

Synthesis of 3,4-Dibromo-2,5-bis-substituted Thiophenes

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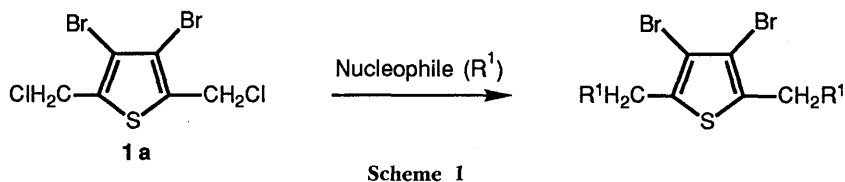
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The reaction of 3,4-dibromo-2,5-bis(chloromethyl)thiophene (**1a**), sufficiently derived from 3,4-dibromothiophene, with several kinds of nucleophiles was investigated. Whereas cyanomethylation of **1a** to 3,4-dibromo-2,5-bis(cyanomethyl)thiophene (**1b**) failed, thiocyanomethylation, bromomethylation, acetoxymethylation, and hydrolysis readily proceeded to afford the corresponding 3,4-dibromo-2,5-bis(thiocyanomethyl) (**1c**), bis(hydroxymethyl) (**1d**), bis(bromomethyl) (**1e**), and bis(acetoxymethyl) thiophenes (**1f**) in good yields (62-88%). The thiophene (**1a**) was reacted with aliphatic amines, such as dimethylamine, trimethylamine, pyrrolidine, piperidine, and morpholine, to produce 2,5-bis(aminomethyl)thiophenes (**1g-k**) in yields varying from 40% to 96%. The reaction of **1a** with pyridine furnished the mono- (**1l**) and bis-pyridinium salts (**1m**), respectively, dependent upon the amount of pyridine used. The mono-salt (**1l**) was, on purification, hydrolyzed to the hydroxymethyl mono-salt (**1n**) in 76% yield from **1a**.

1. Introduction

Among bifunctional thiophene derivatives, 2,5-bis(chloromethyl)thiophene²⁾ is regarded as a useful key compound toward the formation of various 2,5-bis-substituted thiophenes. However, it is thermally unstable and gradually decomposes upon heating or upon exposure to light. Therefore, 3,4-dibromo-2,5-bis(chloromethyl)thiophene (**1a**), being more stable than 2,5-bis(chloromethyl)thiophene, might be recommended as an alternative key compound in order to obtain various 3,4-dibromo-2,5-bis-substituted thiophenes *via* nucleophilic reactions of **1a** (Scheme 1).



It was reported recently that several 2,5-disubstituted thiophenes indicate a potential pharmacological activity.^{2,3)} Introducing bromine at the 3- and 4-positions on the thiophene ring should make the compound more active, since it is known that 3,4-dibromo- and dichloro-2,5-thiophene dinitriles show a significant plant fungicidal activity, e.g., against bean mildew.⁴⁾

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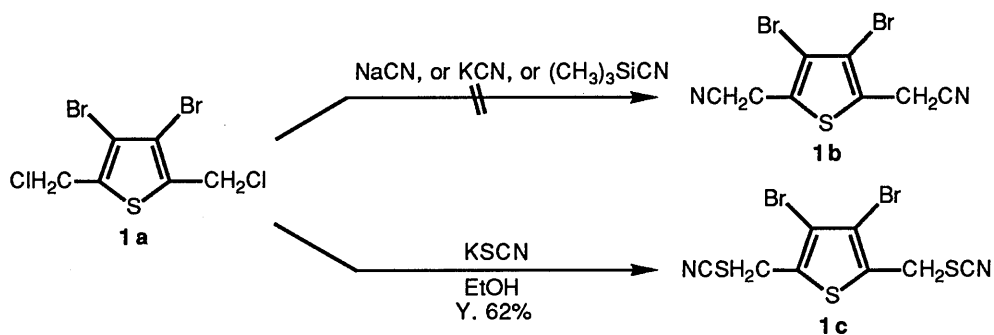
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We describe here the preparation of 3,4-dibromo-2,5-bis-substituted thiophenes by way of nucleophilic reactions of 3,4-dibromo-2,5-bis(chloromethyl) thiophene.

2. Results and Discussion.

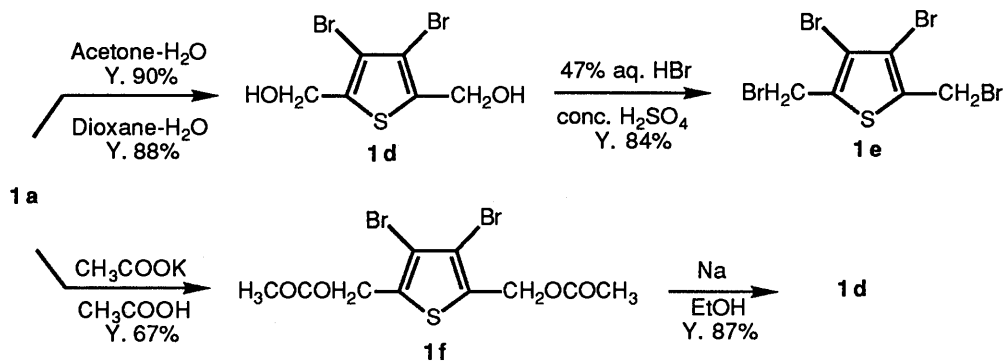
3,4-Dibromo-2,5-bis(chloromethyl)thiophene, which served as the starting compound to various 2,5-bis-substituted thiophenes, was prepared in an improved yield (87%) by modifying the reported procedure⁵ (see experimental section).

Whereas 2,5-bis(chloromethyl)thiophene reacted with NaCN to give 2,5-bis(cyanomethyl)thiophene⁶, an attempted synthesis of 3,4-dibromo-2,5-bis(cyanomethyl)thiophene (**1b**) upon treatment of **1a** with NaCN, KCN, or $(\text{CH}_3)_3\text{SiCN}$ failed, a resinous material being formed in all reactions (Scheme 2).



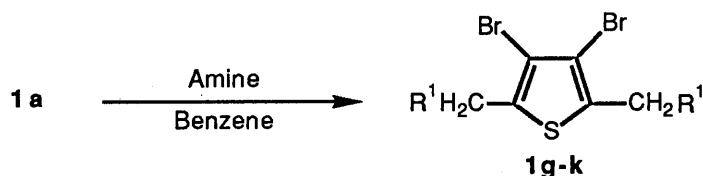
However, compound **1a** reacted with KSCN to afford the bis(thiocyanomethyl)thiophene (**1c**) in 62% yield. This difference might be due to polymerization of **1b** once formed, as **1b** possesses acidic methylenic protons.

Hydrolysis of **1a** easily proceeded upon treatment of **1a** with aqueous acetone or dioxane to afford the corresponding bis(hydroxymethyl)thiophene (**1d**) in 90% and 88% yield, respectively. Also, compound **1d** was obtained *via* the hydrolysis of the bis(acetoxymethyl)thiophene (**1f**), derived from **1a** using a mixture of CH_3COOH and CH_3COOK in 67% yield. The treatment of **1d** with 47% hydrobromic acid in the presence of concen-



trated H_2CO_4 provided the bis(bromomethyl)thiophene (**1e**) in 84% yield, which is as stable as **1a** (Scheme 3).

Reaction of **1a** with aliphatic amines, such as dimethylamine, trimethylamine, pyrrolidine, piperidine, and morpholine, afforded the corresponding bis(aminomethyl)thiophenes (**1g-k**) in yields varying from 40% to 96% (Scheme 4, **Table 1**).

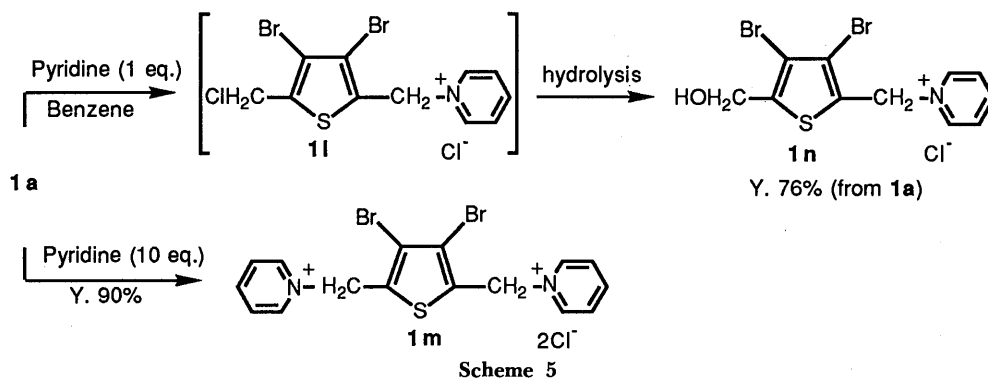


Scheme 4

Table 1 Preparation of 3,4-Dibromo-2,5-bis(aminomethyl) thiophenes (**1g-k**).

Run	Amines	Product	R ¹	Yield (%)
1	Dimethylamine	1g	-NH(CH ₃) ₂	40
2	Trimethylamine	1h	-N ⁺ (CH ₃) ₃ Cl ⁻	96
3	Pyrrolidine	1i	-N(CH ₂) ₄ -	65
4	Piperidine	1j	-N(CH ₂) ₅ -	81
5	Morpholine	1k	-N(CH ₂) ₂ O(CH ₂) ₂ -	71

On the other hand, reaction of **1a** with pyridine resulted in the formation of the mono- (**1l**) and bis-pyridinium salts (**1m**), respectively, dependent upon the amount of pyridine used (Scheme 5).



The mono-salt (**1l**) is formed with an equimolar amount of pyridine in refluxing benzene and the bis-salt (**1m**) is formed with 10 fold excess of pyridine in 90% yield. Compound **1l** is, however, unstable; it is hydrolyzed, upon purification, to the hydroxymethyl mono-pyridinium salt (**1n**) in 76% yield from **1a**.

3. Experimental

General. All of the melting points were determined in a Yanagimoto microapparatus and are uncorrected. The IR spectra were measured as KBr pellets on a JASCO A-102 infrared spectrometer. The ^1H NMR spectra were recorded at 100 MHz with a JEOL FX-100 NMR spectrometer in DMSO-d_6 or CDCl_3 using Me_4Si as an internal reference. The mass spectra were obtained on a JEOL JMS-OISG-2 mass spectrometer at 75 eV using a direct inlet system.

Material. 3,4-Dibromothiophene was prepared by the reported procedure.⁷⁾

3,4-Dibromo-2,5-bis(chloromethyl)thiophene (1a). Through a stirred mixture of 3,4-dibromothiophene (12.1 g, 50 mmol), paraformaldehyde (4.5 g), and anhydrous zinc chloride (5.0 g) in CCl_4 (25 ml) was passed dry HCl gas at 50°C for 3 h. The solid material formed was dissolved in CHCl_3 (50 ml) and then dry HCl gas was passed through the solution for an additional 1 h. The whole mixture was extracted with CHCl_3 , and the extracts were washed with water, diluted aqueous NaHCO_3 , and water. After the extracts being dried over MgSO_4 , the solvent was removed *in vacuo* to leave a residue, which was recrystallized to give **1a** (14.6 g, 87%): Colorless needles (petroleum ether, bp $30\text{--}70^\circ\text{C}$); mp $66.5\text{--}67.5^\circ\text{C}$ (lit.⁵⁾ $68\text{--}69^\circ\text{C}$).

3,4-Dibromo-2,5-bis(thiocyanomethyl)thiophene (1c). To a stirred solution of **1a** (1.0 g, 3 mmol) in EtOH (12 ml) was added dropwise a solution of KSCN (700 mg, 7 mmol) in EtOH (12 ml), and the resulting mixture was then heated at $50\text{--}60^\circ\text{C}$ for 2 h. After being cooled to room temperature, the whole mixture was extracted with CHCl_3 and treated as described above to give **1c** (710 mg, 62%): Colorless prisms (petroleum ether, bp $30\text{--}70^\circ\text{C}$); mp $136\text{--}137^\circ\text{C}$ (lit.⁵⁾ $135.5\text{--}136.5^\circ\text{C}$).

3,4-Dibromo-2,5-bis(hydroxymethyl)thiophene (1d). A stirred solution of **1a** (300 mg, 0.9 mmol) in a mixture of acetone (10 ml) and H_2O (5 ml) was heated under reflux for 24 h. After being cooled to room temperature, the reaction mixture was evaporated *in vacuo* and the solid material obtained was dissolved into CHCl_3 and treated as described above to afford **1d** (243 mg, 90%): Colorless prisms (CHCl_3); mp $169\text{--}171^\circ\text{C}$; ^1H NMR (DMSO-d_6) $\delta = 4.57$ (4H, d, $J = 5.6$ Hz), 5.79 (2H, t, $J = 5.6$ Hz); IR 3254 (OH) cm^{-1} ; MS m/z 302 (M^+), 301 (M^+), and 300 (M^+). Found: C, 24.13; H, 2.23%. Calcd for $\text{C}_6\text{H}_6\text{Br}_2\text{O}_2\text{S}$: C, 23.86; H, 2.00%.

In a similar manner, compound **1d** was obtained from **1a** (1.0 g, 3 mmol), dioxane (20 ml), and H_2O (10 ml) in 88% yield.

3,4-Dibromo-2,5-bis(bromomethyl)thiophene (1e). To a stirred mixture of **1a** (500 mg, 1.7 mmol) in 47% hydrobromic acid (20 ml) was added dropwise conc. H_2SO_4 (13 ml) under ice-cooling and the whole mixture was heated at $60\text{--}70^\circ\text{C}$ for 15 h. After being cooled to room temperature, the reaction mixture was extracted with CH_2Cl_2 and the extracts were washed with water, aqueous NaHCO_3 , and water and treated as described above to give **1e** (600 mg, 84%): Colorless needles (petroleum ether, bp $30\text{--}70^\circ\text{C}$); mp $115\text{--}116^\circ\text{C}$; ^1H NMR (CDCl_3) $\delta = 4.62$ (4H, s); IR 2960 (C-H) cm^{-1} ; MS m/z 431 (M^+), 429 (M^+), 427 (M^+), 425 (M^+), and 423 (M^+). Found: C, 17.11; H, 1.09%. Calcd for $\text{C}_6\text{H}_4\text{Br}_4\text{S}$: C, 16.85; H, 0.94%.

3,4-Dibromo-2,5-bis(acetoxymethyl)thiophene (1f). A stirred mixture of **1a** (1.0 g, 3 mmol) and potassium acetate (530 mg, 7.5 mmol) in glacial acetic acid (15 ml) was heated under reflux for 8 h. After being cooled to room temperature, the reaction mixture was extracted with CHCl_3 and treated as described above to give **1f** (760 mg, 67%): Colorless needles (hexane); mp 52-53°C; $^1\text{H NMR}$ (CDCl_3) $\delta = 2.10$ (6H, s), 5.20 (4H, s); IR 1740 ($\text{C}=\text{O}$) cm^{-1} ; MS m/z 388 (M^+), 386 (M^+), and 384 (M^+). Found: C, 30.98; H, 2.58%. Calcd for $\text{C}_{10}\text{H}_{10}\text{Br}_2\text{O}_4\text{S}$: C, 31.11; H, 2.61%.

Preparation of 1d from 1f. After a stirred mixture of **1f** (400 mg, 1 mmol) and Na (100 mg, 4.4 mmol) in dry EtOH (20 ml) was stirred at room temperature for 15 h, to the mixture was added CHCl_3 . The CHCl_3 solution was washed with water, diluted aqueous HCl, and water, and treated as described above to afford **1d** (260 mg, 87%) as colorless prisms.

3,4-Dibromo-2,5-bis(dimethylaminomethyl)thiophene (1g). A stirred mixture of **1a** (1.0 g, 3 mmol) and 50% aqueous dimethylamine (1.0 ml) in benzene (15 ml) was heated at 40-50°C for 23 h. After being cooled to room temperature, the reaction mixture was extracted with benzene and the extracts were treated as described above to give **1g** (432 mg, 40%): Colorless plates (petroleum ether, bp 30-70°C); mp 71-72°C; $^1\text{H NMR}$ (CDCl_3) $\delta = 2.30$ (12H, s), 3.62 (4H, s); IR 1350 (C-N) cm^{-1} ; MS m/z 358 (M^+), 356 (M^+), and 354 (M^+). Found: C, 33.99; H, 4.78; N, 8.08%. Calcd for $\text{C}_{10}\text{H}_{16}\text{Br}_2\text{N}_2\text{S}$: C, 33.73; H, 4.53; N, 7.87%.

3,4-Dibromo-2,5-bis(trimethylaminomethyl)thiophene dichloride (1h). A stirred mixture of **1a** (1.0 g, 3 mmol) and 30% aqueous trimethylamine (1.43 g) in benzene (15 ml) was heated at 40-50°C for 70 h. After being cooled to room temperature, the reaction mixture was extracted with CH_2Cl_2 and the extracts were treated as described above to give **1h** (1.15 g, 96%): Colorless powder (hexane and CH_2Cl_2); mp 205°C (decomp.); $^1\text{H NMR}$ (DMSO-d_6) $\delta = 3.20$ (18H, s), 4.93 (4H, s); IR 2970 (C-H) cm^{-1} ; MS m/z 457 ($\text{M}^+ - \text{CH}_3$). Found: C, 28.05; H, 5.50; N, 5.27%. Calcd for $\text{C}_{12}\text{H}_{22}\text{Br}_2\text{Cl}_2\text{N}_2\text{S} \cdot 3\text{H}_2\text{O}$: C, 28.20; H, 5.52; N, 5.48%.

3,4-Dibromo-2,5-bis(pyrrolidinomethyl)thiophene (1i). A stirred mixture of **1a** (200 mg, 0.6 mmol) and pyrrolidine (0.5 ml) in benzene (10 ml) was heated at 40-50°C for 6 h. After being cooled to room temperature, the reaction mixture was extracted with CH_2Cl_2 and the extracts were treated as described above to afford of **1i** (159 mg, 65%): Colorless plates (petroleum ether, bp 30-70°C); mp 89-91°C; $^1\text{H NMR}$ (CDCl_3) $\delta = 1.72$ -1.96 (8H, m), 2.50-2.72 (8H, m) 3.82 (4H, s); IR 2800 (C-H) and 1344 (C-N) cm^{-1} ; MS m/z 410 (M^+), 408 (M^+), and 406 (M^+). Found: C, 41.67; H, 4.92; N, 6.86%. Calcd for $\text{C}_{14}\text{H}_{20}\text{Br}_2\text{N}_2\text{S}$: C, 41.19; H, 4.94; N, 6.86%.

3,4-Dibromo-2,5-bis(piperidinomethyl)thiophene (1j). A stirred mixture of **1a** (200 mg, 0.6 mmol) and piperidine (0.5 ml) in benzene (5 ml) was heated at 80-90°C for 2 h. After being cooled to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved into water and to the resultant was added a small amount of charcoal and boiled for a few min. The mixture was filtered off and the filtrate was cooled to 0-5°C. The precipitates formed were collected by filtration and recrystallized to give **1j** (211 mg, 81%): Colorless plates (CH_3OH and H_2O); mp 77-78°C; $^1\text{H NMR}$ (CDCl_3) δ

= 1.35-1.51 (4H, m), 1.51-1.63 (8H, m), 2.35-2.58 (8H, m), 3.66 (4H, s); IR 1335 (C-N) cm^{-1} ; MS m/z 438 (M^+), 436 (M^+), and 434 (M^+). Found: C, 43.88; H, 5.71; N, 6.19%. Calcd for $\text{C}_{16}\text{H}_{24}\text{Br}_2\text{N}_2\text{S}$: C, 44.05; H, 5.55; N, 6.42%.

3,4-Dibromo-2,5-bis(morpholinomethyl)thiophene (1k). A stirred mixture of **1a** (200 mg, 0.6 mmol) and morpholine (0.5 ml) in benzene (10 ml) was heated at 50-60°C for 8 h. After being cooled to room temperature, the reaction mixture was extracted with CH_2Cl_2 and the extracts were evaporated *in vacuo* to leave a residue which, on recrystallization, afforded **1k** (187 mg, 71%): Colorless plates (petroleum ether, bp 30-70°C); mp 71-72°C; ^1H NMR (CDCl_3) δ = 2.30 (12H, s), 3.62 (4H, s); IR 1350 (C-N) cm^{-1} ; MS m/z 358 (M^+), 356 (M^+), and 354 (M^+). Found: C, 33.99; H, 4.78; N, 8.08%. Calcd for $\text{C}_{14}\text{H}_{20}\text{Br}_2\text{N}_2\text{O}_2\text{S}$: C, 33.73; H, 4.53; N, 7.87%.

3,4-Dibromo-2,5-thienobis [N-(methylene)pyridinium] dichloride (1m). A stirred mixture of **1a** (1.0 g, 3 mmol) in pyridine (5 ml) was heated under reflux for 15 h. After being cooled to room temperature, the precipitates formed were collected by filtration and washed with 10 ml of ether for several times to give **1m** (1.34 g, 90%): Colorless powder; mp 215°C (decomp.); IR 1630 (C=C, pyridine) cm^{-1} ; MS m/z 339 ($\text{M}^+ - 2\text{C}_5\text{H}_5\text{N}$). Found: C, 34.85; H, 3.42; N, 4.96%. Calcd for $\text{C}_{16}\text{H}_{14}\text{Br}_2\text{Cl}_2\text{N}_2\text{S} \cdot 3\text{H}_2\text{O}$: C, 34.87; H, 3.66; N, 5.08%.

N-(3,4-dibromo-5-hydroxymethyl-2-thienylmethyl)pyridinium chloride (1n). A stirred mixture of **1a** (1.0 g, 3 mmol) and pyridine (1 ml) in benzene (15 ml) was heated at 80-90°C for 15 h. After being cooled to room temperature, the precipitates formed were collected by filtration and treated as described above to afford **1n** (1.13 g, 76% from **1a**): Colorless powder (H_2O); mp 186.5-188°C; IR 1630 (C=C, pyridine) cm^{-1} ; MS m/z 308 ($\text{M}^+ - \text{C}_6\text{H}_5\text{N}$). Found: C, 31.69; H, 2.92; N, 3.38%. Calcd for $\text{C}_{11}\text{H}_{10}\text{Br}_2\text{ClNOS} \cdot \text{H}_2\text{O}$: C, 31.64; H, 2.90; N, 3.35%.

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(The author has prepared **1a** as follows; after HCl gas was passed through a stirred mixture of 3,4-dibromothiophene (24.2 g, 0.1 mol), paraformaldehyde (4.5 g), and zinc chloride (5.0 g) in CCl_4 (25 ml) being kept below 60°C for 30 min and then at 60-65°C for additional 1 h, the reaction mixture was poured into water and the organics were extracted with ether. The extracts were washed with water, diluted aqueous Na_2CO_3 , and water, and dried over K_2CO_3 . The solvent was removed *in vacuo* to leave a residue, which was distilled to afford **1a** (30%) and 3,4-dibromo-2-chloromethylthiophene (33%), respectively.)
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