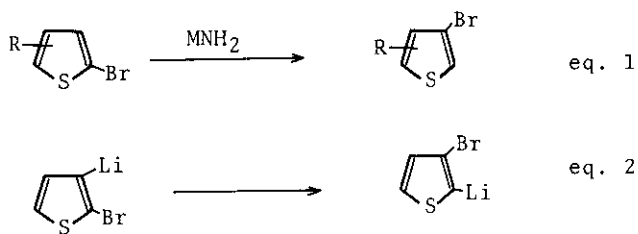


SYNTHESIS OF 2-SUBSTITUTED 3,5-DIBROMOTHIOPHENES THROUGH BASE-CATALYZED HALOGEN DANCE REACTION OF 2,5-DIBROMOTHIOPHENE

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Abstract — Treatment of 2,5-dibromothiophene with LDA in THF at -78°C, followed by quenching with electrophiles afforded the corresponding 2-substituted 3,5-dibromothiophenes in good yield.

It is well known that 2-bromothiophenes are easily convertible to 3-bromothiophenes on treatment with metal amide in liquid ammonia^{1,2} (eq. 1). Furthermore, 2-bromo-3-lithiothiophene, generated from 2-bromo-3-iodothiophene, underwent a rapid halogen-metal exchange reaction similar to the base-catalyzed halogen dance (BCHD)³. This reaction is noted for the other thienyllithium compounds to ultimately give the stable 2-lithiothiophene derivatives³ (eq. 2).



However, lithiation of 2,5-dibromothiophene (1) with lithium diisopropylamide (LDA) in THF or ether at -70°C was known to give 2,5-dibromo-3-lithiothiophene (2) which behaved like a normal lithium reagent and 2,5-dibromo-3-trimethylsilyl thiophene (3) was obtained by quenching with trimethylchlorosilane⁴. We examined the same reaction during the investigation of a synthesis of 3-substituted 2,5-dibromothiophenes, which would be useful precursors giving poly-substituted thiophenes. The lithiothiophene formed in this reaction was found to be 3,5-dibromo-2-lithiothiophene (4), which would be derived from 2 by BCHD mechanism. The results of our studies are described in this paper. (Scheme 1).

Scheme 1

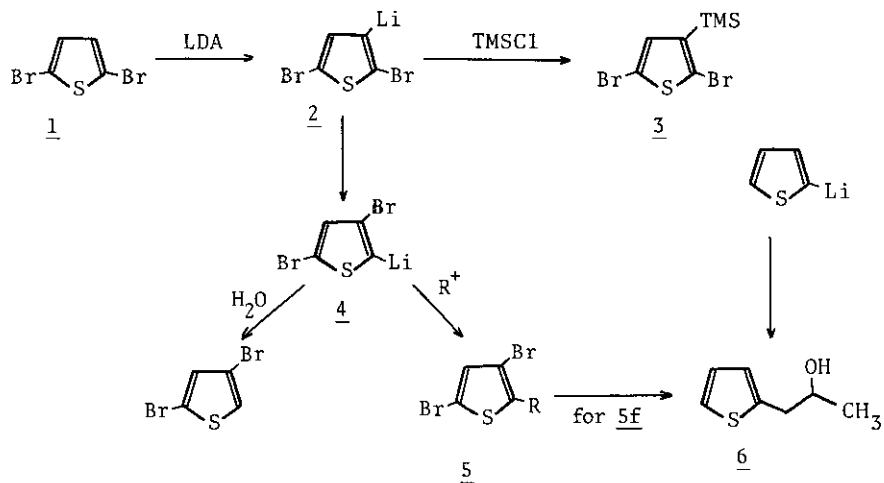




Table 1. 2-Substituted 3,5-Dibromothiophenes: (5a)-(5j)

5	R	Yield (%)	bp (torr)	1H NMR ($CDCl_3$) δ 4H
5a	$-CH_3$	95	70-75°C (2) ^a	6.92
5b	$-CH_2CH_3$	80	90-95°C (3)	6.80
5c	$-CH_2CH=CH_2$	68	108-113°C (3)	6.97
5d	$-CHO$	85	117-120°C (3)	7.19
5e	$-COOEt$	72	130-135°C (3)	7.12
5f	$-CH_2CH(OH)CH_3$	73	136-140°C (3)	7.00
5g	$-CH_2CH(OH)Et$	68	138-144°C (3)	6.95
5h		63	180-185°C (3)	6.95
5i		77	163-167°C (3)	6.93
5j	$-SCH_3$	45	154-159°C (3)	7.40

^alit.⁵ bp 48-55°C (0.35-0.45)

Treatment of 1 with LDA (1.1 equi. mol, THF, -78°C, 0.5 h), followed by quenching with water at the same temperature gave 3,5-dibromothiophene in nearly quantitative yield without recovery of any trace amount of 1. This fact indicates that 2 initially generated from 1, was rapidly converted to 4 even at -78°C. The same reaction by the use of methyl iodide instead of water gave 3,5-dibromo-2-methylthiophene (5a)⁵. In a similar fashion, ethyl iodide, allyl bromide, N,N-dimethylformamide, ethyl chloroformate, propylene oxide, butylene oxide, cyclohexene oxide, cyclohexanone, dimethyl disulfide were used to give the corresponding 2-substituted 3,5-dibromothiophene (5b)-(5j), respectively. The results are summarized in the Table 1.

In addition, in order to confirm that substituents were introduced to the 2-position, 5f was led to 1-methyl-2-(2-thienyl)ethanol (6). Treatment of 5f with n-BuLi (3 equi. mol, THF, -78°C) afforded 6⁶, which was identical with the authentic sample prepared by the reaction of 2-lithiothiophene with propylene oxide, in all respects.

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6. 95 % yield, bp 75-80°C (3 torr), ¹H NMR (CDCl₃) δ 1.22 (3H, d, J=7 Hz), 2.91 (2H, d, J=6 Hz), 3.80-4.17 (1H, m), 6.87-7.03 (2H, m), 7.20 (1H, d,d, J=6 and 1.5 Hz).

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