A SYNTHESIS OF BENZO[b]NAPHTHO[2,3-d]THIOPHENE DERIVATIVES via BENZO[b]THIOPHENE-2,3-QUINODIMETHANE INTERMEDIATES

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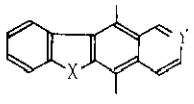
Abstract ——— 2-Methyl- and 2-ethyl-3-(α-aryl)hydroxymethylbenzo[b]-thiophene (6a)-(6d) were heated at 400°C for 5 min to yield the corresponding benzo[b]naphtho[2,3-d]thiophene derivatives (9a)-(9d), respectively. In a similar fashion, the alcohol (8a) gave 5-methyl-benzo[b]naphtho[2,3-d]thiophene (9e) and 5,10-dimethyl derivative (3). 8-Methoxy 5-methyl- (9f) and 5-phenyl derivative (9g) were obtained from the corresponding alcohols (8b) and (8c), respectively.

Much attention has been focussed on the carbazole alkaloid, ellipticine (1)[1] and related compounds for their attractive biological importance. The reported antitumor properties for these alkaloids have stimulated interest in these isosteric heterocycles. For this reason, the sulfur isoster of 1, that is thia-ellipticine (2)[2] and its congener[3] were synthesized for the biological evaluation. From the close structural similarity between 2 and linear tetracyclic poly-condensed thiophenes, we have been interested in a synthesis of benzo[b]naphtho-[2,3-d]thiophene derivatives such as 3, which might exhibit the carcinogenic and mutagenic activities[4].

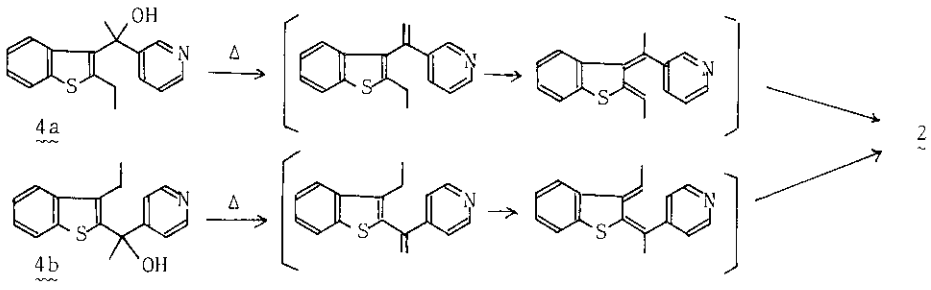


1: X=NH, Y=N

2: X=S, Y=N

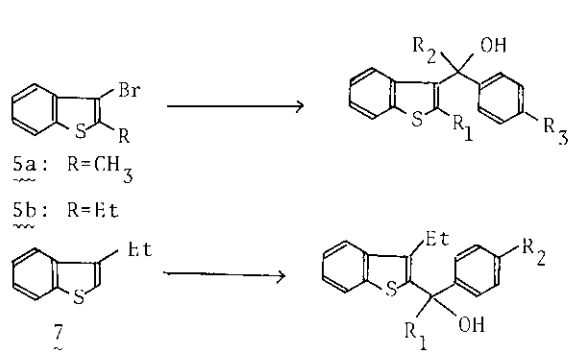
3: X=S, Y=CH

Previously, we investigated a new synthesis of 2 and related compounds by thermal cyclization of some tertiary alcohols such as 4a and 4b[5] (Scheme 1). For the synthesis of benzo[b]naphtho[2,3-d]thiophenes, we successively examined this cyclization reaction of secondary and tertiary alcohols bearing benzo[b]thiophene and phenyl groups as an extention of the previous work. We wish to report the results of our studies in this paper.



Scheme 1

The alcohols used for thermal decomposition were prepared as follows: Lithiation of 3-bromo-2-methylbenzo[b]thiophene (5a)[6] with n-BuLi in THF at -78°C for 0.5 hr, followed by quenching with p-anisaldehyde and benzophenone gave the corresponding alcohols (6a) and (6b), respectively. In a similar fashion, 3-bromo-2-ethylbenzo[b]thiophene (5b)[7] afforded the alcohols (6c) and (6d). Lithiation of 3-ethylbenzo[b]thiophene (7)[8] [lithium diisopropylamide (LDA), THF, 0°C-room temperature, 1 hr], followed by quenching with acetophenone, p-methoxyacetophenone and benzophenone [-78°C-room teperature, 3 hr] yielded the corresponding alcohols (8a), (8b) and (8c), respectively (Scheme 2). Yields and physical data were listed in the Table 1.



6a: R_1=CH_3, R_2=H, R_3=OCH_3
6b: R_1=CH_3, R_2=C_6H_5, R_3=H
6c: R_1=Et, R_2=H, R_3=OCH_3
6d: R_1=Et, R_2=C_6H_5, R_3=H

8a: R_1=CH_3, R_2=H
8b: R_1=CH_3, R_2=OCH_3
8c: R_1=C_6H_5, R_2=H

Scheme 2

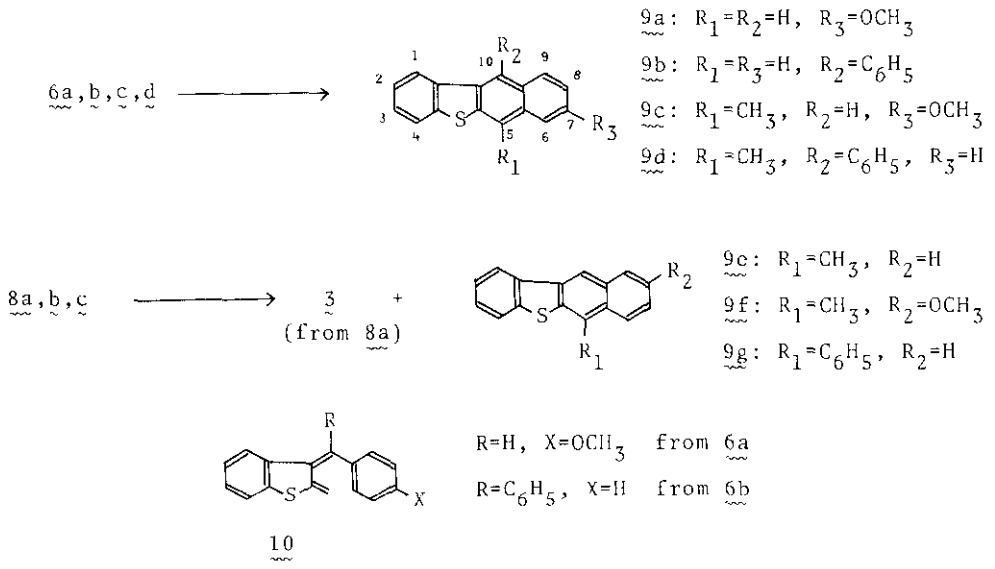
Table 1. Yields and physical data of alcohols (6) and (8)

Alcohol[a]	Yield (%)	Formula	High Resolution Mass Spectra m/e (Calcd.)	NMR ($CDCl_3$) Spectra[c] δ
6a	72	$C_{17}H_{16}O_2S$	284.0841 (284.0896)	2.48 (3H, s), 3.69 (3H, s), 6.21 (1H, s)
6b[b]	82	$C_{22}H_{18}OS$		1.81 (3H, s), 5.35 (1H, s)
6c	78	$C_{18}H_{18}O_2S$	298.1022 (298.1026)	1.17 (3H, t, J 7.5 Hz), 2.78 (2H, q, J 7.5 Hz), 3.55 (3H, s), 5.96 (1H, s)
6d	79	$C_{23}H_{20}OS$	344.1217 (344.1233)	1.03 (3H, t, J 7.2 Hz), 2.24 (2H, q, J 7.2 Hz)
8a	68	$C_{18}H_{18}OS$	282.1089 (282.1078)	0.84 (3H, t, J 7.6 Hz), 2.10 (3H, s), 2.61 (2H, q, J 7.6 Hz)
8b	65	$C_{19}H_{20}O_2S$	312.1160 (312.1182)	1.00 (3H, t, J 7.5 Hz), 2.02 (3H, s), 2.59 (2H, q, J 7.5 Hz), 3.73 (3H, s)
8c	42	$C_{23}H_{20}OS$	344.1235 (344.1233)	0.86 (3H, t, J 7.4 Hz), 2.63 (2H, q, J 7.4 Hz)

a All alcohols were isolated as an oil except 6b. b mp 129-130°C, Anal. Calcd. for $C_{22}H_{18}OS$: C: 79.96; H, 5.49; Found: C, 79.77; H, 5.35. c Only characteristic signals are given.

These alcohols were then subjected to thermal decomposition. The alcohol (6a) was heated at 410°C[9] for 5 min and the resulting reaction mixture was chromatographed on silica gel[10] to give 7-methoxybenzo[b]naphtho[2,3-d]thiophene (9a)[11] in 18 % yield. Apparently, 9a was formed through cyclization of the benzo[b]thiophene-2,3-quinodimethane intermediate (10) derived from 6a by elimination of water. In a similar fashion, 10-phenyl- (9b), 7-methoxy-5-methyl- (9c) and 5-methyl-10-phenyl derivative (9d) were obtained from 6b, 6c and 6d, respectively. Thermal reaction of 8a showed rather different mode of decomposition and 5-methylbenzo[b]naphtho-[2,3-d]thiophene (9e) was obtained as the main product. In this reaction, the expected product (3) was also obtained, though in low yield (12 %). However, in the case of 8b and 8c, 8-methoxy-5-methyl- (9f) and 5-phenylbenzo[b]naphtho-[2,3-d]thiophene (9g) were yielded, respectively, without formation of the corresponding 5,10-disubstituted cyclization products[12] (Scheme 3). The reaction conditions and yields and physical data of products were shown in the Table 2. Thus, 2-alkyl-3-(α-aryl)hydroxymethylbenzo[b]naphthothiophenes and 3-alkyl-2-(α-aryl)-hydroxymethylbenzo[b]thiophenes were found to be easily convertible to benzo[b]-naphtho[2,3-d]thiophenes. This method would be applicable to a short-step syn-

thesis of some linear poly-cyclic thiophene derivatives.



Scheme 3

Table 2. Yields and physical data of cyclization products (3) and (9a)-(9g)

Alcohol	Reaction temp. and time (min)	Product	Yield (%)	mp (°C)	Mass Spectra M^+, m/e	NMR ($CDCl_3$) Spectra[a] δ
6a	410°C (5 min)	9a	18	206-207	264	3.78 (3H, s)
6b	400°C (5 min)	9b	28	114-116	310	8.25 (1H, s)
6c	410°C (5 min)	9c	22	152-154	278	2.78 (3H, s), 3.94 (3H, s), 7.48 (1H, s), 8.31 (1H, s)
6d	400°C (5 min)	9d	30	159-160	324	2.85 (3H, s)
8a	400°C (7 min)	3	12	133-135	262	2.88 (3H, s), 3.21 (3H, s)
		9e	39	120-122	248	2.76 (3H, s), 8.29 (1H, s)
8b	420°C (7 min)	9f	48	137-138	278	2.82 (3H, s), 3.92 (3H, s), 8.28 (1H, s)
8c	420°C (5 min)	9g	32	150-152	310	8.25 (1H, s)

a Only characteristic signals are given.

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9. Pyrolysis was examined under a variety of conditions in the range of 250-450°C. 400-410°C was found to give the best results.
10. Benzene-hexane (1·3) was used as an eluent for isolation of 9a, 9c and 9f. Hexane was used for isolation of other cyclization products
11. All cyclization products gave satisfactory microanalyses.
12. The reasonable mechanistic feature is under investigation. Most possibly, methyl group would be easily removable as methane by chain reaction on aromatization of the cyclization intermediates

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