by use of thick layer (5 mm) silica plates in place of the column chromatography.

6-*N*-(4-Azido-2-nitrophenyl)amino-1-hexyl-β-D-glucopyranoside (1b). By a similar procedure to that above **1b** was prepared in 17% yield as a low-melting solid: mp 45°C; IR (Nujol) 4.74 μm (N_3).

Anal. Calcd for $C_{18}H_{27}N_5O_8$: C, 48.97; H, 6.16; N, 15.86. Found: C, 48.69; H, 6.38; N, 15.63.

3-*N*-(4-Azido-2-nitrophenyl)amino-1-propyl-β-D-glucopyranoside (1c). A mixture of 3.78 g (15.5 mmol) of **3c**, 6.15 g (15 mmol) of **4**, 3.46 g (15 mmol) of silver oxide,[8] 2.5 g of anhydrous sodium sulfate, and 65 mL of dry methylene chloride was stirred for 2 days at room temperature. The mixture was filtered and the filtrate was treated with 2.0 mL of pyridine and 2.9 mL (40 mmol) of acetic anhydride. After 5 h at 25 °C the volatiles were removed by rotary evaporation with care being taken not to heat the flask above 65 °C. The residue was chromatographed on a silica column using chloroform as an eluant. The first fraction consisted of the acetate of **3c** (90% recovery). The second band consisted of the acetate of **1c** and a smaller amount of another product. A second purification by preparative TLC (silica, $CHCl_3$) did not separate these two components. The mixture was deacetylated in ammonia–methanol. The solvent was evaporated and the residue was treated with 2 mL of methanol and enough ethyl acetate to precipitate all of the glucose which was formed. The mixture was filtered and the filtrate was evaporated. The residue was stirred with chloroform yielding an orange powder which was filtered and dried in vacuo: yield 480 mg (52%); mp 116–117.5 °C. This material showed a single spot of TLC and azide absorption at 4.72 μm. Anal. Calcd for $C_{15}H_{21}N_5O_8$: C, 45.10; H, 5.30; N, 17.53. Found: C, 44.90; H, 5.30; N, 17.27.

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Registry No.—**1a,** 65496-00-6; **1b,** 65495-92-3; **1c,** 65495-93-4; **2,** 28166-06-5; **3a,** 65495-94-5; **3b,** 65495-95-6; **3c,** 64309-10-0; 4-fluoro-3-nitroaniline, 364-76-1; 10-amino-1-decanol, 23160-46-5; 3-amino-1-propanol, 156-87-6; 6-amino-1-hexanol, 4048-33-3; tetra-*O*-acetyl-α-D-glucopyranosyl bromide, 572-09-8.

References and Notes

(1) (a) For a general review of the use of photoaffinity labels, see J. R. Knowles, *Acc. Chem. Res.*, **5**, 156 (1972); (b) G. W. J. Fleet, R. R. Porter, and J. R. Knowles, *Nature (London)*, **224**, 511 (1969).
(2) M. B. Perry and L. L. W. Heung, *Can. J. Biochem.*, **50**, 510 (1971), have prepared some other types of glucose derivatives with photolabile groups.
(3) W. Pigman and N. Richtmeyer, *J. Am. Chem. Soc.*, **64**, 369 (1962).
(4) We are deeply indebted to Doreen Lynch for developing this procedure. Only sketchy experimental details are given in ref 1b, and we have found that if conditions are not carefully controlled the major product is 4-hydroxy-3-nitrophenyl azide.
(5) Aryl azides are heat and light sensitive. It is advisable to cover flasks, etc., with aluminum foil during laboratory operations and to store products in refrigerators.
(6) Use of 1 equiv of amino alcohol and a tertiary amine, e.g., triethylamine, led to reduced yields.
(7) Obtained from Sigma Chemical Co., St. Louis, Mo. This material was used directly without purification.
(8) R. Willstätter and A. Pfannenstiel, *Ber.*, **37**, 4744 (1904).
(9) HLPC analysis of this product on a 2 ft × 1/8 in. Corasil column at 150 psi showed one major (>99%) product using benzene as eluent.
(10) The configurations of **1a–c** are assigned by analogy with numerous examples of glycosides prepared by silver salt catalyzed reactions of **4**. See ref 3 and G. Wulff, G. Rohle, and W. Krüger, *Ber.*, **105**, 1097 (1972).

Rearrangements of Acyloxyfurans and Thiophenes

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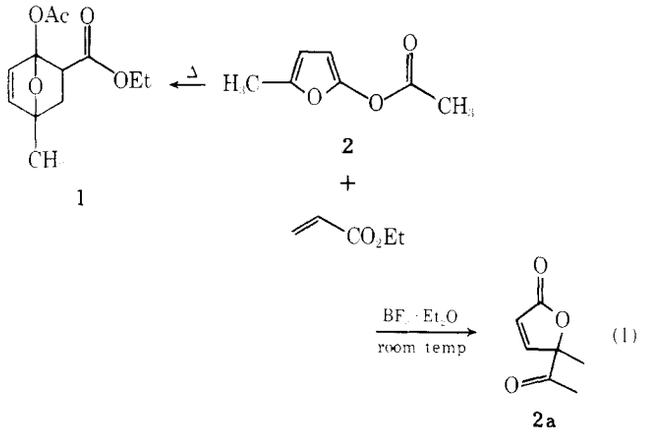
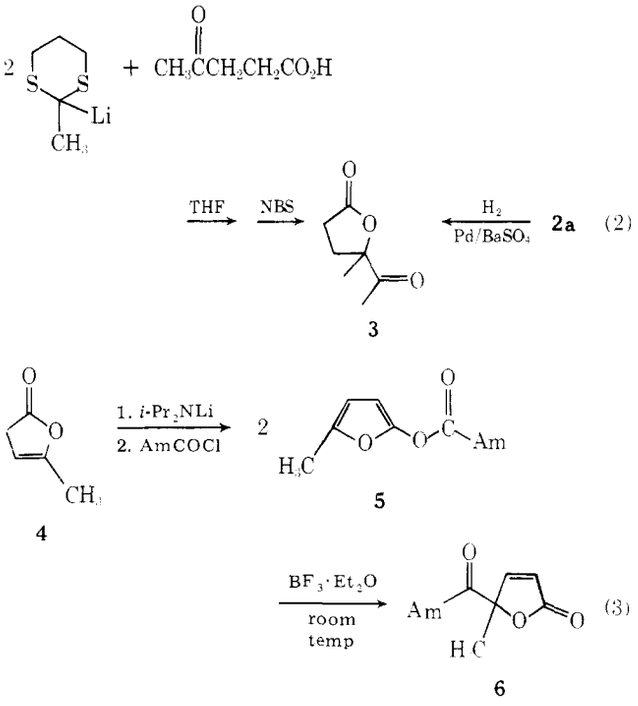
As part of a program for the synthesis of medium-ring compounds, the preparation of the bicyclic ester **1** became necessary. This could be accomplished in moderate yield by the Diels–Alder reaction shown in eq 1. Attempts to improve

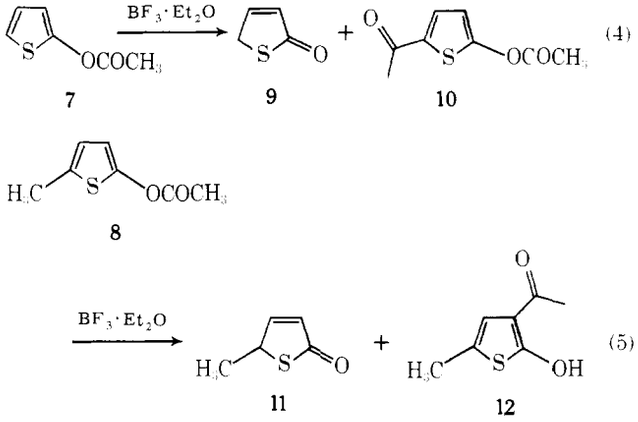


the yield by the use of Lewis acids such as boron trifluoride etherate provided the unexpected lactone **2a** in good yield. The structure of this novel rearrangement product was proven by hydrogenation[1] to butyrolactone **3** and independent synthesis of **3** by the reaction of levulinic acid with 2 equiv of 2-methyldithiane,[2] followed by oxidative removal of the dithiane moiety using NBS[3] (eq 2). Although the presence of diverse functionality should make this type of compound a versatile synthon, a literature search indicated that the preparation of this class of ketolactones had not been previously reported. Therefore, we sought to probe the extent of this rearrangement with other esters. Compound **5** was readily synthesized by quenching the lithium enolate[4] of angelicalactone **4** with

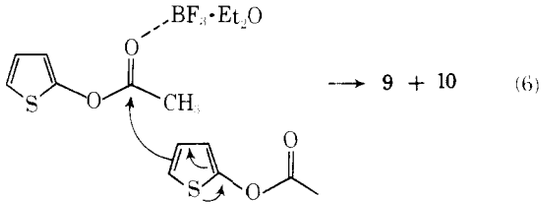


hexanoyl chloride (eq 3). Reaction of **5** with boron trifluoride etherate afforded ketolactone **6** in 40% isolated yield. A possible mechanism for this intriguing rearrangement would be one analogous to the Lewis acid catalyzed Fries rearrangement.[5]

The reactions of thiophene analogues **7** and **8**[6] produced the mixtures shown in eq 4 and 5.



Compounds **9** and **10** could arise from intermolecular attack as illustrated in eq 6.



A similar scheme can account for the formation of compounds **11** and **12** from thiophene **8**.

Experimental Section

NMR spectra were obtained with a Varian (A60) NMR spectrometer. The chemical shifts are reported in δ, using tetramethylsilane as reference. All melting points were taken upon a Fisher-Johns block and are uncorrected. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn. Organic solutions were dried over sodium sulfate.

General Procedure for the Synthesis of 2 and 5. A solution of

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