

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF COLORADO]

The Effect of Benzoyl Peroxide on the Bromination of Methylthiophenes by N-Bromosuccinimide¹

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In the course of our work dealing with the synthesis of possible amino acid antagonists, we had occasion to study the reaction of 2- and 3-methylthiophenes with N-bromosuccinimide. Of particular interest was the preparation of thiophene intermediates which could be used in the synthesis of β -3-thienylalanine.

Steinkopf and co-workers^{3,4} reported that they obtained side chain bromination in the reaction of bromine with 2- and 3-methylthiophenes only after the thiophene ring had been completely brominated.

Buu-Hoi and Lecocq⁵ obtained brominated side-chain derivatives of α -methyl-naphthalene, 2-methylfuran and 2,5-dimethylfuran by the reaction with N-bromosuccinimide. With 2,5-dimethylthiophene the yields were lower because of the greater ease of nuclear substitution in the thiophene ring.

The results of Schmid and Karrer⁶ on the catalytic effect exerted by benzoyl peroxide in initiating and maintaining the free radical formation necessary for side-chain bromination of toluene by N-bromosuccinimide suggested the possibility of introducing a bromine atom into the side chain of 2- and 3-methylthiophene without ring bromination.

Recently Campaigne and LeSuer⁷ prepared 3-bromomethylthiophene by treating 3-methylthiophene with N-bromosuccinimide in the presence of benzoyl peroxide. We have obtained similar results. In this paper we wish to report on the effect of benzoyl peroxide on the bromination of 2- and 3-methylthiophenes by one and two molar equivalents of N-bromosuccinimide.

When 2-methylthiophene (I) was treated with one equivalent of N-bromosuccinimide without benzoyl peroxide, a good yield of monobromo-2-methylthiophene was obtained by distillation of the crude product. This material was about 66% 2-methyl-5-bromothiophene (III) and 34% 2-thenyl bromide (II). With benzoyl peroxide present the major fraction consisted primarily of 2-thenyl bromide (II) (84%), but contained some 2-methyl-5-bromothiophene (III). The composition of these fractions was estimated by analysis for total bromine and for hydrolyzable bromine,

the latter being a measure of side chain bromination. These conclusions were confirmed by fractional distillation analysis.

In the absence of benzoyl peroxide, 3-methylthiophene reacted with one molar equivalent of N-bromosuccinimide to form a mixture of monobromo-3-methylthiophenes which consisted of approximately 90% 2-bromo-3-methylthiophene (XII) and 10% 3-thenyl bromide (XIII); with benzoyl peroxide the monobromomethylthiophene fraction contained 90% 3-thenyl bromide and 10% 2-bromo-3-methylthiophene.⁸

The reaction between 2-methylthiophene and two molar equivalents of N-bromosuccinimide formed a fraction which analyzed correctly for dibromomethylthiophene. Fractional bromine analysis indicated that this sample was practically pure 2-bromomethyl-5-bromothiophene (IV). Benzoyl peroxide did not significantly change the yield or composition of this product. The structure of 2-bromomethyl-5-bromothiophene (IV) was proved by conversion to 5-bromo-2-thenylacetamidomalonate (VI) and 5-bromo-2-thenylacetamidocyanacetate (VII).

When 3-methylthiophene was treated with two molar equivalents of N-bromosuccinimide, a fraction of dibromomethylthiophenes was obtained which contained about 20% 2-bromo-3-bromomethylthiophene (XIV) and 80% 2,5-dibromo-3-methylthiophene (XV). The possibility of the presence of some 2,4-dibromo-3-methylthiophene is not completely ruled out. The addition of benzoyl peroxide gave a dibromo-3-methylthiophene fraction which consisted of about 84% 2-bromo-3-bromomethylthiophene (XIV) and 16% 2,5-dibromo-3-methylthiophene (XV). In one experiment evidence was obtained which indicated that some 3-thenylidene bromide was also formed. The structure of 2-bromo-3-bromomethylthiophene (XIV) was established by condensation with acetamidomalonate to form 2-bromo-3-thenylacetamidomalonate (XVI). A free alpha position was indicated by the ease with which it formed a chloromercuri derivative.

Most of the compounds formed were stable enough to permit distillation *in vacuo*. All 2-thenyl bromide derivatives lost hydrogen bromide and polymerized into tarry masses within a few days even though they were stored in the cold.

(8) In an earlier attempt when a different sample of N-bromosuccinimide was used, only traces of side chain-brominated material were obtained from 2-methyl- and 3-methylthiophenes. This misleading result prompted the preparation of 2-bromo-3-thenyl bromide with two molar equivalents of N-bromosuccinimide. The 2-bromo-3-thenyl bromide has been used for the preparation of β -3-thienylalanine.⁹

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(3) Steinkopf, *Ann.*, **513**, 281 (1934).

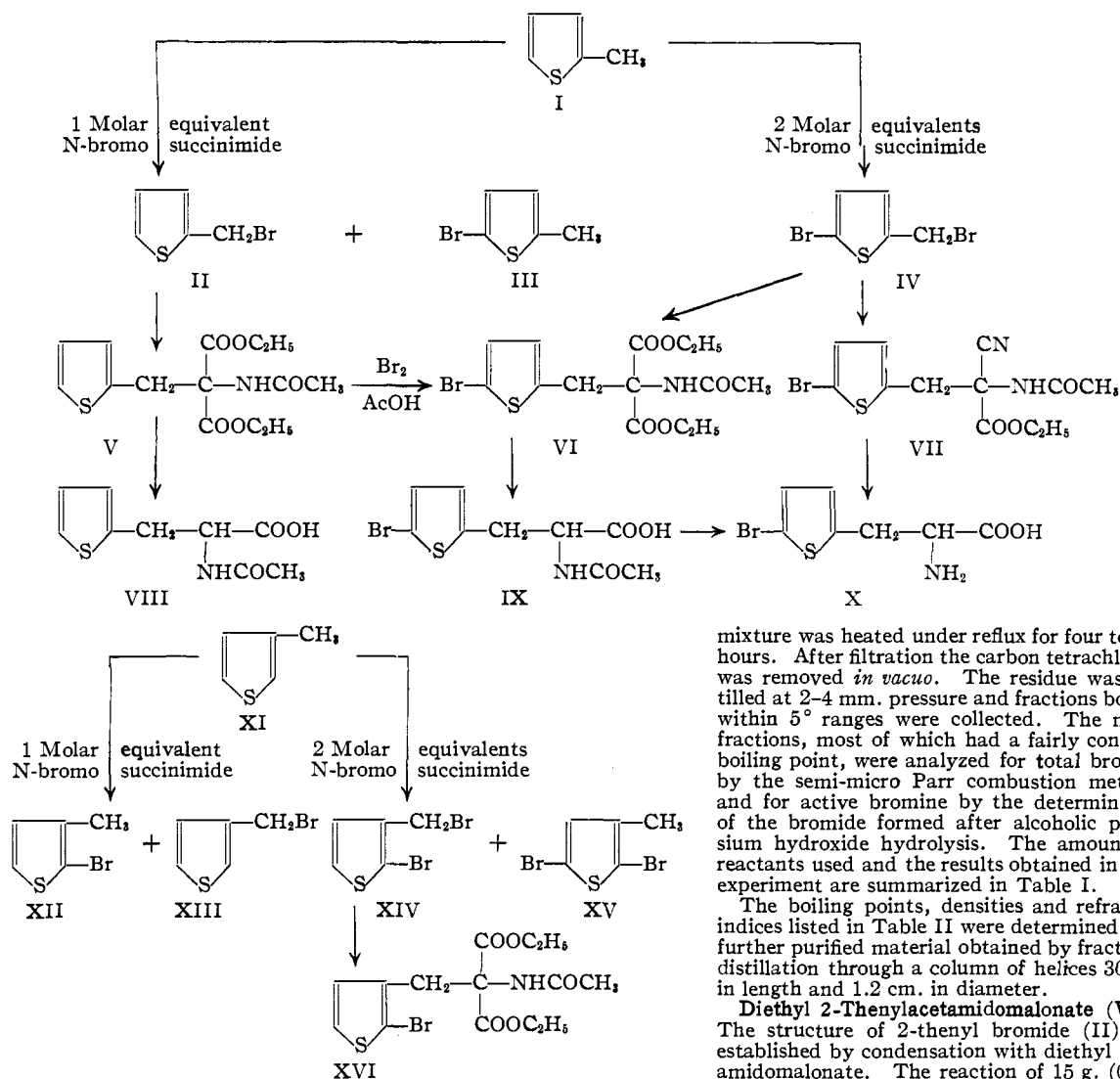
(4) Steinkopf and Jacob, *ibid.*, **515**, 273 (1935).

(5) Buu-Hoi and Lecocq, *J. Chem. Soc.*, 830 (1946), and *Compt. rend.*, **222**, 1441 (1946).

(6) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(7) Campaigne and LeSuer, *THIS JOURNAL*, **70**, 1555 (1948)

(9) Dittmer, *THIS JOURNAL*, **70**, 1205 (1948).



mixture was heated under reflux for four to five hours. After filtration the carbon tetrachloride was removed *in vacuo*. The residue was distilled at 2–4 mm. pressure and fractions boiling within 5° ranges were collected. The major fractions, most of which had a fairly constant boiling point, were analyzed for total bromine by the semi-micro Parr combustion method, and for active bromine by the determination of the bromide formed after alcoholic potassium hydroxide hydrolysis. The amounts of reactants used and the results obtained in each experiment are summarized in Table I.

The boiling points, densities and refractive indices listed in Table II were determined with further purified material obtained by fractional distillation through a column of helices 30 cm. in length and 1.2 cm. in diameter.

Diethyl 2-Thenylacetamidomalonate (V).—The structure of 2-thenyl bromide (II) was established by condensation with diethyl acetamidomalonate. The reaction of 15 g. (0.084 mole) of thenyl bromide (II) with 18.2 g. (0.084 mole) of diethyl acetamidomalonate in 100 ml. of absolute ethanol containing 1.9 g. (0.084 gram atom) of sodium after three hours reflux, followed by concentration, yielded 18.0 g. (67%) of diethyl 2-thenylacetamidomalonate (V), m. p. 115–116°, which was identical with the same compound prepared previously¹⁰ from 2-chloromethylthiophene.

N-Acetyl-β-2-thienylalanine (VIII).—Hydrolysis of 5 g. (0.016 mole) of V by the method of Snyder and co-workers¹¹ gave 2.9 g. (85%) of N-acetyl-β-2-thienylalanine (VIII). The white needles obtained on recrystallization from hot water melted at 130°.

Anal. Calcd. for C₉H₁₁NO₃S: N, 6.57. Found: N, 6.44.

Diethyl 2-(5-Bromo)-thenylacetamidomalonate (VI).—The reaction of 13 g. (0.05 mole) of 2-bromomethyl-5-bromothiophene (IV) with a solution of 50 ml. of absolute ethanol containing 1.15 g. (0.05 gram atom) of sodium and 10.8 (0.05 mole) of diethyl acetamidomalonate yielded 12 g. (0.03 mole, 60%) of slightly-colored product (VI). White needles, m. p. 108°, were obtained by decolorizing

(10) Dittmer, Herz and Chambers, *J. Biol. Chem.*, **166**, 541 (1946).

(11) Snyder, Shekleton and Lewis, *THIS JOURNAL*, **67**, 310 (1945).

This ease of decomposition was not observed with any of the 3-thenyl bromide derivatives.

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Experimental

Reaction of Methylthiophenes with N-Bromosuccinimide.—All of the brominations were conducted with from 0.13 to 0.40 mole of either 2- or 3-methylthiophene with either one or two molar equivalent amounts of N-bromosuccinimide suspended in 50 to 100 ml. of dry carbon tetrachloride. When benzoyl peroxide was used, between 0.10 and 0.25 g. per 0.1 mole of methylthiophene was added when the reaction started and, after ten minutes of refluxing, an additional 0.10 g. was added. Each reaction

TABLE I

DATA ILLUSTRATING THE COMPOUNDS PRESENT IN THE MAJOR DISTILLATION FRACTIONS OBTAINED BY THE BROMINATION OF 2- AND 3-METHYLTHIOPHENES WITH ONE AND TWO MOLAR EQUIVALENTS OF N-BROMOSUCCINIMIDE WITHOUT AND WITH ADDED BENZOYL PEROXIDE

Reactants 2-Methyl- thiophene moles	N-Bromo- succinimide moles	Benzoyl peroxide		B. p.		Yield, g.	Bromine analyses, %		Compounds present (relative amounts in each fraction)
		grams	milli- moles	°C.	Mm.		Active	Total	
0.2	0.2	0		66-70	3 ^a	25.3	15.6	45.1 ^b	{ 2-Methyl-5-bromothiophene (66%) 2-Thenyl bromide (34%)
.2	.2	0.7	2.9	75-80	3 ^a	22.8	38.0 ^e	44.9 ^b	{ 2-Thenyl bromide (84%) 2-Methyl-5-bromothiophene (16%)
.13	.26	0		84-87	2 ^a	16.8	29.2 ^c	62.1 ^d	2-Bromomethyl-5-bromothiophene (nearly pure)
.13	.26	0.3	1.2	82-87	2 ^a	16.9	32.0 ^c	61.5 ^d	2-Bromomethyl-5-bromothiophene (nearly pure)
3-Methylthiophene									
0.22	0.22	0		57-60	4 ^a	10.1	5.0	44.0 ^b	{ 2-Bromo-3-methylthiophene (90%) 3-Thenyl bromide (10%)
.28	.28	0.7	2.9	68-73	4 ^a	24.0	40.0 ^e	45.0 ^b	{ 3-Thenyl bromide (90%) 2-Bromo-3-methylthiophene (10%)
.2	.4	0		26-30	2 ^f	10.7	1.8	44.8 ^b	2-Bromo-3-methylthiophene (nearly pure)
				50-80	2 ^f	15.6	7.0	62.2 ^d	{ 2,5-Dibromo-3-methyl thiophene (77%) 2-Bromo-3-bromomethylthiophene (23%)
				34-37	2	10.2	3.1	44.0 ^b	2-Bromo-3-methylthiophene (nearly pure)
.4	.8	0.45	1.9	70-73	2 ^f	31.0	26.1 ^c	62.3 ^d	{ 2-Bromo-3-bromomethylthiophene (84%) 2,5-Dibromo-3-methylthiophene (16%)

^a These distillations were made in an all-glass Claisen distilling apparatus with no refluxing and considerable overheating of the vapors. ^b Total bromine calculated for monobromomethylthiophenes, 45.2%. ^c Active bromine calculated for bromomethylbromothiophenes, 31.1%. ^d Total bromine calculated for dibromomethylthiophenes, 62.2%. ^e Active bromine for thenyl bromides, 45.2%. ^f These distillations were made through a column of helices 30 cm. in length.

TABLE II

PHYSICAL PROPERTIES OF MONO- AND DI-BROMO COMPOUNDS OF 2- AND 3-METHYLTHIOPHENES

Compound, thiophene-	Formula	Bromine, %				Boiling point		<i>d</i> ₂₀ ²⁰	<i>n</i> _D ²⁰
		Total		Active		°C.	Mm.		
2-Methyl-5-bromo-	C ₆ H ₅ SBr	45.2	45.1	0.0	0.5	29	1.8	1.552	1.5687
2-Bromomethyl- ^f	C ₆ H ₅ SBr	45.2	44.6	45.2	40.4 ^a	55	1.5	1.605	1.6050
2-Bromomethyl-5-bromo- ^c	C ₆ H ₄ SBr ₂	62.2	62.7	31.1	28.7	71	1.2	2.022	1.6406
2-Bromo-3-methyl- ^d	C ₆ H ₅ SBr	45.2	44.0	0.0	0.3	27	1.8	1.571	1.5714
3-Bromomethyl- ^{e, g}	C ₆ H ₅ SBr	45.2	45.8	45.2	40.6 ^b	50	1.5	1.616	1.6035
2,5-Dibromo-3-methyl- ^d	C ₆ H ₄ SBr ₂	62.2	62.4	0.0	3.1	55	2	1.972	1.6126
2-Bromo-3-bromomethyl-	C ₆ H ₄ SBr ₂	62.2	62.7	31.1	32.0	78	2	2.025	1.6363

^a Still contains 2-methyl-5-bromothiophene. ^b Still contains 2-bromo-3-methylthiophene. ^c Previously prepared by Steinkopf.³ ^d Previously described by Steinkopf and Jacob.⁴ ^e Campaigne and LeSuer⁷ prepared this compound: b. p. 75-78 (1 mm.), *d*₄²⁰ 1.635, *n*_D²⁰ 1.604. ^f M. p. -10°. ^g M. p. -9°.

an acetone solution of the product, concentrating, chilling and diluting with water.

Anal. Calcd. for C₁₄H₁₃BrNO₂S: C, 42.86; H, 4.62; N, 3.57. Found: C, 42.5; H, 5.05; N, 3.60.

The same compound (VI) was also obtained by brominating diethyl 2-thenylacetamidomalonate (V).¹⁰ A solution of 5.0 g. (0.031 mole) of bromine in 50 ml. of glacial acetic acid was slowly added with stirring to 10 g. (0.032 mole) of diethyl 2-thenylacetamidomalonate dissolved in 60 ml. of glacial acetic acid and 25 ml. of water. Dilution with water yielded 11.4 g. (0.029 mole, 91%) of nearly white needles. On recrystallization from 40% ethanol, the compound VI melted at 107-108°; mixed melting point with the first sample, 107-108°.

N-Acetyl-β-2-(5-bromo)-thienylalanine (IX).—Eleven and three-tenths gram (0.029 mole) of VI, hydrolyzed as in the preparation of VIII above, gave 7.9 g. (94%) of IX. The product melted at 177° after recrystallization from 20% ethanol.

Bromination of 1 g. of VIII in the manner described above gave 0.75 g. of IX, m. p. 177°.

Anal. Calcd. for C₉H₁₀BrNO₂S: N, 4.79; neut. equiv., 292. Found: N, 4.82; neut. equiv., 295.

Ethyl 2-(5-Bromo)-thenylacetamidocyanacetate (VII).—Thirteen grams (0.05 mole) of IV was added to 50 ml. of absolute ethanol containing 1.15 g. (0.05 gram atom) of

sodium and 8.5 g. (0.05 mole) of ethyl acetamidocyanacetate. A reaction occurred immediately and a precipitate appeared. The mixture was refluxed for one and one-half hours. The alcohol was evaporated *in vacuo* and 50 ml. of water was added to the residue. The water was evaporated *in vacuo*; the residue was again diluted with 100 ml. of water and chilled for two days. Seventeen grams of dark colored material separated. The product was dissolved in 75 ml. of acetone and treated repeatedly with charcoal until the color of the solution had become a light orange. The solution was concentrated to 40 ml. in a vacuum and chilled for a day. The yield of yellow crystals was 5.2 g. An additional 5.7 g. was recovered from the mother liquor, giving a total of 10.9 g. (0.03 mole, 60%). Recrystallization from 30% ethanol yielded shiny white plates of VII, m. p. 116.5-117°.

Anal. Calcd. for C₁₂H₁₃BrN₂O₂S: N, 8.12. Found: N, 8.04.

β-2-(5-Bromo)-thienylalanine (X).—A solution obtained by the hydrolysis of 7.2 g. (0.025 mole) of IX with 40 ml. of 10% sodium hydroxide for four hours was treated with charcoal, filtered, diluted with 50 ml. of ethanol, neutralized with concentrated hydrochloric acid to pH 6 and chilled. One and two-tenths grams of nearly white plates separated. The mother liquor was evaporated to dryness *in vacuo*, triturated with 30 ml. of water and

filtered. The residue was washed with a little water, ethanol and ether and weighed 1.2 g. Acidification of the filtrate yielded 3.6 g. of unhydrolyzed starting material. The yield of crude amino acid (X), 2.4 g., was therefore 78% of the material which reacted.

The product was dissolved in 25 ml. of hot water containing 3 ml. of concentrated hydrochloric acid, treated with charcoal, filtered, diluted with 30 ml. of ethanol while hot and neutralized with concentrated ammonium hydroxide. The pure amino acid separated on cooling. It melted at 235–238° (capillary) with decomposition and at 256° on a Dennis melting point bar. Another recrystallization did not change the melting point when taken in a capillary tube, but raised the melting point on the bar to 262°.

Anal. Calcd. for $C_7H_9BrNO_2S$: N, 5.60. Found: N, 5.47.

The amino acid was also obtained when 5 g. of VII was refluxed with 50 ml. of 10% sodium hydroxide for eighteen hours. The hot solution was treated with charcoal, filtered, neutralized to pH 6 with concentrated hydrochloric acid and cooled. The precipitate, when purified as before, yielded 1.3 g. of X. Another 280 mg. was recovered by working up the mother liquors.

Two hundred and fifty milligrams of X, when treated with the calculated amount of sodium hydroxide and phenyl isocyanate in the usual manner,¹² yielded 300 mg. of the α -phenylureido derivative of X. Recrystallization from 30% ethanol gave white plates, m. p. 166–167° (capillary), 172–173° on the Dennis melting point bar.

Anal. Calcd. for $C_{14}H_{13}BrN_2O_3S$: neut. equiv., 369. Found: neut. equiv., 367.

Four hundred and twenty milligrams of the N-carboxy derivative of X was obtained by treating 500 mg. of X with the calculated amounts of sodium hydroxide and carbobenzoxy chloride. Recrystallization from dilute ethanol gave white crystals, m. p. 109–110°.

Anal. Calcd. for $C_{15}H_{14}BrNO_4S$: neut. equiv., 384. Found: neut. equiv., 390.

Diethyl 3-(2-Bromo)-thenylacetamidomalonate (XVI).—Four grams (0.0156 mole) of the lachrymatory material (XIV) obtained by the bromination of 3-methylthiophene with two molar equivalents of N-bromosuccinimide was added to 40 ml. of absolute ethanol containing 0.36 g. (0.0156 gram atom) of sodium and 3.38 g. (0.0156 mole) of diethyl acetamidomalonate. The mixture was refluxed for three hours, cooled and diluted with some water. After evaporation to dryness *in vacuo*, more water was added and the mixture was again evaporated to dryness *in vacuo*. The residue was diluted with a little water, chilled, filtered and washed with water. The yield of slightly-colored product was 5.5 g. (90%). Recrystallization from 50% ethanol gave shiny white plates of XVI, m. p. 84.5–85°.

(12) Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen," 5th ed., Julius Springer Verlag, Berlin, 1931, p. 517.

Anal. Calcd. for $C_{14}H_{13}BrNO_2S$: C, 42.86; H, 4.62; N, 3.57. Found: C, 43.0; H, 4.27; N, 3.38.

This compound (XVI) formed a chloromercuri derivative, m. p. 216°.

Summary

The effect of benzoyl peroxide on the bromination of 2-methyl- and 3-methylthiophene by the action of N-bromosuccinimide has been investigated.

When one molar equivalent of N-bromosuccinimide was permitted to react with 2-methylthiophene, the product was mainly 2-methyl-5-bromothiophene with some 2-thenyl bromide. The addition of benzoyl peroxide to this reaction mixture resulted in the formation of mostly 2-thenyl bromide.

When two molar equivalents of N-bromosuccinimide were allowed to react with 2-methylthiophene, the main product was 2-bromomethyl-5-bromothiophene. Benzoyl peroxide did not affect the yield of 2-bromomethyl-5-bromothiophene. The 2-bromomethyl-5-bromothiophene was condensed with ethyl acetamidocyanacetate and diethyl acetamidomalonate to yield solid derivatives which were characterized and hydrolyzed to β -2-(5-bromo)-thienylalanine.

When one molar equivalent of N-bromosuccinimide was permitted to react with 3-methylthiophene in the absence of benzoyl peroxide, the product was mainly 2-bromo-3-methylthiophene, whereas in the presence of benzoyl peroxide 3-bromomethylthiophene was the chief product.

When two molar amounts of N-bromosuccinimide were reacted with 3-methylthiophene in the absence of benzoyl peroxide, the main product was 2,5-dibromo-3-methylthiophene with some 2-bromo-3-bromomethylthiophene. The addition of benzoyl peroxide resulted in the formation of mainly 2-bromo-3-bromomethylthiophene and some 2,5-dibromo-3-methylthiophene. The 2-bromo-3-bromomethylthiophene was characterized and converted to the diethyl 2-bromo-3-thenylacetamidomalonate.

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