J. Org. Chem. **1982**, *47*, 1755–1759 **1755**

Application of Regioselective Thiophene Lithiation to the Synthesis of Thiophene Analogues of Xanthones and Thioxanthones

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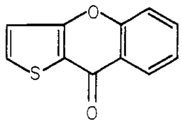
Received October 26, 1981

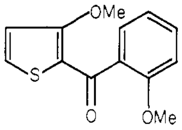
Treatment of 3-(*p*-tolyloxy)thiophene (**3**) with phenyllithium followed by carbonation with CO_2 was found to be a convenient procedure for the preparation of the thiophene-2-carboxylic acid **4**, which was cyclized to **5** with PPE. Treatment of **3** with butyllithium followed by carbonation gave the thiophene-2,5-dicarboxylic acid **8** which was cyclized to **9**. Alkaline permanganate oxidation of **4** gave the diacid **10**, which was cyclized to the tricyclic acid **11**. Similar lithiation reactions were observed with additional 3-(aryloxy)thiophenes and with 3-(arylthio)thiophenes, and xanthone analogues were prepared from the resulting intermediates.

A number of antiallergy agents possess xanthone-like structures, and with this in mind we decided to explore new synthetic routes to thiophene-containing structures.

The only reported synthesis of 9*H*-thieno[3,2-*b*][1]-benzopyran-9-one (**1**) is that of Morel et al.,[1] who condensed 3-methoxythiophene[2] with *o*-anisoyl chloride and cyclized the resulting dimethoxy ketone **2** with pyridinium chloride. We envisioned that compounds such as **1** could be prepared from 3-(aryloxy)thiophenes via regioselective lithiation/carbonation[2,3] and cyclization to the tricyclic system.



1

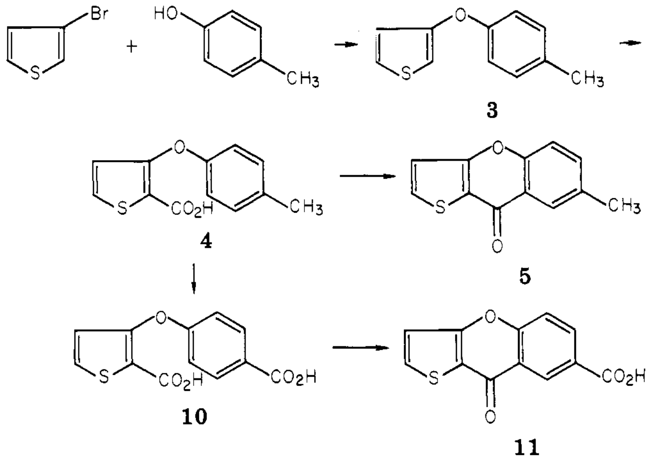


2

This concept was realized in the following manner. 3-Bromothiophene was condensed[4] with *p*-cresol (Scheme I) to give **3**. Treatment of this substance with 1 equiv of phenyllithium was followed by carbonation with solid CO_2 in ether at −78 °C. Only one product was isolated, and this was shown to be **4**, on the basis of its NMR spectrum and its cyclization to **5** with PPE in refluxing chloroform.[5]

The lithiation/carbonation of 3-phenoxythiophene was examined in detail, and the results are summarized in Scheme II. By use of conditions similar to those described above, 3-phenoxythiophene-2-carboxylic acid (**6**) was obtained in good yield and was cyclized to the unsubstituted xanthone analogue **1**.[1] However, when the entire acidic product from the lithiation/carbonation was subjected to the cyclization conditions, a small amount of acidic material remained. This was identified (NMR) as 4-phenoxythiophene-2-carboxylic acid (**7**) and comprised 1.7% of the original carboxylic acid mixture. Thus, the regioselectivity of the lithiation/carbonation of 3-phenoxythiophene was 98.3%. When the lithiation was conducted with 2 equiv of *n*-butyllithium at 0 °C, again two acids were formed. In this case, the second product was the thiophene-2,5-dicarboxylic acid (**8**), which amounted to 40% of the product. This substance was cyclized to the xanthone analogue with the carboxy function on the thiophene ring (**9**).

Scheme I



Alkaline permanganate oxidation of **4** gave dicarboxylic acid **10** which was cyclized with PPE in refluxing chloroform. The tricyclic acid **11** was obtained in good yield, accompanied by the corresponding ethyl ester (Scheme I).

Alkaline permanganate oxidation of **12** gave the corresponding tricarboxylic acid, which, on cyclization, again gave **11**. This presumably arose via intramolecular ipso substitution followed by decarboxylation. Cyclization of **12** proceeded normally (Scheme III).

It was found that xanthone analogues could also be prepared by ether formation from substituted ethyl salicylates (Scheme IV). In this way, the chloro and methoxy derivatives **13** and **14** were obtained. Similarly, starting with 2-bromothiophene and ethyl salicylate, we prepared the xanthone analogue **15** (a derivative of a hitherto unreported ring system).

Thioxanthone analogues could also be prepared by making use of the regioselective lithiation reaction (Scheme V). Refluxing a solution of *p*-toluenethiol and 3-bromothiophene in dimethylformamide in the presence of cuprous oxide and potassium hydroxide[6] gave the thioether **16**. Lithiation/carbonation of **16** proceeded essentially as described for the (aryloxy)thiophenes, and the single isomer isolated **17** was cyclized to the thioxanthone analogue **18** with PPE in refluxing chloroform.[5]

The lithiation/carbonation of 3-(phenylthio)thiophene was carefully examined, but no evidence for the presence of an isomeric product was obtained. However, as in the case of 3-phenoxythiophene, dilithiation of 3-(phenylthio)thiophene could be accomplished with 2 equiv of *n*-butyllithium (Scheme VI). Carbonation and cyclization

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[1] Henrio, G.; Morel, J.; Pastour, P. *Tetrahedron* **1977**, *33*, 191.

[2] Gronowitz, S., *Ark. Kemi* **1958**, *12*, 239.

[3] Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

[4] Ashby, J.; Ayad, M.; Meth-Cohn, O. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1104.

[5] Similar conditions were used in a related case by Rajšner, M.; Svåtek, E.; Metyš, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 1366.

[6] Bacon, R. G. R.; Stewart, O. J. *J. Chem. Soc.* **1965**, 4953.

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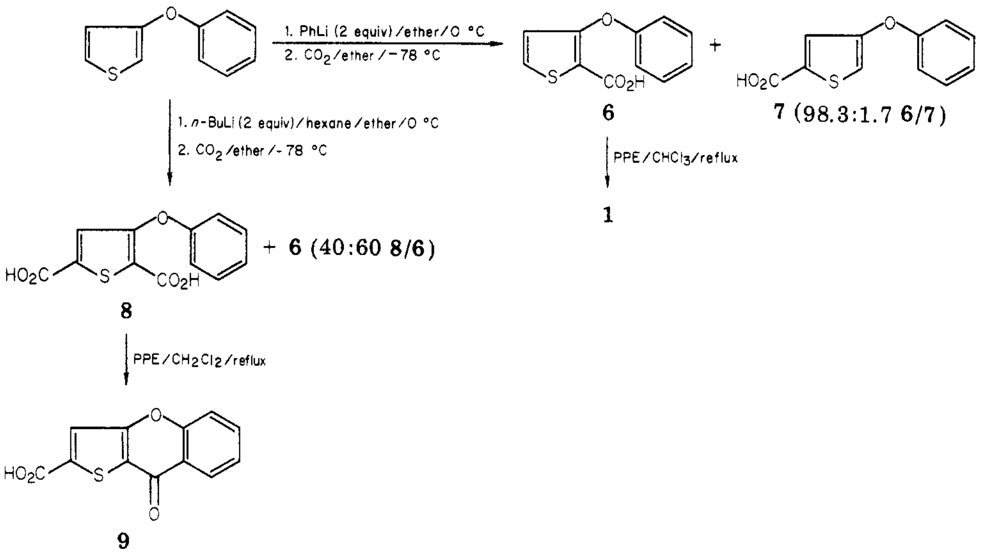
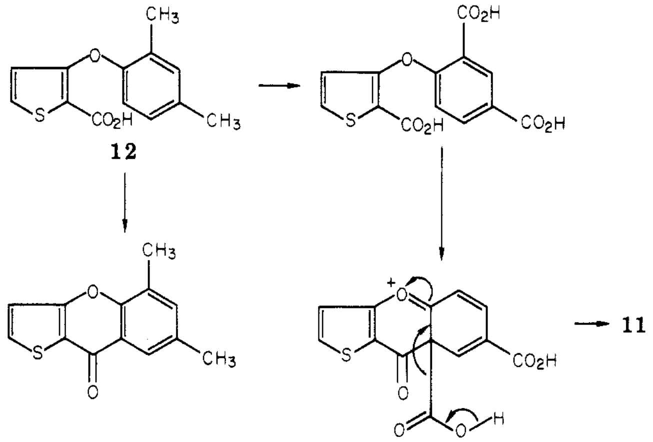
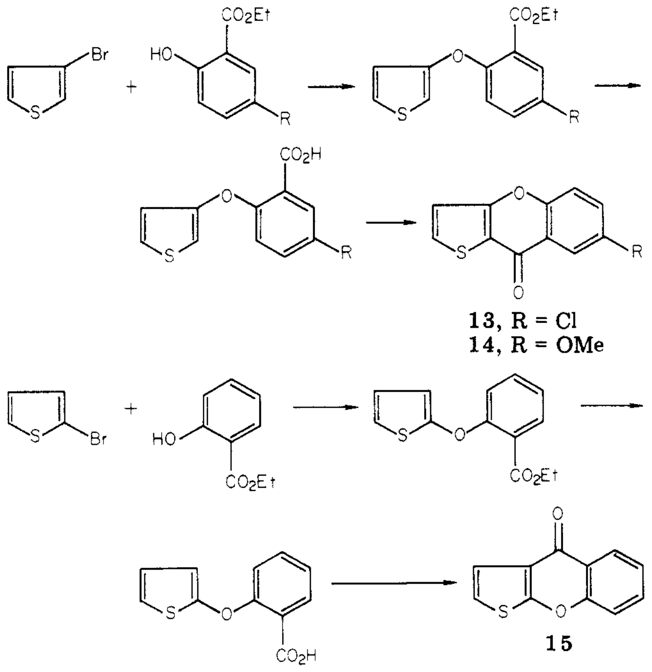
Scheme II



Scheme III

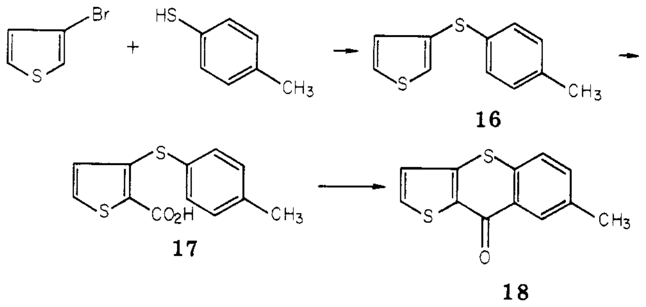


Scheme IV

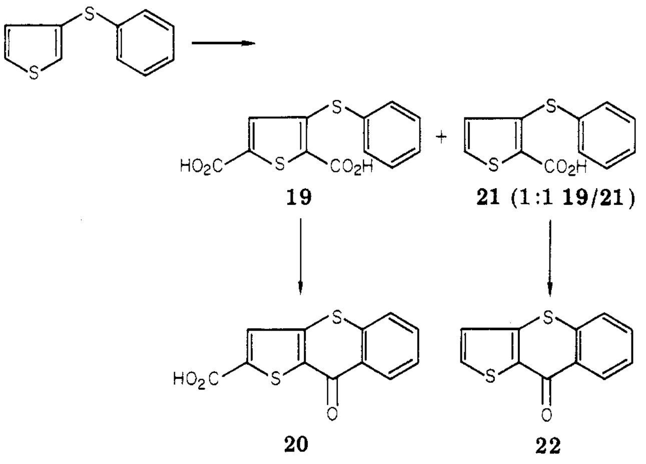


of the resulting diacid **19** gave the tricyclic carboxylic acid **20**. Carboxylic acid **21** was cyclized to the known thioxanthone analogue **22**.[7]

Scheme V



Scheme VI



Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. NMR spectra were obtained on a Varian A-60A, EM-390, or XL-100 instrument. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer, and mass spectra on an AEl MS 902 spectrometer.

Preparation of (Aryloxy)- and (Arylthio)thiophenes (Table I). Method A. 3-(*p*-Tolyloxy)thiophene (3). A mixture of 3-bromothiophene (100 g, 0.61 mol), *p*-cresol (70 g, 0.65 mol), copper bronze (5 g), and anhydrous potassium carbonate (30 g, 0.22 mol) was refluxed for 7 days. The reaction mixture

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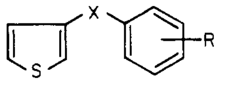
(7) Steinkopf, W.; Schmitt, H. F., *Justus Liebigs Ann. Chem.* **1938**, *533*, 264.

(8) Klosa, J. *Arch. Pharm.* (*Weinheim, Ger.*) **1956**, *289*, 143.

Table I. Preparation of (Aryloxy)- and (Arylthio)thiophenes[a]



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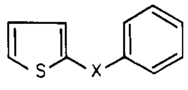
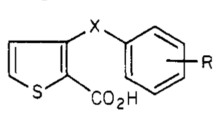


II

compd	type	X	R	method[b]	reaction time	% yield	bp, °C (mmHg)
	I	O	H	A	8 days	50	110 (0.05)
	I	O	2,4-Me_2	A	7 days	18	108 (0.1)
3	I	O	4-Me	A	7 days	86	110 (0.05)
	I	O	2-CO_2Et, 4-Cl	A[c]	4 days	9	146 (0.85)
	I	O	2-CO_2Et, 4-OMe	A[c]	4 days	16	158 (0.5)
	II	O	2-CO_2Et	A	4 days	8	110 (0.07)
16	I	S	4-CH_3	B	36 h	24	100 (0.05)
	I	S	H	B	36 h	47	100 (0.05)

[a] Satisfactory analytical data (± 0.4% for C and H) were obtained for all compounds listed in the table. [b] Method of preparation; see text of Experimental Section. [c] The starting material, ethyl 5-chloro-2-hydroxybenzoate [bp 132–135 °C (11 mmHg)], was obtained by a method used previously for the preparation of the corresponding methyl ester.[8] The methoxy ester was obtained by a similar procedure [bp 135–137 °C (13 mmHg)].

Table II. 3-(Aryloxy)- and 3-(Arylthio)thiophene-2-carboxylic Acids[a,b]



compd	X	R	% yield	mp, °C
4	O	4-Me	65	135-136
6	O	H	64	129-130
12	O	2,4-Me_2	82	130-132
17	S	4-Me	66	191-193
21	S	H	74	190-192

[a] See footnote *a*, Table I. [b] All compounds were recrystallized from EtOAc/petroleum ether (bp 30-60 °C).

was cooled and then stirred with chloroform (300 mL). The mixture was filtered and the extraction process repeated on the residue. The combined chloroform filtrates were washed with 10% NaOH (2 × 300 mL) and water (300 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue distilled to give **3** (100 g, 86%) as a colorless oil: bp 110 °C (0.05 mmHg); NMR ($CDCl_3$) δ 2.26 (s, 3 H, CH_3), 6.47 (dd, J = 1.5, 3 Hz, 1 H, thiophene 4-H), 7.00 (m, 6 H). Anal. Calcd for $C_{11}H_{10}OS$: C, 69.43; H, 5.29. Found: C, 69.79; H, 5.46.

Method B. 3-(Phenylthio)thiophene. A mixture of 3-bromothiophene (100 g, 0.61 mol), thiophenol (68 g, 0.61 mol), potassium hydroxide 35 g, 0.63 mol), cuprous oxide (44 g, 0.39 mol), and dimethylformamide (600 mL) was refluxed for 36 h under nitrogen. The reaction mixture was cooled to room temperature and then added to a 1:1 mixture of 6 N HCl and ice (total volume, 1 L). The mixture was extracted with benzene (2 × 400 mL). The combined benzene extracts were washed with 2 N NaOH (2 × 500 mL) and water (500 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue distilled to give 3-(phenylthio)thiophene: 55 g (47%); pale yellow oil; bp 100 °C (0.05 mmHg); NMR ($CDCl_3$) δ 6.90 (dd, J = 2, 4 Hz, 1 H, thiophene 4-H) 7.10 (m, 7 H); mass spectrum, *m/e* (relative intensity) 192 (M^+, 100), 115 (20). Anal. Calcd for $C_{10}H_8S_2$: C, 62.45; H, 4.19. Found: C, 62.76; H, 4.28.

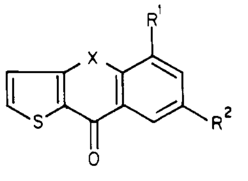
General Procedure for the Preparation of 3-(Aryloxy)- and 3-(Arylthio)thiophene-2-carboxylic Acids (Table II). 3-(*p*-Tolyloxy)thiophene-2-carboxylic Acid (4). To a solution of **3** (15.0 g, 0.08 mol) in dry ether (100 mL), stirred at 0 °C under dry nitrogen, was added 2.72 M phenyllithium in benzene (35 mL, 1.1 equiv). The solution was stirred at 0 °C for 5 h and then poured into a dry ice/ether slurry at −78 °C. The mixture was allowed to warm to room temperature. Water (150 mL) was added, the layers were separated, and the aqueous phase was extracted with ether (300 mL). The aqueous phase was acidified to pH 3 with 3 N HCl and extracted with ether (2 × 500 mL). The ether solution was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a solid, which was recrystallized from ethyl acetate/petroleum ether (bp 30–60 °C) to give **4**: 12.0 g (65%); mp 135–136 °C; NMR (Me_2SO-d_6) δ 2.20 (s, 3 H, CH_3), 6.65 (d, J = 5.5 Hz, 1 H, thiophene 4-H), 6.99 (q, J = 8.5 Hz, 4 H), 7.77 (d, J = 5.5 Hz, 1 H, thiophene 5-H) 12.30 (s, 1 H, CO_2H). Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30. Found: C, 61.83; H, 4.22.

General Procedure for the Preparation of the Xanthone Analogues Listed in Table III. 7-Methyl-9*H*-thieno[3,2-*b*][1]benzopyran-9-one (5). A solution of **4** (8.0 g, 0.034 mol) and PPE (50 g) in chloroform (25 mL) was refluxed for 18 h. The reaction mixture was cooled to room temperature, poured into ice/water (600 mL) and stirred for 18 h. The solid which separated out was filtered off and washed with water (50 mL). Recrystallization from ethyl acetate/ether gave **5**: 5.0 g (68%); mp 180–182 °C; NMR (Me_2SO-d_6) δ 2.50 (3, 3 H, CH_3), 7.36 (d, J = 3 Hz, 1 H, 3-H), 7.60 (m, 2 H, Ar H), 8.00 (s, 1 H, Ar H), 8.20 (d, J = 3 Hz, 1 H, 2-H). Anal. Calcd for $C_{12}H_8O_2S$: C, 66.64; H, 3.72. Found: C, 66.34; H, 3.84.

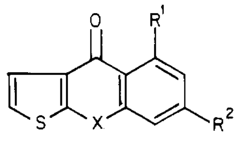
General Procedure for Alkaline Permanganate Oxidation (Table IV). 3-(4-Carboxyphenoxy)thiophene-2-carboxylic Acid (10). Potassium permanganate (45 g) was added in portions with stirring to a solution of **4** (14.0 g, 0.06 mol) in 5% NaOH (1.5 L) during 2 H. The reaction was exothermic. Stirring was maintained for an additional 30 min and then for 2.5 h at 100 °C. The reaction mixture was filtered while hot, and the volume reduced to 500 mL by evaporation under reduced pressure. The solution was acidified with 6 N HCl and the resulting solid was filtered off and recrystallized from methanol/ethyl acetate to give **10**: 7.0 g (44%); mp 229–231 °C; NMR (Me_2SO-d_6) δ 7.03 (m, 3 H, thiophene 4-H and 2 Ar H), 7.90 (m, 3 H, thiophene 5-H and 2 Ar H), 12.35 (s, 2-CO_2H); mass spectrum, *m/e* (relative intensity) 264 (M^+, 20), 127 (100), 121 (10). Anal. Calcd for $C_{12}H_8O_5S$: C, 54.54; H, 3.05. Found: C, 54.49; H, 3.03.

Lithiation of 3-Phenoxythiophene: Isolation of 4-Phenoxythiophene-2-carboxylic Acid (7). To a stirred solution of 3-phenoxythiophene (15.0 g, 0.085 mol) in ether (100 mL), maintained at 0 °C under a nitrogen atmosphere was added dropwise a solution of phenyllithium in benzene (45 mL of a 2.72 M solution, 2.1 equiv). The reaction mixture was stirred at 0 °C for 5 h and then poured into a dry ice/ether mixture at −78 °C. After the mixture attained room temperature, water (250 mL) was added. The layers were separated, and the aqueous phase extracted with ether (300 mL). The aqueous solution was acidified to pH 3 with 3 N HCl and extracted with ether (3 × 250 mL). The ether solution was dried over $MgSO_4$ and the solvent removed under reduced pressure to give the crude product (12.0 g). This material was treated with PPE as described above. The solid product was dissolved in CH_2Cl_2 (350 mL) and extracted with 2 N NaOH (2 × 100 mL). The aqueous solutions were combined and washed with CH_2Cl_2 (150 mL). The CH_2Cl_2 solutions were combined, washed with water (150 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure and recrystalli-

Table III. Xanthone Analogues[a]



III

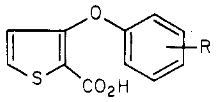


IV

compd	type	X	R¹	R²	% yield	mp, °C
5	III	O	H	Me	68[c]	180-182
11	III	O	H	CO_2H	32[d] 46[b,d]	325-327
	III	O	H	CO_2Et	14[d]	167-169
	III	O	Me	Me	77[e]	179-181
1	III	O	H	H	83[f,i]	157-159
13	III	O	H	Cl	69[g]	195-197
14	III	O	H	OMe	82[d]	169-171
15	IV	O	H	H	33[f]	149-151
18	III	S	H	CH_3	87[h]	181-183
22	III	S	H	H	90[f,j]	157-159

[a] See footnote *a* of Table I. [b] From cyclization of 3-(2,4-dicarboxyphenoxy)thiophene-2-carboxylic acid (Scheme II). [c] EtOAc/ether as recrystallization solvent. [d] MeOH as recrystallization solvent. [e] EtOAc as recrystallization solvent. [f] EtOAc/petroleum ether (bp 30–60 °C) as recrystallization solvent. [g] EtOH as recrystallization solvent. [h] MeOH/EtOAc as recrystallization solvent. [i] Reference 1 gives mp 159 °C. [j] Reference 7 gives mp 161.5 °C.

Table IV. 3-Substituted Thiophene-2-carboxylic Acids from Alkaline Permanganate Oxidation Reactions[a,b]



compd	R	% yield	mp, °C
10	4-CO_2H	44	229-231
	2,4-$(CO_2H)_2$	34	230-232

[a] See footnote *a* of Table I. [b] Compounds were recrystallized from MeOH/EtOAc.

zation from ethyl acetate/petroleum ether (bp 30–60 °C) gave **1**: 9.1 g (83%); mp 157–159 °C (see Table III). The combined aqueous NaOH solutions were acidified with 3 N HCl and extracted with CH_2Cl_2 (2 × 100 mL). The combined dichloromethane solutions were washed with water (100 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give **7**: 0.2 g (1.7% of the 12 g of carbonated material); mp 125–127 °C; NMR ($CDCl_3$) δ 6.93 (d, *J* = 2 Hz, 1 H, thiophene 2-H), 7.20 (m, 5 H, phenoxy protons), 7.62 (d, *J* = 2 Hz, 1 H, thiophene 4-H), 8.88 (s, 1 H, CO_2H). Anal. Calcd for $C_{11}H_8O_3S$: C, 59.99; H, 3.66. Found: C, 60.07; H, 3.75.

Dilithiation of 3-Phenoxythiophene: Preparation of 3-Phenoxythiophene-2,5-dicarboxylic Acid (8) and 9-Oxo-9*H*-thieno[3,2-*b*][1]benzopyran-2-carboxylic Acid (9). To a stirred solution of 3-phenoxythiophene (12.0 g, 0.068 mol) in ether (100 mL), maintained at 0 °C under a nitrogen atmosphere, was added dropwise a solution of *n*-butyllithium in hexane/ether (70:30, 68 mL of a 2.17 M solution, 2.1 equiv). The reaction mixture was stirred at 0 °C for 4 h and then poured into a dry ice/ether mixture at −78 °C. After the mixture attained room temperature, water (200 mL) was added. The layers were separated, and the aqueous phase was extracted with ether (300 mL). The aqueous solution was acidified to pH 3 with 3 N HCl and extracted with ether (3 × 250 mL). The ether solution was dried over $MgSO_4$, and the solvent was removed to give the crude product (12.0 g), which was recrystallized from ethyl acetate/methanol (9:1) to give **8**: 4.1 g (23%); mp 293–295 °C dec; NMR (Me_2SO-d_6) δ 7.25 (m, 6 H, including 7.21, s, 1 H, thiophene proton), 13.0 (br s, 2 H, CO_2H; mass spectrum, *m/e* (relative intensity) 264 (M^+, 30), 171 (100), 77 (30). Anal. Calcd for $C_{12}H_8O_5S$: C, 54.54; H, 3.05. Found: C, 54.76; H, 3.33. The remaining material was added to polyphosphate ester (100 g) and chloroform (35 mL) and the solution refluxed for 18 h. The reaction mixture was added to ice/water (250 mL), and the mixture was stirred for 18 h and filtered. The solid was stirred with 10% NaOH (100 mL) and heated to 60 °C. The mixture was filtered and the filtrate extracted with dichloromethane (200 mL). The aqueous phase was acidified with 3 N HCl, and the resulting solid was filtered off, washed with water, and dried to give **9**: 1.2 g (7% from 3-phenoxythiophene); mp 290–292 °C; NMR (Me_2SO-d_6) δ 7.7 (m, 5 H, including 7.90, s, 3-H); IR 1710 cm^{-1}; mass spectrum, *m/e* (relative intensity) 246 (M^+, 100), 229 (20), 201 (15). Anal. Calcd for $C_{12}H_6O_4S$: C, 58.53; H, 2.45. Found: C, 58.64; H, 2.45.

Dilithiation of 3-(Phenylthio)thiophene: Preparation of 3-(Phenylthio)thiophene-2,5-dicarboxylic Acid (19) and 9-Oxo-9*H*-thieno[3,2-*b*][1]benzothiopyran-2-carboxylic Acid (20). This study was carried out by using procedures similar to those described above. The dicarboxylic acid **19** was recrystallized from methanol/ethyl acetate (9:1) to give material with a melting point of 327–329 °C: 44% yield; NMR (Me_2SO-d_6) δ 6.75 (s, 1 H, thiophene H), 7.56 (s, 5 H, Ar H), 11.5 (br s, 2 H, CO_2H); mass spectrum, *m/e* (relative intensity) 280 (M^+, 100), 236 (30), 187 (77). Anal. Calcd for $C_{12}H_8O_4S_2$: C, 51.41; H, 2.87. Found: C, 51.80; H, 3.15. The tricyclic acid **20** was obtained from **19**: 49% yield; mp 325–327 °C; NMR (Me_2SO-d_6) δ 7.8 (m, 3 H, Ar H, 8.13 (s, 1 H, thiophene H), 8.46 (m, 1 H, Ar H); mass spectrum, *m/e* (relative intensity) 262 (M^+, 100), 218 (20), 217 (20), 189 (20). Anal. Calcd for $C_{12}H_6O_3S_2$: C, 54.94; H, 2.30. Found: C, 55.26; H, 2.55.

3-(2-Carboxy-4-methoxyphenoxy)thiophene. A solution of 3-(2-carbethoxy-4-methoxyphenoxy)thiophene (18.0 g, 0.065 mol) in ethanol (70 mL) and 4 N NaOH (50 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature, and the solvents were removed under reduced pressure. Water (100 mL) was added, the solution filtered, and the filtrate acidified with 6 N HCl. The solid was filtered off and recrystallized from ethyl acetate/petroleum ether (bp 30–60 °C) to give the acid: 14.0 g (86%); mp 135–137 °C; NMR (Me_2SO-d_6) δ 3.74 (s, 3 H, OCH_3), 6.46 (dd, *J* = 1.5, 3 Hz, 1 H, thiophene 2-H), 6.80 (dd, *J* = 1.5, 5.5 Hz, 1 H, thiophene 4-H), 7.03 (d, *J* = 2 Hz, 2 H, Ar H), 7.30 (m, 2 H, thiophene 5-H, Ar H). Anal. Calcd for $C_{12}H_{10}O_4S$: C, 57.58; H, 4.02. Found: C, 57.88; H, 4.21.

3-(2-Carboxy-4-chlorophenoxy)thiophene was prepared by a procedure similar to that described above. The acid was obtained in 93% yield: mp 122–124 °C; NMR (Me_2SO-d_6) δ 7.0 (m, 2 H, thiophene protons), 7.15 (d, *J* = 9 Hz, 1 H, Ar 6-H), 7.67 (m, 2 H, Ar 5-H, thiophene proton) 7.90 (d, *J* = 3.0 Hz, 1 H, Ar 3-H). Anal. Calcd for $C_{11}H_7ClO_3S$: C, 51.87; H, 2.77. Found: C, 51.99; H, 2.58.

2-(2-Carboxyphenoxy)thiophene was also prepared by a similar procedure. The acid was obtained in 74% yield: mp

122–124 °C; NMR (Me_2SO-d_6) δ 6.62 (dd, $J = 1.8$, 3.9 Hz, 1 H, thiophene 3-H), 6.88 (dd, $J = 3.9$, 6.0 Hz, 1 H, thiophene 4-H), 7.07 (dd, $J = 1.8$, 6.0 Hz, 1 H, thiophene 5-H), 7.18 (dd, $J = 1.2$, 8.1 Hz, 1 H, Ar 6-H), 7.28 (dt, $J = 1.2$, 7.2 Hz, 1 H, Ar 4-H), 7.58 (dt, $J = 1.8$, 7.2 Hz, 1 H, Ar 5-H), 7.90 (dd, $J = 1.8$, 7.8 Hz, 1 H, Ar 3-H). Anal. Calcd for $C_{11}H_8O_3S$: C, 59.98; H, 3.66. Found: C, 60.00; H, 3.69.

Acknowledgment. We thank Dr. H. B. Renfroe for valuable discussions and for his encouragement and support of this work and Dr. H. W. Gschwend for advice concerning the preparation of the manuscript. We also express our gratitude to Dr. R. K. Rodebaugh for discussions concerning the interpretation of the NMR data and for providing spectra (XL-100 spectrometer). We thank Mrs. L. Raabis for providing IR and NMR spectra (A-60A and EM-390 spectrometers), Mr. C. Shimanskas for the mass spectra, Mr. G. Robertson and his staff for microanalytical data, and Mrs. D. Vivian and Mrs. R. Prieston for preparing the typescript.

Registry No. 1, 54449-13-7; **3**, 42057-01-2; **4**, 81028-66-2; **5**, 81028-67-3; **6**, 81028-68-4; **7**, 81028-69-5; **8**, 81028-70-8; **9**, 81028-71-9; **10**, 81028-72-0; **10** 2′-CO_2H derivative, 81028-73-1; **11**, 81028-74-2; **12**, 81028-75-3; **13**, 81028-76-4; **14**, 81028-77-5; **15**, 81028-78-6; **16**, 42057-02-3; **19**, 81028-79-7; **20**, 81028-80-0; **21**, 81028-81-1; **22**, 58580-05-5; I (X = O; R = H), 63285-84-7; I (X = O; R = 2,4-Me_2), 81028-82-2; I (X = O; R = 2-CO_2Et, 4-Cl), 81028-83-3; I (X = O; R = 2-CO_2Et, 4-OMe), 81028-84-4; I (X = S; R = H), 16718-11-9; III (X = O; R^1 = H; R^3 = CO_2Et), 81028-85-5; III (X = O; R^1 = Me; R^3 = Me), 81028-86-6; III (X = S; R^1 = H; R^3 = Me), 72899-39-9; 3-(2-carboxy-4-methoxyphenoxy)thiophene, 81028-87-7; 3-(2-carboxy-4-chlorophenoxy)thiophene, 81028-88-8; 2-(2-carboxyphenoxy)thiophene, 81028-89-9; *p*-cresol, 106-44-5; 3-bromothiophene, 872-31-1; thiophenol, 108-98-5.

Notes

Free-Radical Diazo Coupling. A New General Reaction of Diazonium Salts

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Received May 29, 1981

The reaction of nucleophiles at the β-nitrogen of arenediazonium salts and the importance of the electrophilic aromatic diazo coupling are well-known.[1] We have in recent years shown[2] the very important role played by polar effects in the reactions of nucleophilic alkyl radicals with electron-deficient aromatic compounds; diazonium salts, owing to their positive charge and the high electron-affinity,[3] are particularly interesting in this connection.

We now describe new general synthesis of alkylaryldiazenes on the basis of the reactions of Scheme I: addition of alkyl radicals to arenediazonium cations (eq 1) and reduction of the intermediate azo radical cation adducts by metal salts (M^{n+}, eq 2). Equation 1 has been recently postulated in pulse radiolisis studies of arenediazonium salts.[4]

Scheme I

$$R\cdot + N{\equiv}N^+\text{-}Ar \rightarrow RN{=}\dot{N}^+\text{-}Ar \qquad (1)$$

$$RN{=}\dot{N}^+\text{-}Ar + M^{n+} \rightarrow RN{=}NAr + M^{(n+1)+} \qquad (2)$$

Several sources of alkyl radicals R· were found suitable for this reaction. For example, alkyl iodides (RI; R = methyl, primary, secondary, or tertiary alkyl, or benzyl) give rise cleanly in the presence of arenediazonium salts and reducing metal salts ($M^{n+} = Ti^{3+}$ or Fe^{2+}) to the arylalkyldiazenes (1) according to the stoichiometry of eq 3. The results obtained with some iodides are reported

$$2ArN_2^+ + RI + 2M^{n+} \rightarrow \underset{\mathbf{1}}{ArN{=}NR} + ArI + 2M^{(n+1)+} + N_2 \qquad (3)$$

in Table I (for a useful comparison only, the results for 4-chlorobenzenediazonium sulfate are reported; other substituents compatible with the reducing medium used give similar results).

The reaction can be explained by the mechanism of Scheme II. The aryl radical coming from the decompo-

Scheme II

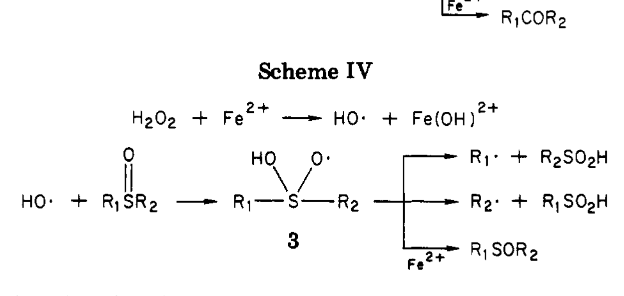
$$ArN_2^+ + Ti(III) \rightarrow Ar\cdot + N_2 + Ti(IV)$$

$$Ar\cdot + RI \rightarrow ArI + R\cdot$$

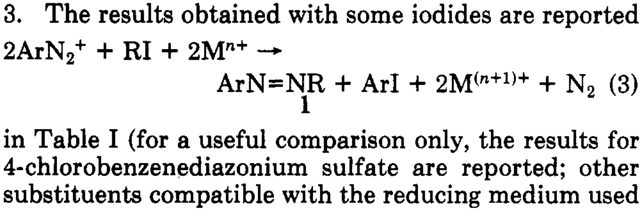
$$R\cdot + N{\equiv}N^+\text{-}Ar \rightleftarrows RN{=}\dot{N}^+\text{-}Ar$$

$$RN{=}\dot{N}^+\text{-}Ar + Fe^{2+}(Ti^{3+}) \rightarrow RN{=}NAr + Fe^{3+}(Ti^{4+})$$

Scheme III



Scheme IV



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