The Reactions of Halothiophenes with Metal Amides. A Convenient Preparation of β-Bromothiophenes[1]

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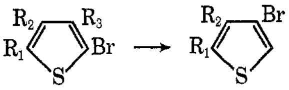
A new, convenient, and efficient synthesis of the very useful β-bromothiophenes by the metal amide catalyzed rearrangement of the readily available α isomers is reported.

While diazonium compounds are generally acknowledged to be key synthetic intermediates in the preparation of substituted benzenes, the corresponding position in the thiophene series is held largely by bromo compounds.[2] Unfortunately, only the α-bromothiophenes are readily available by direct electrophilic substitution.[2] Consequently, several indirect methods for introducing substituents into the β position of thiophenes have been developed.[3] Nevertheless, β-bromothiophenes, because they can be converted quantitatively to the versatile β-lithio derivatives,[4] are still viewed as the most suitable entry into the β-substituted thiophene series.[3,5]

The synthesis of 3-bromo- and 3,4-dibromothiophene usually involves exhaustive bromination of thiophene to 2,3,5-tribromo- and 2,3,4,5-tetrabromothiophene, respectively, followed by selective removal of the 2 and 5 bromine atoms with Grignard reagents,[6] lithium reagents,[7] or zinc and acid.[8,9] Substituted β-bromothiophenes often require even more elaborate synthetic procedures.[10,11] This paper reports an alternative synthesis of a variety of β-bromothiophenes (**2**) which does not require the preparation of intermediate polybromothiophenes but proceeds directly by rearrangement of the easily prepared[2] or commercially available α-bromo isomers (**1**).

The prototype for this synthesis is the conversion of 2-bromothiophene (**1a**) to 3-bromothiophene (**2a**) with sodium amide in liquid ammonia. Variations of this reaction are listed in Table I. Although the conditions were not necessarily optimized in every case, changes from those indicated in Table I and the Experimental Section often lead to lower yields.[1]



1 **2**

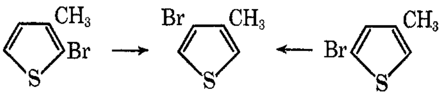
The major identifiable side products of these halogen rearrangements are polyhalothiophenes, dehalogenated thiophenes, and aminothiophenes, in accordance with the mechanism proposed for this reaction.[12] Formation of the first two products is usually favored by shorter reaction times, or by lower concentrations of metal amide in solution, as when the relatively insoluble lithium or sodium amides[13] are utilized. Aminothiophene production is favored by high concentrations of metal amide in solution, as is obtained with potassium amide. Some compounds (**1b**,**c**,**d**) are resistant to amination even with potassium amide, while others (**1a**,**e**,**f**) give substantial amounts of aminothiophenes[12] or their decomposition products with this reagent. In fact, the preparation of the relatively unstable 3-aminothiophene in 74% yield (as the acetamide) from **1a** and 2 equiv of potassium amide in liquid ammonia is in itself of considerable synthetic value.[14]

TABLE I
REACTIONS OF BROMOTHIOPHENES WITH METAL AMIDES

	Reactant (**1**)				Conditions[a]	% yield
Series	R_1	R_2	R_3	Moles	Amide (equiv)	of **2**[b,c]
a	H	H	H	0.5	$NaNH_2$ (2)	73
b	CH_3	H	H	0.1	KNH_2 (6)	72
c	H	H	CH_3	0.1	KNH_2 (3)	67[b]
d	Benzo		H	0.1	KNH_2 (6)	87
e	CH_3	Br	H	0.05	$NaNH_2$ (3)	64
f	Br	H	H	1.0	$NaNH_2$ (4)	73[c]

[a] 20 ± 5 min in refluxing liquid ammonia. [b] **2c** is 3-methyl-4-bromothiophene (R_1 = H, R_2 = Me). [c] **2f** is 3,4-dibromothiophene (R_1 = H, R_2 = Br).

Bromine migration also can occur from an α to an opposite β position. This characteristic is particularly useful in the preparation of **2c** since **1c** may replace the alternate reactant **3** which is very difficult to obtain in reasonable yield and purity.[15] For example, bromination of the readily available[4] 2-lithio-4-methylthiophene leads to virtually inseparable mixtures of **1c** and **3**. Since the use of one of these mixtures, instead of pure **1c**, in the rearrangement does not improve the yield of **2c**, **1c** probably is as good a starting material as **3** in this synthesis.



1c **2c** **3**

With unsubstituted metal amides the rearrangement is apparently of synthetic value only for bromothiophenes (Table II). Use of a substituted amide, however, leads to a substantial improvement in the yield of 3-iodothiophene (Table III). Other halothiophenes do

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[1] Abstracted in part from the Ph.D. dissertation of H. W. A., Texas Christian University, 1968.

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[6] S. Gronowitz, *ibid.*, **7**, 267 (1954).

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[8] S. Gronowitz, *Acta Chem. Scand.*, **13**, 1045 (1959).

[9] S. Gronowitz and T. Raznikiewicz, *Org. Syn.*, **44**, 9 (1964).

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[12] (a) M. G. Reinecke and H. W. Adickes, *J. Amer. Chem. Soc.*, **90**, 511 (1968); (b) M. G. Reinecke, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14**, (2) C68 (1969).

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TABLE II

REACTIONS OF 2-CHLORO- AND 2-IODOTHIOPHENE WITH METAL AMIDES[a]

Reactant (0.1 mol)	Amide (0.6 mol)	Product
2-Chlorothiophene	$NaNH_2$	92% recovery
2-Chlorothiophene	KNH_2	Tars
2-Iodothiophene	$NaNH_2$	37% 3-iodothiophene
2-Iodothiophene	KNH_2	Tars

[a] 15 min, NH_3(l), −33°.

TABLE III

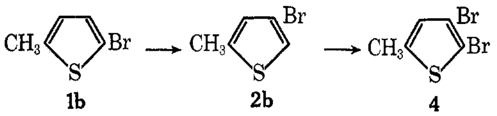
REACTIONS OF HALOTHIOPHENES WITH METAL ANILIDES[a]

Reactant thiophene	Anilide	Product thiophene
2-Iodo[b]	$KNCH_3C_6H_5$	3-Iodo (77%)
2-Chloro[c]	$KNCH_3C_6H_5$	76% recovery
1a	$KNCH_3C_6H_5$	**2f** (38%); 2,3,4-tribromo (36%)
1a	$NaNHC_6H_5$	**2f** (46%); 2,3,4-tribromo (38%)
1a	$KNHC_6H_5$	**2f** (34%); 2,3,4-tribromo (49%)
1e[d]	$KNCH_3C_6H_5$	**2e** (21%); 2-methyl-3-bromo (21%); 2,3,4-tribromo-5-methyl (9%)
1f	$NaNHC_6H_5$	**2f** (80%)

[a] Unless otherwise noted, all reactions run as follows: 0.1 mol of reactant, 0.2 mol of anilide, 20 min, NH_3(l), −33°, no other thiophene products in >1% yield. [b] 0.6 mol of anilide, 15 min, 5% side product. [c] 0.05 mol, 0.15 mol of anilide, 2 hr. [d] 0.04 mol, 0.12 mol of anilide.

not respond as markedly to this variation primarily because of changes in product distribution.

During the course of this work an improved preparation of **1e** was developed (see Experimental Section), and a synthesis of the previously unknown **4** was carried out utilizing the rearrangement which is the subject of this paper.



1b **2b** **4**

Experimental Section

Boiling points are uncorrected. All spectra were taken on vpc collected samples. Infrared spectra were taken as films on a Beckman IR-10 or a Perkin-Elmer 237 instrument and were calibrated with a polystyrene film. Nmr spectra were obtained with a Varian A-60 spectrometer and calibrated in τ units relative to TMS. Unless otherwise noted, gas chromatographic analyses were carried out on an Aerograph Autoprep A-700 or a Beckman GC-II using a 12 ft × 0.25 in. column of either 12% Carbowax 20M or 10% Carbowax 4000 on Gas-Chrom R.

Starting Materials.—2-Bromothiophene (**1a**), 2-chlorothiophene, and 2,5-dibromothiophene (**1f**) were purchased from Eastman Organics and purified by distillation prior to use. 5-Bromo-2-methylthiophene (**1b**),[16] 2-bromobenzothiophene (**1d**),[17] and 2-iodothiophene[18] were prepared according to the indicated literature procedures. The remaining reactants (**3**, **1c**, and **1e**) were synthesized as described below.

3-Methylthiophene.[19]—To a 500-ml, three-necked Morton flask equipped with a stirrer and a condenser set for distillation were added 37 g (0.33 mol) of 3-thiophenecarboxaldehyde[20] and 250 ml of ethylene glycol. The flask was immersed in a cold water bath and 30 ml of 97% hydrazine was slowly added with stirring. The solution was distilled until the temperature of the vapors reached 135°. The distillate was extracted with ether, and the extract was washed with 50 ml of water. When the glycol solution had cooled to room temperature, the ether extract and 70 g of KOH pellets were added to the flask. The mixture was cautiously heated and stirred. After the KOH had dissolved, the distillation was continued. When the temperature of the vapors reached 135°, large quantities of nitrogen were given off, and heating was immediately reduced. When the evolution of nitrogen had ceased, the distillation was resumed until the temperature reached 145°. The distillate was extracted with two 75-ml portions of ether. The ether extracts were washed with two 25-ml portions of 5% HCl and with 25 ml of water. The ether extract was dried over $CaCl_2$, and the solution was distilled through a Nestor–Faust Teflon annular spinning band fractionating column. The fraction boiling at 114–116° (lit.[21] bp 115.4°) was collected to give 29.1 g (90%) of 3-methylthiophene: ir 755 cm^{-1} (3-substituted thiophene);[22] nmr (neat) τ 7.92 (d, $J \approx 1$ Hz, 3, CH_3), 3.25 (m, 2, 2 and 4 H), 2.98 (m, 1, 5 H).[23]

2-Bromo-3-methylthiophene (**1c**).—To a solution of 4.9 g of 3-methylthiophene in 25 ml of dioxane at room temperature was added dropwise with magnetic stirring 8 g of bromine in 50 ml of dioxane. After 30 min had elapsed the mixture was poured into 200 ml of water and extracted with two 100-ml portions of ether. The combined ether layers were washed with 25 ml of 1 *N* NaOH and two 25-ml portions of water. Distillation of the dried extracts (Na_2SO_4) gave 7.5 g (85%) of **1c** as a colorless oil (>99% pure by vpc), bp 76–78° (30 mm) [lit.[24] bp 68–70° (18 mm)]; micro bp[25] 174.5° (lit.[15] 173–176°); ir 692 cm^{-1} (2,3-disubstituted thiophene);[22] nmr (neat) τ 8.27 (s, 3, CH_3), 3.71 (d, $J = 5.5$ Hz, 1, 4 H), 3.35 (d, $J = 5.5$ Hz, 1, 5 H) [lit.[26] ($DCCl_3$) 4 H, 3.38, d; 5 H, 3.03, d; $J = 5.3$ and 5.5 Hz].

2-Bromo-4-methylthiophene (**3**).—To a 100-ml, three-necked Morton flask, equipped with a magnetic stirring bar, reflux condenser with a nitrogen bubbler, and a serum cap, was added 10.1 g (0.102 mol) of 3-methylthiophene in 50 ml of anhydrous ether. The flask was swept with nitrogen, and 0.11 mol of commercial *n*-butyllithium in *n*-hexane was injected into the stirred mixture. The mixture was heated at reflux for 1 hr and cooled in an ice bath, and 15 g (0.094 mol) of bromine was slowly added from an additional funnel. The mixture was poured into 100 ml of cold 1 *N* NaOH, the layers were separated, and the ether layer was washed with 100 ml of water and dried over Na_2SO_4. The ether was removed by distillation, and the residue was analyzed on a 15 ft 20% DC QF-1 on Chromosorb W column at 132°. Two distinct but inseparable peaks were observed in a 1:3 ratio in order of increasing retention time. An nmr spectrum (CCl_4) of this mixture was very similar to that of **1c** except that the methyl peak (τ 7.8) had a decided low-field shoulder and the doublet (τ 3.3) overlapped a tightly coupled multiplet as might be obtained from a 2,4-disubstituted thiophene ($J_{2,4} = 1.2$–1.9 Hz).[27] The 5 H doublet at τ 2.9 has $J = 5.5$ Hz, thereby eliminating the presence of a 3,4-disubstituted isomer from consideration ($J_{2,5} = 2.8$–3.2 Hz).[27] An infrared spectrum of this mixture contained a new peak at 730 cm^{-1} characteristic of some 2,4-disubstituted thiophenes.[28]

Variations of this synthesis involving different solvents or lithium reagents failed to improve the product ratio beyond 1:1.

3,5-Dibromo-2-methylthiophene (**1e**).—To a 2-l. three-necked Morton flask equipped with a stirrer, a reflux condenser, and an addition funnel was added a mixture of 49 g (0.50 mol) of 2-methylthiophene[29] in 250 ml of dioxane. After 1 l. of dioxane containing 160 g (1 mol) of bromine was slowly added, the mixture was stirred at room temperature for 2 hr and then heated to reflux until the evolution of HBr ceased (approximately 2 hr). The mixture was cooled and poured into 2 l. of water, the layers

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[24] Reference 19, p 211.

[25] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, p 32.

[26] Reference 19, pp 80, 84.

[27] Reference 22, p 117.

[28] S. Gronowitz, P. Moses, and A. Hornfeldt, *Ark. Kemi*, **17**, 237 (1961).

[29] Aldrich Chemical Co.

were separated, and the aqueous layer was washed twice with ether. The combined organic layers were washed with 250 ml of 1 *N* NaOH, and 250 ml of water, and dried over $CaCl_2$. The ether was removed by distillation, and the residue was vacuum distilled to give 127 g (97%) of 3,5-dibromo-2-methylthiophene (**1e**): bp 48-55° (0.35-0.45 mm) [lit.[30] bp 98.5-100° (10 mm)]; nmr (CCl_4) τ 7.70 (s, 3, CH_3) and 3.16 (s, 1, 4 H); ir 781, 812, 948 cm^{-1}.

General Procedure for Preparing β-Bromothiophenes (1 → 2).—Since commercial sodium and lithium amides gave erratic results, all metal amides were prepared[31] in liquid ammonia in a three-necked Morton flask equipped with a stirrer, a Dry Ice–acetone condenser, and an addition funnel. If the reaction was to be carried out with a metal anilide a 10% excess of the desired aniline was added at this time. After 10 min of stirring, the metal anilide was ready for use.

The bromothiophene was added as rapidly as possible, and after the reaction was complete sufficient NH_4Cl was added to destroy the excess amide. After the ammonia was evaporated with the aid of a lukewarm water bath, water was added to the residue and the organic layer was separated. Any insoluble tars were removed by filtration. The aqueous solution was extracted with three portions of ether, and the extracts were washed with four portions of 1 *N* HCl and one of water and then dried over $CaCl_2$. The ether was removed by distillation and the residue fractionally distilled to give the product. Reaction time, temperature, yield, the ratio of amide to thiophene, and the scale of the reaction are noted in Tables I, II, and III.

Product Identification.—3-Bromothiophene (**2a**),[9] 2,3,4-tribromothiophene,[7] 4-bromo-2-methylthiophene (**2b**),[11] 3-bromobenzothiophene (**2d**),[32] and 3,4-dibromothiophene (**2f**)[8] were identified by comparison of their infrared and nmr spectra and vpc retention times with those of authetic samples prepared by the cited methods. 3-Iodothiophene was identified by comparison of its nmr[33] and infrared[34] spectra with those in the literature. 3-Bromo-4-methylthiophene (**2c**) was identified by comparison of its infrared spectrum with that in the literature[10] and from its nmr spectrum (CCl_4) [τ 7.80 (d, $J \approx 1$ Hz, 3, CH_3), 3.16 (m, 1, 5 H), 2.91 (d, $J = 3.5$ Hz, 1, 2 H)].[27,35] 2-Methyl-3-bromothiophene was identified from its nmr spectrum[35] (CCl_4) [τ 7.67 (s, 3, CH_3), 3.23 (d, $J = 5.5$ Hz, 1, 4 H), 3.07 (d, $J = 5.5$ Hz, 1, 5 H)] and infrared spectrum[10] (695 cm^{-1}, 2,3-disubstituted thiophene).[22] 2,3,4-Tribromo-5-methylthiophene was identified by its melting point, 86.5–87° (lit.[36] mp 86°) and nmr spectrum (CCl_4, τ 7.60, s). 3,4-Dibromo-2-methylthiophene (**2e**) was identified from its nmr spectrum (CCl_4) [τ 7.55 (s, 3, CH_3), 2.93 (s, 1, 5 H)] and from the nonidentity of its infrared spectrum (728, 840, 880 cm^{-1}) with that of the starting material (**1e**) and the other possible α-methyldibromothiophene **4** synthesized as outlined below.

2,3-Dibromo-5-methylthiophene (**4**).—To a 50-ml, three-necked Morton flask equipped with a magnetic stirring bar, a reflux condenser, and an addition funnel were added 10 ml of dry benzene and 5 g (0.021 mol) of 4-bromo-2-methylthiophene (**2b**) prepared from the reaction of 5-bromo-2-methylthiophene (**1b**) with KNH_2 as described in this paper. The mixture was cooled in an ice bath, and 3.3 g (0.021 mol) of bromine in 20 ml of dry benzene was added with stirring over a period of 3 hr. The mixture was stirred at room temperature for 10 hr and then heated to reflux until HBr was no longer given off (about 30 min). The mixture was poured into 100 g of ice water, the layers were separated, and the aqueous layer was washed with two 50-ml portions of ether. The combined benzene and ether layers were dried over $CaCl_2$. The solvents were removed by distillation through a 40-cm Vigreux column. Vacuum distillation of the residue gave 4.5 g (84%) of 2,3-dibromo-5-methylthiophene (**4**): bp 76-78° (0.75 mm); nmr (CCl_4) τ 2.46 (q, 1, 4 H), 7.61 (d, 3, CH_3), $J_{CH_3-H} \approx 1$ Hz;[35] ir 2910, 1540, 1443, 1320, 1170, 1000, 830, 815 cm^{-1}.

Anal.[37] Calcd for $C_5H_4Br_2S$: C, 23.64; H, 1.57; Br, 62.44. Found: C, 23.29; H, 1.62; Br, 62.31.

3-Acetamidothiophene.—Using the general procedure for preparing β-bromothiophenes described above, 81.5 g (0.5 mol) of 2-bromothiophene was treated with 2 equiv of KNH_2 in liquid NH_3 at −33° for 15 min. The combined acid extracts were cooled with ice, basified with 50% NaOH, and quickly extracted with four portions of ether. Rather than attempt isolation of the relatively unstable[14] 3-aminothiophene itself, a fivefold excess of acetic anhydride was immediately added to the combined, undried ether extracts. Removal of the ether and excess acetic anhydride at reduced pressure on a rotary evaporator left a crystalline residue which upon recrystallization from water with the aid of Norit gave 52 g (74%) of 3-acetamidothiophene: mp 146-147° (lit.[14] mp 147-148°); ir 755 cm^{-1} (3-substituted thiophene);[22] nmr (acetone-d_6) τ 7.91 (s, CH_3), 6.39 (s, NH), 2.4-3.0 (m, characteristic of 3-substituted thiophenes,[33] ArH).

Registry No.—**1c**, 14282-76-9; **1e**, 29421-73-6; **2a**, 872-31-1; **2b**, 29421-92-9; **2c**, 30318-99-1; **2d**, 7342-82-7; **2e**, 30319-01-8; **2f**, 3141-26-2; **4**, 30319-03-0; 2,3,4-tribromothiophene, 3141-25-1; 2-methyl-3-bromothiophene, 30319-05-2; 2,3,4-tribromo-5-methylthiophene, 30319-06-3.

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