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2-Alkylation Reactions of Thiophene and 1-Methylpyrrole with Trialkylboranes

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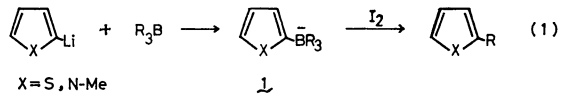
Synopsis. The reactions of iodine with ate-complexes prepared from trialkylboranes and 2-thienyllithium or 1-methyl-2-pyrrolyllithium were found to give the corresponding 2-alkylthiophenes or 1-methyl-2-alkylpyrroles, respectively, in good yields.

Useful methods for obtaining functionalized organic compounds can be found by employing a heterocycle with one hetero atom either as a precursor, reagent, or vehicle for the formation. The most general synthesis of pyrroles and thiophenes involves, as observed in the Knorr reaction, condensation of a carbonyl compound with the corresponding hetero atom containing compound.[1] On the other hand, probably the most available procedure for the synthesis of 2-alkylated derivatives of such heterocycles involves the reaction of the corresponding 2-lithio derivatives with alkyl halides.[2] However, the synthesis is satisfactory only for primary alkyl halides which readily undergo nucleophilic substitution reactions. In the case of *s*-alkyl halide, it may involve a competitive elimination reaction.[3] We wish to report that the reaction of 2-lithiothiophene or 2-lithio-1-methylpyrrole with trialkylboranes, followed by treatment with iodine gives the corresponding 2-alkylated derivatives in good yields (Eq. 1).[4]



X=S, N-Me

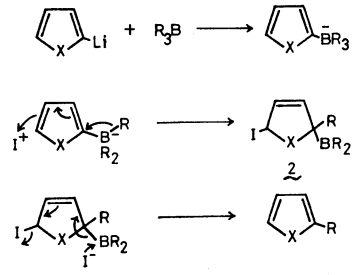
Addition of an equimolar amount of butyllithium in ether to thiophene in ether containing tetramethylethylenediamine (TMEDA) at room temperature resulted in quantitative metalation to give 2-lithiothiophene, which was then treated at room temperature with a solution of triisobutylborane in THF. The reaction of the resulting solution of the ate-complex (**1**) thus obtained with iodine, followed by the usual alkaline hydrogen peroxide oxidation to remove the residual organoborane, provided 2-isobutylthiophene in a 95% yield. The results of reactions with representative trialkylboranes are summarized in Table 1.

In the present reaction, secondary alkyl and aryl groups appear to be introduced as readily as primary alkyl groups. It seems that the reaction proceeds through the same type of reaction path as considered in the reaction of 1-alkynyltriorganoborates with iodine,[5] *i.e. via* three stages: (1) coordination of trialkylboranes with the carbanion derived from the heterocyclic compound, (2) iodine cation attack of the 5-position in the hetero ring with migration of an alkyl group from boron to 2-position, and (3) intermediate (**2**) gives the product by the elimination of dialkyliodoborane (Eqs. 2, 3, and 4).

Table 1. 2-Alkylation of thiophene and 1-methylpyrrole with trialkylboranes[a]

Hetero-cycle	Organoborane R_3B R=	Product	Yield %[b]
Thiophene	Propyl	2-Propylthiophene	62
	Butyl	2-Butylthiophene	91
	Isobutyl	2-Isobutylthiophene	95
	s-Butyl	2-*s*-Butylthiophene	100
	Octyl	2-Octylthiophene	66
	Cyclopentyl	2-Cyclopentylthiophene	100
	Phenyl[c]	2-Phenylthiophene	42[d]
1-Methyl-pyrrole[e]	Propyl	1-Methyl-2-propylpyrrole	92
	Butyl	1-Methyl-2-butylpyrrole	98
	Isobutyl	1-Methyl-2-isobutylpyrrole	80
	s-Butyl	1-Methyl-2-*s*-butylpyrrole	95
	Hexyl	1-Methyl-2-hexylpyrrole	70
	Cyclopentyl	1-Methyl-2-cyclopentylpyrrole	73

a) Thiophene or 1-methylpyrrole: trialkylborane= 1.2:1 b) Based on organoborane used. Analyzed by VPC. c) Prepared from PhMgBr and BF_3 etherate. d) Refluxed for 4 h. e) Metalation of 1-methylpyrrole: To a stirred solution of 1-methylpyrrole and TMEDA in dry ether was added butyllithium, followed by heating at reflux temperature for 2 h.



Experimental

Materials. All the chemicals and solvents were purified by distillation. Trialkylboranes were prepared by the usual procedure.[6]

The IR and NMR spectra were taken on a Hitachi-Perkin-Elmer Model 125 spectrophotometer and Hitachi R-22 spectrometer at 90 MHz using tetramethylsialne as an internal standard, respectively.

General Procedure. A representative procedure for the preparation of 2-butylthiophene is as follows. A dry 50 ml-flask equipped with a magnetic stirring bar, a septum inlet, and a reflux condenser was flushed with nitrogen. The flask

was charged under nitrogen gas with thiophene (0.378 g, 4.5 mmol), TMEDA (0.627 g, 5.4 mmol) and anhydrous ether (5 ml). Butyllithium (4.5 mmol, 3 ml of 1.5 M solution in ether) was then added at room temperature and the mixture was stirred for 1 h. After metalation was complete, tributylborane (3 mmol, 2 ml of 1.5 M solution in THF) was added at room temperature, followed by reflux for 2 h. The solution was cooled to −78 °C and iodine (1.143 g, 4.5 mmol) in 10 ml of dry ether was added. The reaction mixture was stirred for 30 min and allowed to warm to room temperature. After being stirred for 2 h, the mixture was treated with 5 ml of 3 M aqueous sodium hydroxide and 5 ml of 30% hydrogen peroxide at room temperature for 2 h. Saturation of the aqueous solution with potassium carbonate yielded an organic phase. The product was extracted with ether and analyzed by VPC. Analysis indicated the presence of 2.73 mmol (91%) of 2-butylthiophene. An analytically pure material was obtained by preparative VPC. (10% Carbowax 20 M on Uniport B, 3 m) with Varian autoprep Model-2800.

Identification of the Products. *2-Propylthiophene*: n_D^{20} 1.5060. Found: C, 66.48; H, 7.86%. Calcd for $C_7H_{10}S$: C, 66.61; H, 7.99%. Mass; m/e=126 (M^+). IR(neat); 3050, 1460, 850, 820, 690 cm^{-1}. NMR (CCl_4); τ, 9.00 (3H, t, J=6.0 Hz), 8.40 (2H, m), 7.18 (2H, t, J=7.0 Hz), 2.90—3.40 (3H, m).

2-Butylthiophene: n_D^{20} 1.5064. Found: C, 68.47; H, 8.51%. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.62%. Mass; m/e=140 (M^+). IR (neat); 3050, 1460, 850, 820, 690 cm^{-1}. NMR (CCl_4); τ, 9.10 (3H, t, J=7.0 Hz), 8.45 (4H, m), 7.20 (2H, t, J=7.0 Hz), 2.92—3.36 (3H, m).

2-Isobutylthiophene: n_D^{20} 1.4980. Found: C, 68.63; H, 8.59%. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.62%. Mass; m/e=140 (M^+). IR (neat); 3050, 1460, 1385, 1370, 1170, 700 cm^{-1}. NMR (CCl_4); τ, 9.05 (6H, d, J=6.0 Hz,) 8.08 (1H, m), 7.30 (2H, d, J=7.0 Hz), 2.92—3.35 (3H, m).

2-s-Butylthiophene: n_D^{20} 1.5006. Found: C, 68.63; H, 8.58%. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.62%. Mass; m/e=140 (M^+). IR(neat); 3050, 1450, 1380, 860, 820, 690 cm^{-1}. NMR (CCl_4); τ, 9.15 (3H, t, J=6.0 Hz), 8.76 (3H, d, J=7.0 Hz), 8.43 (2H, m), 7.20 (1H, m), 2.92—3.35 (3H, m).

2-Octylthiophene: n_D^{20} 1.4922. Found: C, 73.21; H, 10.35%. Calcd for $C_{12}H_{20}S$: C, 73.40; H, 10.27%. Mass; m/e=196 (M^+). IR (neat); 3050, 1450, 850, 820, 690 cm^{-1}. NMR (CCl_4); τ, 9.10 (3H, t, J=6.0 Hz), 8.10—8.80 (12H, m), 7.17 (2H, t, J=7.0 Hz), 2.90—3.35 (3H, m).

2-Cyclopentylthiophene: n_D^{20} 1.5365. Found: C, 70.88; H, 7.98%. Calcd for $C_9H_{12}S$: C, 71.00; H, 7.94%. Mass; m/e=152 (M^+). IR (neat); 3050, 1440, 859, 820, 690 cm^{-1}. NMR (CCl_4); τ, 7.72—8.55 (8H, m), 6.75 (1H, m), 2.90—3.33 (3H, m).

2-Phenylthiophene: Mp 34—35 °C. Found: C, 74.82; H, 5.11%. Calcd for $C_{10}H_8S$: C, 74.96; H, 5.03%. Mass; m/e=160 (M^+). IR (Nujol); 3050, 1940, 1780, 1590, 1440, 860, 825, 760, 690 cm^{-1}. NMR (CCl_4); τ, 2.18—3.18 (8H, m).

1-Methyl-2-propylpyrrole: n_D^{20} 1.504. Found: C, 77.85; H, 10.59%. Calcd for $C_8H_{13}N$: C, 77.99; H, 10.64%. Mass; m/e=123 (M^+). IR (neat); 3100, 1500, 1310, 1100, 710 cm^{-1}. NMR (CCl_4); τ, 9.00 (3H, t, J=7.0 Hz), 8.37 (2H, m), 7.52 (2H, t, J=7.0 Hz), 6.48 (3H, s), 4.06—4.35 (2H, m), 3.17 (1H, t, J=2 Hz).

1-Methyl-2-butylpyrrole: n_D^{20} 1.486. Found: C, 78.89; H, 10.96%. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02%. Mass; m/e=137 (M^+). IR (neat); 3100, 1500, 1310, 1100, 710 cm^{-1}. NMR (CCl_4); τ, 9.04 (3H, t, J=6.0 Hz), 8.35 (4H, m), 7.50 (2H, t, J=7.0 Hz), 6.48 (3H, s), 4.06—4.35 (2H, m), 3.17 (1H, t, J=2 Hz).

1-Methyl-2-isobutylpyrrole: n_D^{20} 1.515. Found: C, 78.83; H, 11.11%. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02%. Mass; m/e=137 (M^+). IR (neat); 3100, 1490, 1380, 1360, 1090, 700 cm^{-1}. NMR (CCl_4); τ, 9.05 (6H, d, J=6.4 Hz), 8.16 (1H, m), 7.64 (2H, d, J=7.0 Hz), 4.50 (3H, s), 4.06—4.35 (2H, m), 3.17 (1H, t, J=2 Hz).

1-Methyl-2-s-butylpyrrole: n_D^{20} 1.454. Found: C, 78.65; H, 11.13%. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02%. Mass; m/e=137 (M^+). IR (neat); 3100, 1490, 1310, 1100, 700 cm^{-1}. NMR (CCl_4); τ, 9.11 (3H, t, J=7.3 Hz), 8.80 (3H, d, J=6.4 Hz), 8.44 (2H, m), 7.36 (1H, m), 6.42 (3H, s), 4.06—4.35 (2H, m), 3.17 (1H, t, J=2 Hz).

1-Methyl-2-hexylpyrrole: n_D^{20} 1.482. Found: C, 79.85; H, 11.63%. Calcd for $C_{11}H_{19}N$: C, 79.94, H, 11.59%. Mass; m/e=165 (M^+). IR (neat); 3100, 1490, 1310, 1090, 700 cm^{-1}. NMR (CCl_4); τ, 9.10 (3H, t, J=5.0 Hz), 8.20—8.82 (8H, m), 7.49 (2H, t, J=8 Hz), 6.46 (3H, s), 4.06—4.35 (2H, m), 3.17 (1H, t, J=2 Hz).

1-Methyl-2-cyclopentylpyrrole: n_D^{20} 1.518. Found: C, 80.55; H, 10.06%. Calcd for $C_{10}H_{15}N$: C, 80.48, H, 10.13%. Mass; m/e=149 (M^+). IR (neat); 3100, 1490, 1100, 715 cm^{-1}. NMR (CCl_4); τ, 7.82—8.59 (8H, m), 7.04 (1H, m), 6.46 (3H, s), 4.06—4.35 (2H, m), 3.17 (1H, t, J=2 Hz).

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