Synthesis of 2-Aryloxymethyl-3-aminomethylbenzo[*b*]thiophenes and 2,3-Diaryloxymethylbenzo[*b*]thiophenes

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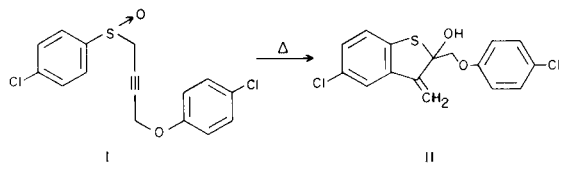
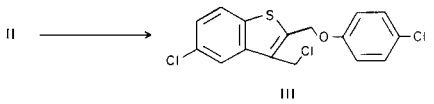
In the course of a study related to an unusual "*ortho* Claisen" rearrangement of aryl prop-2-ynyl sulfoxides (1,2), we secured the following derivative (II) as an intermediate.



I II

Compound II was readily transformed by an allylic rearrangement into the 2-aryloxymethyl-3-chloromethylbenzo[*b*]thiophene (III).



III

This conversion provides a very simple access to compounds of the type III. The latter were readily transformed into the appropriate 3-aminomethyl or 3-aryloxymethyl derivatives by standard methods (3). Many of these compounds are currently under evaluation as antifungal agents as well as antitumor agents.

EXPERIMENTAL

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were not corrected. Nuclear Magnetic Resonance (nmr) spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass-spectral data were obtained on a Hitachi-Perkin-Elmer RMU-6E single focus low resolution instrument at 70 ev. Microanalyses were performed by Mrs. Dorothy Schecter in this department.

Synthesis of 2-Aryloxymethyl-3-chloromethylbenzo[*b*]thiophene (III).

Compound II (1,2) (16.9 g., 0.05 mole) in carbon tetrachloride (150 ml.) was refluxed with phosphorus pentachloride (11.5 g., 0.06 mole) for 6 hours. The reaction mixture was cooled and chloroform (300 ml.) was added. The resultant solution was washed with 5% sodium hydroxide solution, sodium chloride solution and water, respectively and dried (sodium sulfate). Removal of solvent gave a white crystalline solid. This was recrystallized from methylene chloride-petroleum ether (30-60°), yield 13.60 g. (76%), m.p. 132°, nmr (deuteriochloroform), 4.78 δ (s, 2H), 5.30 δ (s, 2H), 6.80-7.85 δ (m, 7H), molecular ion peak at 356.

Anal. Calcd. for $C_{16}H_{11}Cl_3OS$: C, 53.90; H, 3.09. Found: C, 54.02; H, 3.14.

Condensation of Compound III with Secondary Amines.

General Procedure.

2-(*p*-Chlorophenoxymethyl)-3-(chloromethyl)5-chlorobenzo[*b*]-thiophene (III) (0.01 mole) was refluxed under nitrogen with the appropriate amine (0.02 mole) in chloroform (200 ml.) for 8 hours. Removal of solvent gave a white solid which was taken in ether (250 ml.). The ether insoluble white residue was found to be the secondary amine hydrochloride and was discarded. The ether solution was washed with water, dried (sodium sulfate) and solvent removed *in vacuo* to give the tertiary amine as a solid. This was purified by recrystallization from ether-petroleum ether (30-60°). The aminomethyl derivatives thus obtained are listed in Table I.

Condensation of 2-(*p*-Chlorophenoxymethyl)-3-chloromethyl-5-chlorobenzo[*b*]thiophene (III) with Potassium Phenoxides.

The phenoxide was prepared by refluxing the appropriate phenol (0.011 mole) with potassium hydroxide (0.01 mole) in 95% ethanol (50 ml.) for 1 hour. To this ethanol solution compound III (0.01 mole, 3.58 g.) in tetrahydrofuran (THF, 100 ml.) was added slowly and the reaction mixture was refluxed for 6 hours, cooled and filtered. Solvent was removed from the filtrate and the residual solid was dissolved in chloroform (400 ml.). The chloroform solution was washed with water and dried (sodium sulfate). Removal of chloroform gave a white solid which was recrystallized from methylene chloride-petroleum ether (30-60°). The aryloxymethyl derivatives thus prepared are listed in Table II.

Acknowledgments.

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REFERENCES

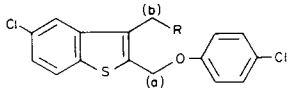
(1) K. C. Majumdar and B. S. Thyagarajan, *J. Chem. Soc. Chem. Commun.*, 83 (1972).

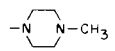
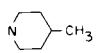
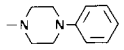
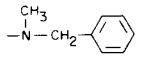
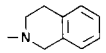
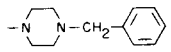
(2) K. C. Majumdar and B. S. Thyagarajan, *Int. J. Sulfur Chem.*, **2**, 93 (1972).

(3) J. J. Lewis, M. Martin-Smith, T. C. Muir, S. N. Nanjappa and S. T. Reid, *J. Med. Chem.*, **6**, 711 (1963).

TABLE I

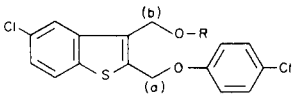
2-Aryloxymethyl-3-aminomethylbenzo[*b*]thiophenes



	R	M.p. (°C)	% Yield	Molecular formula	Analysis, % Calcd. C	H	N	Found C	H	N	NMR ($CDCl_3$): (in δ) (a)	(b)
1		118	80	$C_{20}H_{19}Cl_2NO_2S$	58.82	4.64	3.43	58.75	4.67	3.32	5.31(s,2H)	3.65(s,2H)
2		132	89	$C_{21}H_{21}Cl_2NOS$	62.07	5.17	3.44	62.25	4.94	3.26	5.38(s,2H)	3.61(s,2H)
3		108	80	$C_{21}H_{22}Cl_2N_2OS$	59.85	5.22	6.65	59.70	5.33	6.26	5.33(s,2H)	3.66(s,2H)
4		130	73	$C_{22}H_{23}Cl_2NOS$	62.86	5.47	3.33	62.96	5.44	3.03	5.36(s,2H)	3.65(s,2H)
5		157	72	$C_{26}H_{24}Cl_2N_2OS$	64.59	4.96	5.79	64.30	4.94	5.66	5.28(s,2H)	3.65(s,2H)
6		84	85	$C_{24}H_{21}Cl_2NOS$	65.16	4.75	3.17	65.39	4.96	3.07	5.23(s,2H)	3.60(s,2H)
7		100	71	$C_{20}H_{19}Cl_2NOS$	61.22	4.86	3.58	61.32	4.93	3.43	5.35(s,2H)	3.76(s,2H)
8		129-130	72	$C_{25}H_{21}Cl_2NOS$	66.08	4.62	3.08	66.05	4.68	3.00	5.35(s,2H)	3.83(s,2H)
9		96-97	80	$C_{22}H_{23}Cl_2NOS$	62.85	5.47	3.33	62.96	5.60	3.30	5.36(s,2H)	3.61(s,2H)
10		98	76	$C_{22}H_{23}Cl_2NOS$	62.85	5.47	3.33	62.88	5.58	3.23	5.38(s,2H)	3.16-4.26(q,2H) (c)
11		118	75	$C_{27}H_{26}Cl_2N_2OS$	65.19	5.23	5.63	65.17	5.28	5.42	5.28(s,2H)	3.61(s, 2H)

(c) AB pattern (coupling constant, 14 cps) possibly resulting from the non-equilibrium of the methylene protons (b) due to the methyl group in the 2-position of the piperidine ring.

TABLE II



2,3-Diaryloxymethylbenzo[*b*]thiophenes

	R	M.p. (°C)	% Yield	Molecular formula	Analysis % Calcd. C	Calcd. H	Found C	Found H	NMR ($CDCl_3$): (in δ) (a) (s, 2H)	(b) (s, 2H)
1	*p*-cresyl	130	81	$C_{23}H_{18}Cl_2O_2S$	64.33	4.19	64.22	4.20	5.30	5.18
2	*p*-chlorophenyl	148	84	$C_{22}H_{15}Cl_3O_2S$	58.73	3.34	58.63	3.33	5.31	5.20
3	*p*-bromophenyl	155	77	$C_{22}H_{15}BrCl_2O_2S$	53.44	3.04	53.43	3.01	5.30	5.18
4	*o*-bromophenyl	136	71	$C_{22}H_{15}BrCl_2O_2S$	53.44	3.04	53.44	3.03	5.43	5.33
5	*p*-SCH_3 phenyl	117	78	$C_{23}H_{18}Cl_2O_2S_2$	59.87	3.90	59.74	3.90	5.30	5.18
6	2,4-dichlorophenyl	167.5	76	$C_{22}H_{14}Cl_4O_2S$	54.54	2.93	54.52	2.93	5.35	5.26
7	4-chloro-2-methyl-phenyl	124	77	$C_{23}H_{17}Cl_3O_2S$	59.54	3.66	59.58	3.67	5.28	5.18