46.7, 52.0, 53.0, 54.0, 71.9, 73.8, 175.3; mass spectrum (70 eV), m/e (relative intensity) 185 (13, M^+), 167 (60), 154 (31), 141 (100), 128 (16), 126 (14), 106 (22), 88 (20).

Calcd for $C_9H_{15}O_3N$: 185.1052. Found: 185.1051.

(5α)-1-Aza-4β-carbomethoxy-6α-[(*tert*-butyldimethylsilyl)oxy]bicyclo[3.3.0]octane (19). Vinylaziridine **15a** (10 mg, 0.03 mmol) was pyrolyzed as described in the previous experiment for **14a**. The total time of evaporation was kept under 6 min by gently warming the distillation flask. Thin-layer chromatography showed a clean conversion of **15a** (R_f 0.55, silica gel, EtOAc) to the enamine **17** (R_f 0.31, silica gel, EtOAc) and trace amounts of another product of R_f 0.08 (possibly the deprotected enamine). Because of the instability of enamines such as **17**, no attempt was made to isolate **17**. The pyrolysis mixture was hydrogenated over 5% Pd/C (10 mg) in dry methanol (2 mL) at 31 psi for 8 h. The mixture was filtered through Celite, the filter washed with EtOAc, and the filtrate evaporated to yield 4 mg of a clear oil, which was chromatographed (1.5% deactivated neutral alumina, acid-free EtOAc/hexane, 1:1) to give pure **19** as a colorless oil: 3 mg, 30%; R_f 0.50 (silica gel), $CHCl_3$/MeOH/NH_4OH, 85:14:1); IR (neat) 2980, 2940, 2870, 1740, 1260, 1210, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H), 0.85 (s, 9 H), 1.75 (m, 1 H), 1.85–2.03 (m, 3 H), 2.62 (ddd, J_1 = 10.6, J_2 = 7.9, J_3 = 6.0 Hz, 1 H), 2.77 (ddd, J_1 = 11.5, J_2 = 6.9, J_3 = 5.2 Hz, 1 H), 2.96 (ddd, J_1 = 11.5, J_2 = 8.5, J_3 = 6.5 Hz, 1 H), 3.08 (ddd, J_1 = 9.0, J_2 = 8.5, J_3 = 7.9 Hz, 1 H), 3.19 (ddd, J_1 = 10.6, J_2 = 4.8, J_3 = 6.5 Hz, 1 H), 3.54 (dd, J_1 = 7.9, J_2 = 4.0 Hz, 1 H), 3.66 (s, 3 H), 4.03 (dt, J_1 = 5.2, J_2 = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.8 (CH_3), −4.3 (CH_3), 18.0 (C), 25.8 (3 CH_3), 29.4, 36.1, 46.0, 51.5, 53.2, 54.1, 74.2, 74.7, 166.8; mass spectrum (70 eV), m/e (relative intensity) 297 (7), 265 (10), 256 (9), 242 (12), 213 (6), 169 (20), 141 (50), 106 (55), 82 (100).

Calcd for $C_{11}H_{20}O_3NSi$ $(M-57)^+$: 242.1212. Found: 242.1200.

(3α)-1-Aza-2α-(2-carbomethoxyethenyl)-4-oxobicyclo[3.1.0]hexane (21). To a stirred solution of the alcohol **14a** (48 mg, 0.27 mmol) in $CHCl_3$ (1.5 mL) was added MnO_2 (100 mg) in one portion at room temperature. The mixture was protected from the light and stirred for 24 h. It was then centrifugated, and the filter was washed with $CHCl_3$. The filtrate was concentrated to about 4 mL, and more MnO_2 (100 mg) was added. After 2.5 days the suspension was centrifugated again, the filter washed with $CHCl_3$, and the filtrate evaporated to give an oil, which was chromatographed (10% deactivated silica gel, EtOAc/hexane, 9:1) to yield pure **21** as a pale yellow oil: 17 mg, 38%; R_f 0.55 (silica gel, EtOAc); IR (neat) 2930, 2860, 1740, 1720, 1660, 1260, 1020, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (ddd, J_1 = 19.1, J_2 = 9.7, J_3 = 2.9 Hz, 1 H), 2.41 (q, J = 9.7 Hz, 1 H), 2.51 (d, J = 2.0 Hz, 1 H), 2.63 (dd, J_1 = 7.6, J_2 = 2.0 Hz, 1 H), 3.35 (m, 1 H), 3.56 (m, 1 H), 3.70 (s, 3 H), 6.06 (d, J = 15.9 Hz, 1 H), 6.53 (dd, J_1 = 15.9, J_2 = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 30.8 (CH_2), 42.9 (CH), 49.3 (CH_2), 49.9 (CH), 51.7 (CH_3), 123.5 (CH), 143.7 (CH), 165.9 (C), 209.2 (C); mass spectrum (70 eV), m/e (relative intensity) 150 (3), 122 (26), 98 (100), 94 (19), 82 (55), 80 (54), 58 (22). Calcd for C_7H_8ON $(M-59)^+$: 122.0606. Found: 122.0604.

(5α)-1-Aza-4β-carbomethoxy-6-oxobicyclo[3.3.0]oct-2-ene (8). Vinylaziridine **21** (15 mg, 0.08 mmol) was pyrolyzed as described for **14a** and **15a**. The total time of evaporation was kept under 10 min by gently warming the distillation flask. ^1H NMR of the pyrolysate indicated the presence of only the enamine **8**, which was used in the next step without purification: pale yellow oil, 14 mg; R_f 0.18 (silica gel, EtOAC); ^1H NMR ($CDCl_3$) δ 2.2–2.5 (m, 3 H), 3.3–3.6 (m, 2 H), 3.70 (s, 3 H), 3.7 (m, 1 H), 4.88 (m, 1 H), 6.07 (m, 1 H).

(5α)-1-Aza-4α-carbomethoxy-6-oxobicyclo[3.3.0]octane (20b). Method I. Enamine 8 (14 mg, 0.08 mmol) was hydrogenated over 5% Pd/C (10 mg) in glacial AcOH (2.5 mL) at 27 psi for 13 h. The mixture was filtered through Celite, the filter washed with $CHCl_3$, the filtrate passed through a plug of alumina, and the solvent evaporated, to give crude **20a** as an oil: 14 mg; R_f 0.52 (silica gel, $CHCl_3$/MeOH/NH_4OH, 85:14:1); ^1H NMR ($CDCl_3$) δ 2.2–2.5 (m, 4 H), 2.7 (m, 1 H), 2.9–3.2 (m, 3 H), 3.4 (m, 1 H), 3.70 (s, 3 H), 3.7 (m, 1 H). Keto ester **20a** was epimerized to **20b** by using NaOMe/MeOH.[23] Spectroscopic data for **20b** was in agreement with that reported in the literature.[10c,d]

Method II. To a stirred solution of the alcohol **18** (4 mg, 0.22 mmol) in $CHCl_3$ (0.8 mL) at room temperature was added MnO_2 (10 mg) in one portion. After 8 h, the mixture was filtered through Celite, the filter washed with $CHCl_3$, and the filtrate evaporated to yield 2 mg of an oil, ^1H NMR of which showed signals corresponding to the keto ester **20a**. All attempts to purify **20a** were unsuccessful.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society (AC-16617), to the National Institutes of Health (AI-00564), and to Jeffress Trust Foundation for financial support of this work.

5-Substituted-2-furoic Acids as Latent Dienes for the Preparation of Aryl Ethers and Thioethers via the Diels–Alder Reaction

James A. Cella

General Electric Company/CRD, P.O. Box 8, K1 5A-48, Schenectady, New York 12301

Received February 27, 1987

The construction of aromatic rings is frequency accomplished by means of a Diels–Alder cycloaddition followed by appropriate transformations of the adducts to effect aromatization. In this context, the use of a furan derivative as the dienophilic partner is advantageous since aromatization of the adducts can be effected simply by dehydration.[1]

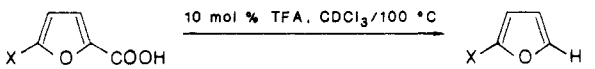
Use of this procedure for the preparation of aromatic ethers and thioethers provides an interesting alternative to the more conventional Williamson and Ullman methods which are incompatible with certain functionalities. The requisite furyl ethers are excellent dienophiles readily obtained by a variety of methods.[2] A potential limitation

(1) Reviews: (a) Wong, H. N. C. *Heterocycles* **1983**, *20* (9), 1815. (b) Wong, H. N. C. *Heterocycles* **1984**, *22* (4), 875. For recent work, see: (c) Potts, K. T.; Walsh, E. B. *J. Org. Chem.* **1984**, *49*, 4101. (d) Maeba, I.; Usami, F.; Furukawa, H. *J. Org. Chem.* **1984**, *49*, 1534. (e) Aleinik, A. F.; et al. *Khim. Farm. Zh.* **1980**, *14*, 49; *Chem. Abstr.* **1980**, *93*, 132312h. (f) Bilovic, D. *Croat. Chem. Acta* **1966**, *38*, 293; *Chem. Abstr.* **1967**, *66*, 55416h. (g) Danyushevskii, Y. L.; Marakatkina, M. A.; Gol'dfarb, Y. L. *Zh. Org. Khim.* **1968**, *4*, 474; *Chem. Abstr.* **1968**, *68*, 114225m. (h) Gribble, G. W.; Kelly, W. J. *Tetrahedron Lett.* **1981**, *22*, 2475. (i) Hart, H.; Shamouilian, S. *J. Org. Chem.* **1981**, *46*, 4874. (j) Aran, V. J.; Soto, J. L. *Synthesis* **1982**, 513. (k) Best, W. M.; Wege, D. *Tetrahedron Lett.* **1981**, *22*, 4877. (l) Hart, H.; Takehira, Y. *J. Org. Chem.* **1982**, *47*, 4370. (m) Nasman, J. A. H. *Synthesis* **1985**, 788. For examples of benzoannelated analogues, see: (n) Sadeghy, B. M. M.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 2237. (o) Camenzind, R.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 1914. (p) Pollart, D. J.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3155. (q) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3839. (r) Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762. (s) Gribble, G. W.; Perni, R. B.; Onan, K. D. *J. Org. Chem.* **1985**, *50*, 2934. (t) Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689. (u) Chacko, E.; Sardella, D. J.; Bornstein, J. *Tetrahedron Lett.* **1976**, 2507. (v) Levy, L.; Kumar, S. V. P. *Tetrahedron Lett.* **1983**, *24*, 1221. (w) Sadler, C. S.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2364.

(2) (a) Petfield, R. J.; Amstutz, E. D. *J. Org. Chem.* **1954**, *19*, 1944. (b) Manly, D. J.; Amstutz, E. D. *J. Org. Chem.* **1956**, *21*, 516. (c) Cava, M. P.; Wilson, C. L.; Williams, C. J. *J. Am. Chem. Soc.* **1956**, *78*, 2303. (d) Clauson-Kaas, N.; Emling, N. *Acta Chem. Scand.* **1952**, *6*, 560. (e) Pelter, A.; Al-Bayati, R.; Lewis, W. *Tetrahedron Lett.* **1982**, *23*, 353. (f) Kraus, G.; Sugimoto, H. *J. Chem. Soc. D* **1978**, 30. (g) Manly, D. G.; Amstutz, E. D. *J. Org. Chem.* **1957**, *22*, 323. (h) Krutosikova, A.; Kovac, J. *Collect. Czech. Chem. Commun.* **1976**, *41*, 2577. (i) Hormi, O. E. O.; Nasman, J. H. *Synth. Commun.* **1986**, *16*, 69. (j) Meister, C.; Scharf, H. D. *Synthesis* **1981**, 737. (k) Fisher, B. E.; Hodge, J. E. *J. Org. Chem.* **1964**, *29*, 776. (l) Meister, C.; Scharf, H. D. *Synthesis* **1981**, 733. (m) Sherman, E.; Dunlop, A. P. *J. Org. Chem.* **1960**, *25*, 1309. (n) Gronowitz, S.; Sorlin, G. *Acta Chem. Scand.* **1961**, *15*, 1419. (o) Gronowitz, S.; Sorlin, G. *Arkiv Kemi* **1962**, *19*, 515. (p) Hofmann, A.; Philipsborn, W. v.; Eugster, C. H. *Helv. Chim. Acta* **1965**, *48*, 1322. (q) Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Org. Chem.* **1984**, *49*, 3819. (r) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167. (s) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *31*, 237.

0022-3263/88/1953-2099$01.50/0

Table I. Approximate Half-Lives for the TFA-Catalyzed Decarboxylation of 5-Substituted-2-furoic Acids

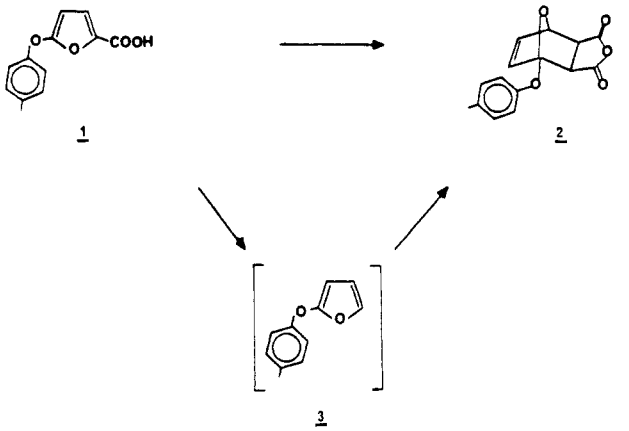


X	$t_{1/2}$	X	$t_{1/2}$
OCH_3	2 min	CH_3	*a*
4-CH_3OPhO	5 min	H	*a*
4-CH_3PhO	10 min	Br	*a*
PhS	7 h		

[a] No decarboxylation after 12 h.

of this approach, from a practical viewpoint, is the lability of alkoxy- and (aryloxy)furans,[3] which dictates that they be used immediately after their preparation. In this note, we report our finding that 5-alkoxy-, 5-(aryloxy)-, or 5-(arylthio)-2-furoic acids serve well as latent, storage-stable precursors for the reactive furyl ether and thioether derivatives.

5-(Aryloxy)- and 5-(arylthio)-2-furoic acid derivatives are poor dienes in Diels–Alder reactions under ordinary conditions.[4] Methyl 5-cresoxy-2-furoate, for example, does not react with maleic anhydride. The acid **1**, however, reacts to give adduct **2** (exo isomer) in good yield.[5] Adduct **2** arises from addition of maleic anhydride to the (aryloxy)furan **3** produced by decarboxylation of **1**.

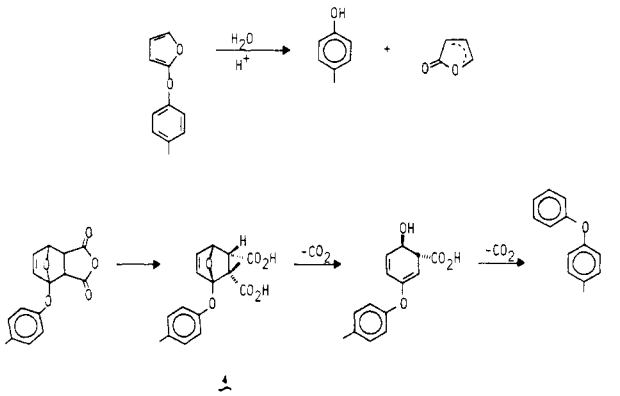


1 **2**

3

Control experiments indicate that thermal decarboxylation of **1** occurs readily at 100 °C in $CDCl_3$ (sealed tube, half-life = 6 h).[6] This decarboxylation, moreover, is markedly accelerated by acids. Addition of 0.02 molar equiv of trifluoroacetic acid to a solution of acid **1** in $CDCl_3$ afforded **3** quantitatively after 15 min at 100 °C.[7] Facile, acid-catalyzed decarboxylation is general for 2-furoic acids containing strongly electron-donating substituents at the 5-position but does not occur for derivatives with electron-withdrawing or mildly donating substituents at the 5-position. Half-lives for the acid-catalyzed decarboxylation of several furans are presented in Table I.

Scheme I



4

The furans produced by this acid-catalyzed decarboxylation are good dienes for Diels–Alder reactions but are somewhat unstable, particularly in an acidic medium.[3] Rather than isolate these intermediates, therefore, it is preferable to trap them in situ by addition of a dienophile. Under these conditions, the adducts suffer spontaneous acid-catalyzed dehydration to afford aromatic derivatives directly.[8] The overall sequence of decarboxylation, Diels–Alder addition, and aromatization is thus affected efficiently in a single vessel without isolation of intermediates. Representative examples of the preparation of aryl ethers and thioethers by reaction of 5-substituted-2-furoic acids with various dienophiles are presented in Table II.

The 5-substituted furoic acid derivatives used in these reactions are readily obtained by bromide displacement from esters of 5-bromo-2-furoic acid[2b] followed by hydrolysis of the ester. Unlike the 2-furyl ethers generated on decarboxylation, the acids are all stable crystalline solids that can be stored indefinitely. As such, they serve as excellent latent sources of the furyl ethers.

A number of side reactions can occur during the sequence of reactions leading to the desired aromatic derivatives. The extent to which these side reactions compete with the desired process is determined to a large extent by the nature and reactivity of the dienophile. Detailed analysis of the reaction of 5-cresoxy-2-furoic acid with maleic anhydride unravels several of the competitive pathways that can be followed. In addition to the major product (62%), 3-cresoxyphthalic anhydride, there are produced *p*-cresol cresylphenyl ether, and butenolide. These products are the result of hydrolytic processes mediated by water generated during aromatization of the initial Diels–Alder adduct. Butenolide and its cohydrolysis product *p*-cresol are formed by acid-catalyzed hydrolysis of the dienophile **3**,[9] a process competitive with the Diels–Alder addition. This competition is more prevalent with less reactive dienophiles and accounts for the low yields obtained in some cases (benzoquinone, naphthoquinone, fumaronitrile, and maleic acid afforded little or none of the desired aromatized adducts under these conditions). The exceptional yields of *N*-arylphthalimides obtained by this sequence attests to the high reactivity of *N*-arylmaleimides as dienophiles. Competitive hydrolysis can be offset somewhat by use of excess dienophile or by the addition of drying agents ($MgSO_4$, molecular sieves,

(3) 2-(Aryloxy)- and 2-alkoxyfurans exhibit ketene–acetal-like reactivity toward acids. On storage, these compounds darken rapidly even in the cold. Darkening is usually accompanied by the formation of a tacky, polymeric residue. See ref 2a and 2b.

(4) We have not investigated the reactivity of these derivatives under high pressures: see (a) Dauben, W. G.; Bunce, R. A. *Tetrahedron Lett.* **1982**, *23*, 4875. (b) Isaacs, N. S.; Vander Beek, P. *Tetrahedron Lett.* **1982**, *23*, 2148. (c) Jurczak, J.; Kowczynski, A.; Kozluk, T. *J. Org. Chem.* **1985**, *50*, 1106 and the reference cited therein. Lewis acid catalysis has been examined to a limited extent, see: (d) Moore, J. A.; Partain, E. M., III. *J. Org. Chem.* **1983**, *48*, 1105. (e) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299. (f) Laszlo, P.; Lucchetti, J. *Tetrahedron Lett.* **1984**, *25*, 4387. (g) Bailey, M. S.; Brisdon, B. J.; Brown, D. W.; Stark, K. M. *Tetrahedron Lett.* **1983**, *24*, 3037.

(5) Conditions: $CDCl_3$/100 °C, sealed tube.

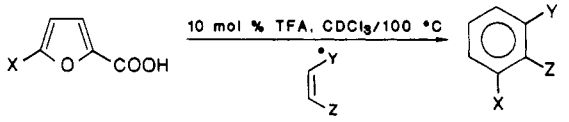
(6) In general, more severe conditions have been reported for decarboxylations of similar furoic acid derivatives; see ref 2b and Schultz, A. G.; Motyka, C. A.; Plummer, N. *J. Am. Chem. Soc.* **1986**, *108*, 1056. Petfield and Amstutz (ref 2a) note that 5-methoxy-2-furoic acid decarboxylates "on gentle heating" to yield 2-methoxyfuran.

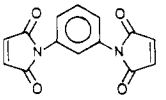
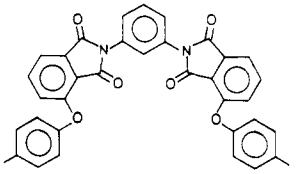
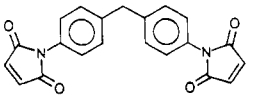
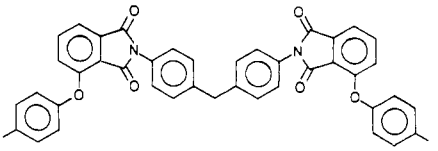
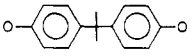
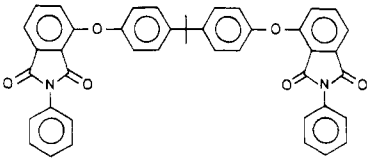
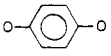
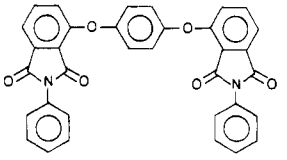
(7) This reaction is conveniently conducted and monitored in a heavy walled, sealed NMR tube (see Experimental Section).

(8) The adducts, formally ketals, require only mildly acidic conditions to initiate the sequence of reactions culminating in aromatization.

(9) See ref 2c–f,j.

Table II. Aryl Ethers and Thioethers via Decarboxylation, Diels–Alder Reaction, and Dehydration Using 2-Carboxy-5-furyl Ethers[a]



5-substituent	dienophile	product	% yield	mp, °C	ref
4-methylphenoxy	maleic anhydride	3-cresoxyphthalic anhydride	65	117–118	13
4-methylphenoxy	*N*-methylmaleimide	*N*-methyl-3-cresoxyphthalimide	40	112	*b*
4-methylphenoxy	*N*-phenylmaleimide	*N*-phenyl-3-cresoxyphthalimide	95	178–179	19
4-methylphenoxy	methyl acrylate	methyl 2-cresoxybenzoate	30	oil	*b*
4-methylphenoxy	acryloyl chloride	2-cresoxybenzoic acid	85	*c*	*b*
4-methylphenoxy	dimethyl fumarate	dimethyl 3-cresoxyphthalate	54	oil	15
4-methylphenoxy			96	235	*b*
4-methylphenoxy			38	200	*b*
phenylthio	*N*-phenylmaleimide	*N*-phenyl-3-(phenylthio)phthalimide	94	146–148	17
4-methoxyphenoxy	*N*-phenylmaleimide	*N*-phenyl-3-(4-methoxyphenoxy)phthalimide	56	178–179	14
3-methoxy	*N*-phenylmaleimide	*N*-phenyl-3-methoxyphthalimide	50	193	16
	*N*-phenylmaleimide		85	163	*b*
	*N*-phenylmaleimide		21	312	*b*

[a] All products were identified by comparison of spectral and chromatographic properties with authentic samples obtained as described in the references or by unambiguous conversions of reported compounds. [b] Preparation and characterization are described in the Experimental Section. [c] Not isolated directly, converted directly to methyl 2-cresoxybenzoate by reaction with diazomethane.

etc.), but only marginal improvements in yield are realized.

The formation of cresylphenyl ether in this reaction is very likely the result of a double eliminative decarboxylation on the diacid **4**, which results from anhydride hydrolysis either before or after Diels–Alder reaction (Scheme I).

This type of fragmentation should occur readily in an acidic medium and may account for low yields often encountered during dehydrative aromatization of similar furan maleic anhydride adducts.[10] The greater hydrolytic stability of an imide ring compared to an anhydride undoubtedly contributes to the high yields of phthalimido ethers obtained when maleimides are employed in this reaction.

In summary, the utility of furoic acids bearing electron-donating groups in the 5-position as synthons for the preparation of aryl ethers by a consecutive decarboxylation, Diels–Alder addition, dehydration sequence has been demonstrated. The ease of preparation of these derivatives and their stability on storage make them particularly attractive. This reaction sequence is well-suited for the preparation of substituted phthalimides since very few side reactions compete with their formation.

Experimental[11] Section

The dienophiles utilized in this work were either obtained commercially or prepared according to literature procedures. 5-Bromo-2-furoyl chloride was prepared from 5-bromo-2-furoic acid (Aldrich) by reaction with PCl_5 in methylene chloride. The product was purified by sublimation (yield, 74.9%). Methyl 5-bromo-2-furoate[2a] was prepared by methanolysis of the acid chloride in the presence of triethylamine (72% yield, mp 63.5–64 °C). Ethyl 5-bromo-2-furoate was prepared by ethanolysis of the acid chloride in the presence of triethylamine (96.7% yield, bp 78–83 °C/2 mm).

Preparation of 5-Substituted-2-furoic Acids. In general, the sodium salt of the appropriate alcohol, phenol, or thiophenol was prepared by reaction with sodium hydride in dry *N,N*-dimethylacetamide (0.2–0.5 M, N_2 atmosphere) at 50–80 °C. When gas evolution ceased, the methyl (or ethyl) 5-bromo-2-furoate was

(10) Newman, M. S.; Lee, V. *J. Org. Chem.* **1977**, *42*, 1478 and reference cited therein.

(11) **General.** Proton NMR spectra were recorded on a Varian EM-390 NMR with TMS as an internal standard. Gas chromatography was carried out on a Varian 6000 gas chromatograph equipped with a flame-ionization detector and a 6 ft glass column packed with 3% OV-17 on Gas Chrom Q. Liquid chromatography was conducted on a Waters liquid chromatograph with a Whatman C-18 reverse phase HPLC column using an acetonitrile–water gradient. All compounds were fully characterized spectroscopically (mass spectroscopy, ^1H NMR, IR, UV, etc.) and by comparison with authentic samples.

added to the solution and the whole was heated at 150 °C for 1.5–2 h. The cool reaction mixture was poured into cold water and extracted with at least three equal volumes of ether. The ether extracts were combined and washed 2× each with equal volumes of water, Claisen's alkali (methanolic KOH), 1.0 N HCl, and brine and dried by passage through a cone of anhydrous $CaSO_4$. Evaporation of the solvent at reduced pressure afforded the crude esters, which were either hydrolyzed directly or purified by distillation, recrystallization, or flash chromatography. In this fashion the following were prepared.

Methyl 5-cresoxy-2-furoate: 86% yield; bp 135–136 °C (1 mm); ^{1}H NMR ($CDCl_3$) 7.1 (m, 5, Ar H, furyl H), 5.5 (d, 1, furyl H), 3.90 (s, 3, CO_2CH_3), 2.37 ppm (s, 3, $ArCH_3$); mass spectrum (field desorption), m/e 232 (M^+).

Methyl 5-(phenylthio)-2-furoate: 82% yield; ^{1}H NMR ($CDCl_3$) 7.28 (m, 6, Ar H, furyl H), 6.64 (d, 1, furyl H), 3.85 ppm (s, 3, CO_2CH_3); mass spectrum, m/e 234 (M^+).

2,2-Bis[4-[(2-carbomethoxy-5-furyl)oxy]phenyl]propane: 83.5% yield; ^{1}H NMR ($CDCl_3$) 7.18 (m, 10, Ar H, furyl H), 6.54 (d, 2, furyl H), 3.87 (s, 6, CO_2CH_3), 1.68 ppm (s, 6, $ArCCH_3$); mass spectrum (field desorption), m/e 476 (M^+).

Hydroquinone bis(2-carbomethoxy-5-furyl ether): mp 128–130 °C; ^{1}H NMR ($CDCl_3$) 7.13 (m, 6, Ar H, furyl H), 5.55 (d, 2, furyl H), 3.90 ppm (s, 6, CO_2CH_3); mass spectrum, m/e 358 (M^+).

Methyl 5-(4-Methoxyphenoxy)-2-furoate. This material was isolated by column chromatography as a byproduct from the reaction of disodiohydroquinone with methyl 5-bromo-2-furoate used to prepare hydroquinone bis(2-carbomethoxy-5-furyl ether):[12] ^{1}H NMR ($CDCl_3$) 6.98 (m, 5, Ar H, furyl H), 5.42 (d, 1, furyl H), 3.86 (s, 3, CO_2CH_3), 3.80 ppm (s, 3, $ArOCH_3$); mass spectrum (field desorption), m/e 248 (M^+).

Hydroquinone bis(2-carbethoxy-5-furyl ether): mp 84–85.5 °C; ^{1}H NMR ($CDCl_3$) 7.13 (s, 4, Ar H and d, 2, furyl H), 5.70 (d, 2, furyl H), 4.30 (q, 4, $CO_2CH_2CH_3$), 1.32 ppm (t, 6, $CO_2CH_2CH_3$); mass spectrum (field desorption), m/e 386 (M^+).

The esters were converted to the corresponding acids by saponification (KOH/methanol–water) followed by acidification (HCl). In this manner, the following acids were prepared.

5-Cresoxy-2-furoic acid: 86% yield; mp 142–144 °C (decarboxylates); ^{1}H NMR ($CDCl_3$) 7.00 (m, 5, Ar H, furyl H), 6.45 (d, 1, furyl H), 2.28 ppm (s, 3, $ArCH_3$); mass spectrum (field desorption), m/e 218 (M^+).

5-(Phenylthio)-2-furoic acid:[2b] 81% yield; mp 139–141 °C; ^{1}H NMR ($CDCl_3$) 7.35 (m, 6, Ar H, furyl H), 6.58 (d, 1, furyl H); mass spectrum (field desorption), m/e 220 (M^+).

5-(4-Methoxyphenoxy)-2-furoic acid: ^{1}H NMR ($CDCl_3$) 7.08 (m, 5, aryl H, furyl H), 5.39 (d, 1, furyl H), 3.80 (s, 3, OCH_3); mass spectrum (field desorption), m/e 234 (M^+).

5-Methoxy-2-furoic acid: mp 137–137.5 °C (decarboxylates); ^{1}H NMR ($CDCl_3$) 7.14 (d, 1, furyl H), 5.50 (d, 1, furyl H), 3.92 (s, 3, OCH_3).

2,2-Bis[4-[(2-carboxy-5-furyl)oxy]phenyl]propane: 100% yield; mp 174.5–176 °C; mass spectrum (field desorption), m/e 448 (M^+).

Hydroquinone bis(2-carboxy-5-furyl ether): NMR (DMSO-d_6) 7.08 (s, 4, Ar H), 6.97 (d, 2, furyl H), 5.58 ppm (d, 2, furyl H); mass spectrum (field desorption), m/e 330 (M^+).

General Procedure for Diels–Alder Reactions. Small-scale reactions (1 mmol or less) were conveniently run and monitored in deuteriochloroform solutions in thick-walled NMR tubes. A solution of the reactants (furoic acid, dienophile, and ca. 10 mol % trifluoroacetic acid) was dissolved in the solvent (substrate concentration = 0.05–0.1 M) at ambient temperature. The tube containing the solution under a positive pressure of N_2 was immersed in a liquid N_2 bath and then evacuated and sealed. The sealed tubes were allowed to reach ambient temperature and were then immersed in a silicone oil bath at 100 °C. The tube was removed periodically and the progress of the reaction was monitored by NMR. When reaction was judged to be complete (usually within 1–2 h) the tube and contents were allowed to cool, the seal was broken, and the products were isolated and purified, usually by column chromatography on silica gel using 20% ethyl acetate in hexane as the eluant. Larger scale reactions were run at 100–150 °C (as required by the solubilities of the reactants) in round-bottomed flasks at atmospheric pressure (slight positive N_2 pressure), using either *o*-dichlorobenzene or chlorobenzene as the solvent. Structures of products and yields are presented in Table II. In all cases, the aryl ether products isolated from these reactions were identified by comparison with authentic samples prepared as described in the literature or by unambiguous methods. Preparations of authentic samples follow.

***N*-Methyl-3-cresoxyphthalimide.** An authentic sample was obtained from the reaction of 3-cresoxyphthalic anhydride[13] with methylamine in acetic acid: mp (dsc) 112 °C; ^{1}H NMR ($CDCl_3$) 7.3 (m, 7, Ar H), 3.12 (s, 3, NCH_3), 2.33 ppm (s, 3, $ArCH_3$).

Methyl 2-Cresoxybenzoate. An authentic sample was prepared by the reaction of sodium cresoxide with methyl 2-iodobenzoate in DMAC in the presence of CuCl (150 °C, 6 h, 74% yield). Product was isolated as an oil, bp 210 °C (15 mmHg): ^{1}H NMR ($CDCl_3$) 6.90 (m, 8, Ar H), 3.81 (s, 3, OCH_3), 2.22 ppm (s, 3, $ArCH_3$).

2-Cresoxybenzoic acid was identified by conversion to methyl 2-cresoxybenzoate (vide supra) by reaction with diazomethane in ether.

1,3-Phenylene-*N*,*N*′-bis(3-cresoxyphthalimide). An authentic sample was prepared by the reaction of 3-cresoxyphthalic anhydride[13] (2 equiv) with *m*-phenylenediamine in DMAC (150 °C, 2 h, 85% yield after crystallization from ethanol): mp (dsc) 235 °C; ^{1}H NMR ($CDCl_3$) 7.15 (m, 18, Ar H), 2.35 ppm (s, 6, $ArCH_3$).

4,4′-Methylenedianiline-*N*,*N*′-bis(3-cresoxyphthalimide). An authentic sample was prepared from the reaction of 3-cresoxyphthalic anhydride[13] with 4,4′-methylenedianiline in acetic acid: mp (dsc) 200 °C; IR (KBr) C=O 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.29 (m, 22, Ar H), 4.00 (s, 2 CH_2), 2.34 ppm (s, 6, $ArCH_3$); mass spectrum (field desorption), m/e 670 (M^+).

***N*-Phenyl-3-methoxyphthalimide.** An authentic sample was obtained from the reaction of aniline with 3-methoxyphthalic anhydride:[16] mp (dsc) 193 °C; ^{1}H NMR ($CDCl_3$) 7.35 (m, 8, Ar H), 3.94 ppm (s, 3, OCH_3); mass spectrum (EI), m/e 253 (100) M^+.

2,2-Bis(4-hydroxyphenyl)propane Bis(*N*-phenyl-3-phthalimidyl ether). An authentic sample was obtained from the reaction of *N*-phenyl-3-nitrophthalimide[14] (2 equiv) with the disodium salt of 2,2-bis(4-hydroxyphenyl)propane in DMAC (100 °C, 95% yield after crystallization from ethanol): mp (dsc) 163 °C; IR (KBr) (C=O) 1770 and 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.40 (m, 24, Ar H), 1.68 ppm (s, 6, $C(CH_3)$); mass spectrum (EI, high resolution), m/e calcd 670.2104, found 670.2096.

Hydroquinone Bis(*N*-phenylphthalimid-3-yl ether). An authentic sample was obtained from the reaction of *N*-phenyl-3-nitrophthalimide[14] (2 equiv) with the disodium salt of hydroquinone in DMAC (100 °C, 2 h, 75% yield): mp (dsc) 312.5 °C; ^{1}H NMR ($CDCl_3$) 7.40 ppm (Ar H, center of complex multiplet); mass spectrum (field desorption), m/e 552 M^+.

Decarboxylation of Furoic Acids. Relative rates of TFA-catalyzed decarboxylations of 5-substituted furoic acids were determined at 100 °C in $CDCl_3$ solution by using NMR spectroscopy. Decarboxylation is accompanied by an upfield shift (approximately 0.8–1.0 ppm) of the proton in the 2-position which is a convenient probe for determining the extent of reaction.

Registry No. 4-MeC_6H_4OH, 106-44-5; PhSH, 108-98-5; 4-HOC_6H_4OH, 123-31-9; cresyl phenyl ether, 1706-12-3; butenolide, 497-23-4; 5-bromo-2-furoyl chloride, 26726-16-9; 5-bromo-2-furoic acid, 585-70-6; methyl 5-bromo-2-furoate, 2527-99-3; ethyl 5-bromo-2-furoate, 6132-37-2; methyl 5-cresoxy-2-furoate, 80224-71-1; methyl 5-(phenylthio)-2-furoate, 93105-00-1; 2,2-bis(4-hydroxyphenyl)propane, 80-05-7; 2,2-bis[4-[(2-carbomethoxy-5-furyl)oxy]phenyl]propane, 113451-97-1; hydroquinone bis(2-carbomethoxy-5-furyl ether), 113451-98-2; methyl 5-(4-meth-

(12) This product is presumably the result of S_N2 displacement on the methyl group of the ester by the disodium salt of hydroquinone followed by "normal" bromide displacement.

(13) Williams, F. J.; Donahue, P. E. *J. Org. Chem.* **1977**, *42*, 3425.
(14) Williams, F. J., Donahue, P. E. *J. Org. Chem.* **1977**, *42*, 3414.
(15) Williams, F. J.; Relles, H. M.; Manello, J. S.; Donahue, P. E. *J. Org. Chem.* **1977**, *42*, 3419.
(16) Newman, M. S.; Kanakarajan, K. *J. Org. Chem.* **1980**, *45*, 3523.
(17) Williams, F. J.; Donahue, P. E. *J. Org. Chem.* **1978**, *43*, 250.

oxyphenoxy)-2-furoate, 80224-74-4; hydroquinone bis(2-carbethoxy-5-furyl ether), 113451-99-3; 5-cresoxy-2-furoic acid, 60698-27-3; 5-(phenylthio)-2-furoic acid, 61942-18-5; 5-(4-methoxyphenoxy)-2-furoic acid, 73420-66-3; 5-methoxy-2-furoic acid, 94084-62-5; 2,2-bis[4-[(2-carboxy-5-furyl)oxy]phenyl]propane, 113452-00-9; hydroquinone bis(2-carboxy-5-furyl ether), 113452-01-0; *N*-methyl-3-cresoxyphthalimide, 113452-02-1; methyl 2-iodobenzoate, 610-97-9; 2-cresoxybenzoic acid, 21905-69-1; 1,3-phenylene-*N*,*N*-bis(3-cresoxyphthalimide), 113452-03-2; *m*-phenylenediamine, 108-45-2; 4,4′-methylenedianiline-*N*,*N*′-bis(3-cresoxyphthalimide), 113452-04-3; 4,4′-methylenedianiline, 101-77-9; *N*-phenyl-3-methoxyphthalimide, 3039-43-8; 3-methoxyphthalic anhydride, 14963-96-3; 2,2-bis(4-hydroxyphenyl)propane bis(*N*-phenyl-3-phthalimidyl ether), 54395-38-9; *N*-phenyl-3-nitrophthalimide, 19065-85-1; hydroquinone bis(*N*-phenylphthalimid-3-yl ether), 54395-39-0; 5-methyl-2-furoic acid, 1917-15-3; 2-furoic acid, 88-14-2; 2-methoxyfuran, 25414-22-6; 2-(4-methoxyphenoxy)furan, 113474-66-1; 2-cresoxyfuran, 60698-28-4; 2-phenylthiofuran, 16003-14-8; maleic anhydride, 108-31-6; *N*-methylmaleimide, 930-88-1; *N*-phenylmaleimide, 941-69-5; methylacrylate, 96-33-3; acryloyl chloride, 814-68-6; dimethyl fumarate, 624-49-7; 3-cresoxyphthalic anhydride, 63181-77-1; *N*-phenyl-3-cresoxyphthalimide, 63181-79-3; methyl 2-cresoxybenzoate, 21905-72-6; dimethyl, 63181-72-6; 1,3-phenylene-*N*,*N*′-bis(phthalimide), 3006-93-7; 4,4′-methylenedianiline-*N*,*N*′-bis(phthalimide), 13676-54-5; *N*-phenyl-3-(phenylthio)phthalimide, 58045-34-4; *N*-phenyl-3-(4-methoxyphenoxy)phthalimide, 63197-27-3.

Dysidazirine, a Cytotoxic Azacyclopropene from the Marine Sponge *Dysidea fragilis*

Tadeusz F. Molinski and Chris M. Ireland*†

Department of Medicinal Chemistry, College of Pharmacy, University of Utah, Salt Lake City, Utah 84112

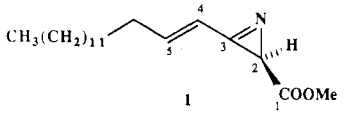
Received November 3, 1987

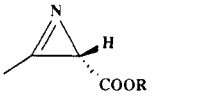
The cosmopolitan sponge *Dysidea fragilis* has been shown to produce several different sesquiterpenes and the nature of these natural products shows a marked geographic variation. For instance the sponge collected from Hawaii yielded the bicyclic sesquiterpenes upial[1] and the nakafurans 8 and 9.[2] Extraction of *D. fragilis* from Brittany, on the other hand, gave a series of sesquiterpenes based on the monocyclic sesquiterpene penlanfuran.[3] In surprising contrast to these reports we have found that *D. fragilis* (Montagu, 1818) collected in Fiji contains no sesquiterpenes but a new cytotoxic azacyclopropene carboxylic acid ester, dysidazirine (1). This represents the first example of this ring strained class of heterocycles from a marine source and, to our knowledge, only the second reported naturally occurring 2*H*-azirine.[4]

Isolation and Structure of Dysidazirine (1). The methanol extract of *D. fragilis* was shown to be cytotoxic against L1210 cells and inhibited the growth of *Pseudomonas aeruginosa*, *Candida albicans*, and *Saccaromyces cerevisiae*. The dichloromethane-soluble portion of this extract was subjected to silica gel chromatography to give dysidazirine (1, $[\alpha]_D$ −165°) *as the major lipophilic component* of the sponge (4.2% of dry weight). Further elution gave a mixture of steroidal 5,7-dienes and their corresponding *endo*-peroxides.[5]

The electron impact mass spectrum of dysidazirine (1) displayed a molecular ion at *m*/*z* 307 and accurate mass measurement of the fragment ion due to the loss of COOMe (*m*/*z* 248.2376) provided the formula $C_{19}H_{33}NO_2$. Analysis of the spectroscopic data of 1 suggested a C-18 fatty acid derivative. Inspection of the ^1H NMR spectrum ($CDCl_3$) revealed a signal at δ 3.72 (s, 3 H) assigned to the methyl protons in a carbomethoxyl group. This was supported by the mass spectral loss of COOMe from the molecular ion (above), together with the ^{13}C NMR spectrum which showed signals at 172.0 ppm (quaternary) and 52.0 ppm (CH_3) and an infrared band at 1736 cm^{-1}. Two strongly coupled proton signals at δ 6.56 (d, 1 H, J = 15.5 Hz) and 6.70 (dt, 1 H, J = 15.5, 6.4 Hz) were assigned to a trans-disubstituted olefin. The signal at 6.70 ppm was further coupled to an allylic methylene signal at 2.37 (m, 2 H) which in turn was connected to a linear C-12 alkyl chain (1.52, m, 2 H; 1.26, br s, 20 H; 0.88, t, 3 H). An unpaired sp^2 signal (156.4 s) in the ^{13}C NMR spectrum was assigned to an imino double bond. The presence of a UV band (λ_{max} 222 nm, ε 16 600) showed that the olefin was conjugated to the imino group but not to the carbomethoxyl group as deduced by the differences in the chemical shifts for the olefinic protons of 1 and those of *trans*-methyl 2-octadecenoate.[6] The remaining ^{13}C NMR signals were an sp^3 methine at 28.1 ppm and those assigned to the alkyl side chain.

Four double-bond equivalents were indicated by the molecular formula; therefore, 1 requires one ring incorporating the imino nitrogen and the sole sp^3 methine carbon (28.1 ppm). This was shown to be a substituted





2*H*-azirine for the following reasons. A gated-coupled ^{13}C NMR spectrum revealed an exceptionally large $^1J_{CH}$ (189.5 Hz) for the C-2 methine carbon (28.1 ppm), typical of 2*H*-azirines.[7] The C-2 signal was shown to be correlated to the H-2 signal at 2.57 (s, 1 H) by a 2D ^1H–^{13}C correlation experiment. This agrees well with the H-2 signal (δ 2.44 ppm) of azirinomycin methyl ester (2).[4] The infrared band at 1770 cm^{-1} is assigned to the imino double bond and the exceptionally high frequency of this C=N stretch also supports a 2,3-disubstituted azirine.[8] The above substructures were assembled to give the structure 1. This was confirmed by long-range 2D ^1H–^{13}C correlations;[9] H-2

†Alfred Sloan Foundation Fellow, 1985–1989; NIH Career Development Awardee, 1987–1992.

(1) Schulte, G.; Scheuer, P. J.; McConnell, O. J. *J. Org. Chem.* **1980**, *45*, 552.
(2) Schulte, G.; Scheuer, P. J.; McConnell, O. J. *Helv. Chim. Acta* **1980**, *63*, 2159.
(3) Guella, G.; Guerriero, A.; Traldi, P.; Petra, F. *Tetrahedron Lett.* **1983**, *24*, 3897.
(4) Azirinomycin (10), an azacyclopropene antibiotic isolated from a strain of the soil bacterium *Streptomyces aureus*, bears a structural similarity to 1; Miller, T. W.; Tristam, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48.
(5) Cf. Gunatilaka, A. A. L.; Gopichand, Y.; Schmitz, F. J.; Djerassi, C. *J. Org. Chem.* **1981**, *46*, 3860.
(6) Prepared from stearic acid by the following route; bromination (Br_2/PBr_3, 48 h) followed by dehydrobromination (potassium *tert*-butoxide/*tert*-butyl alcohol, reflux, 24 h) gave 2-octadecenoic acid which was esterified (MeOH/H_2SO_4, reflux, 16 h) to yield methyl *trans*-2-octadecenoate: δ 5.82 (dt, 1 H, J = 15.7, 1.5 Hz), 6.98 (dt, 1 H, J = 15.7, 6.8 Hz).
(7) Nair, V. *J. Magn. Reson.* **1974**, *6*, 483. Isomura, K.; Taniguchi, H. *Org. Magn. Reson.* **1977**, *9*, 559.
(8) Hassner, A. "Small Ring Heterocycles, Part 1: Aziridines, Azirines, Thiiranes, Thiirenes", from *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E., Eds.; Interscience: New York, 1983; Vol. 42, p 220.
(9) A COLOC experiment, optimized for J_{CH} = 6 Hz, was performed on 1: Kessler, H.; Griesinger, C.; Zarlock, J.; Loosli, H. R. *J. Magn. Reson.* **1984**, *57*, 331.

0022-3263/88/1953-2103$01.50/0