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Regiospecific Synthesis of 3-Alkylfurans and 3-Alkylthiophenes *via* Organoboranes

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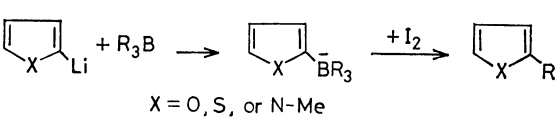
Synopsis. The reaction of bromine or iodine with ate-complexes obtained from trialkylboranes and 3-lithiofuran or 3-lithiothiophene gives the corresponding 3-alkylfurans or 3-alkylthiophenes in good yields, respectively.

Heterocyclic compounds with one hetero atom have been recognized to be useful precursors and reagents for the syntheses of functionalized organic compounds.[1)] Many synthetic procedures of such heterocycles through the alkylation of heterocyclic nuclei have been recently reported.[2–9)] Especially, novel syntheses by the aromatic substitution *via* organoboranes readily obtainable from olefins are being watched with interest.[5–9)] In connection with the synthesis, we reported that the reaction of iodine with ate-complexes prepared from trialkylboranes and 2-lithiofuran,[8)] 2-lithiothiophene[9)] or 1-methyl-2-lithiopyrrole[9)] gave regiospecifically the corresponding 2-alkyl heterocycles in good yields (Scheme 1). One may wonder if the reaction is applicable for the preparation of 3-alkyl heterocycles from organoboranes and the corresponding 3-lithio derivatives. On the other hand, it was reported that there was a large difference of chemical properties between C_2 and C_3 atoms of furans and thiophenes.[10)]



Scheme 1.

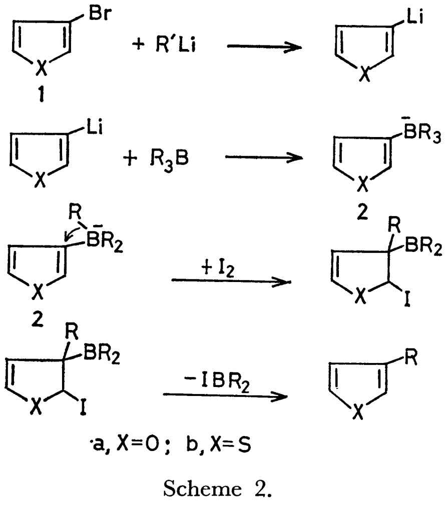
For instance, in the reaction of butyllithium with 3-bromobenzo[*b*]thiophene,[11)] the following carboxylation even at −70 °C gives a mixture of 3-bromobenzo[*b*]thiophene-2-carboxylic acid, benzo[*b*]thiophene-2-carboxylic acid, benzo[*b*]thiophene-3-carboxylic acid, 3-bromobenzo[*b*]thiophene and benzo[*b*]thiophene, indicating that the reaction gives not only the straightforward metal-halogen exchange product but also 3-lithio derivatives as the intermediates. In the course of our studies on the aromatic substitution of heterocycles *via* organoboranes, we attempted the reaction of iodine or bromine with the ate-complexes prepared from trialkylboranes, butyllithium and 3-bromofuran or 3-bromothiophene, and found that the reaction proceeds smoothly without any difficulty to give regiospecifically the corresponding 3-alkylfurans or 3-alkylthiophenes in good yields. The results of reactions with representative trialkylboranes are summarized in Table 1.

In the present reaction, trialkylboranes with bulky alkyl groups such as isobutyl, *s*-butyl, and cyclopentyl seem to give high yields of corresponding 3-alkyl heterocycles. One of the possible procedures for the synthesis of such 3-substituted heterocycles may involve the reaction of 3-lithio derivatives with alkyl halides. Our experiment on the reaction of propyl bromide with 3-lithiothiophene formed from 3-bromothiophene and butyllithium, gave only a trace amount of 3-propylthiophene. Moreover, the synthesis of 3-*s*-alkyl heterocycles by the same method should be hopeless, because secondary alkyl halides readily undergo competitive elimination reactions.[12)] On the other hand, the present reaction is free of this limitation. Secondary groups appear to be introduced more readily than primary groups, as indicated in Table 1. In the case of 3-alkylthiophene synthesis, bromine was found to be more effective as the electrophile than iodine.

TABLE 1. SYNTHESIS OF 3-ALKYLFURANS OR 3-ALKYLTHIOPHENES BY THE REACTION OF ATE-COMPLEXES (**2a** OR **2b**) WITH IODINE OR BROMINE

Heterocycle	Organoborane R_3B, R	Alkyllithium (Solvent)	Halogen	Products[a)] (Yield[b)]/%)
3-Bromofuran	Butyl	BuLi (Et_2O)	I_2	3-Butylfuran (66)
	Butyl	MeLi (THF)		3-Butylfuran (47)
	Isobutyl	BuLi (Et_2O)		3-Isobutylfuran (61)
	Isobutyl	MeLi (THF)		3-Isobutylfuran (61)
	s-Butyl	BuLi (Et_2O)		3-*s*-Butylfuran (91)
	s-Butyl	MeLi (THF)		3-*s*-Butylfuran (85)
	s-Butyl	*t*-BuLi (THF)		3-*s*-Butylfuran (68)
	Cyclopentyl	BuLi (Et_2O)		3-Cyclopentylfuran (76)
	Hexyl	BuLi (Et_2O)		3-Hexylfuran (67)
3-Bromothiophene	Butyl	BuLi (Et_2O)	Br_2	3-Butylthiophene (64)
	Butyl	BuLi (Et_2O)	I_2	3-Butylthiophene (11)
	Isobutyl	BuLi (Et_2O)	Br_2	3-Isobutylthiophene (66)
	Isobutyl	BuLi (Et_2O)	I_2	3-Isobutylthiophene (9)
	s-Butyl	BuLi (Et_2O)	Br_2	3-*s*-Butylthiophene (75)
	s-Butyl	BuLi (Et_2O)	I_2	3-*s*-Butylthiophene (77)
	Cyclopentyl	BuLi (Et_2O)	Br_2	3-Cyclopentylthiophene (81)
	Cyclopentyl	BuLi (Et_2O)	I_2	3-Cyclopentylthiophene (29)
	Hexyl	BuLi (Et_2O)	Br_2	3-Hexylthiophene (54)
	Hexyl	BuLi (Et_2O)	I_2	3-Hexylthiophene (11)

a) All products were either compared with authentic samples or exhibited analytical data and spectra in accodance with the assigned structures. b) Based on the organoborane used and determined by VPC.



Scheme 2.

The reaction mechanism, although not explored in detail, could be considered to proceed through the following pathway (Scheme 2).

Experimental

Materials. All the chemicals and solvents were purified by distillation before use. Trialkylboranes were prepared by the usual procedure.[13] 3-Bromofuran was prepared by the Nazarova's method.[14]

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

General Procedure. A representative procedure for the preparation of 3-*s*-butylfuran is as follows. A dry 50 ml round-bottomed flask equipped with a condenser, a septum inlet and a magnetic stirring bar was flushed with nitrogen. In the flask was placed 3-bromofuran (3 mmol, 0.27 ml) and anhydrous ether (5 ml) under nitrogen gas. Then butyllithium (3 mmol, 1.54 ml of a 1.95 M solution in ether) was added dropwise at −78 °C to form 3-lithiofuran.[15] The mixture was stirred for 30 min. After metallation was complete, tri-*s*-butylborane (3 mmol, 1.5 ml of a 2 M solution in THF) was added to the mixture at −78 °C, followed by stirring for 30 min. The solution was allowed to warm to 0 °C and then stirred again for 30 min. Finally, a solution of iodine (3 mmol, 0.726 g in 10 ml of ether) was fed in at −78 °C. The reaction mixture was allowed again to warm to room temperature and stirred for 2 h. In order to remove the residual organoborane, the mixture was treated with 3 M aqueous sodium hydroxide (2 ml), followed by a dropwise addition of 30% hydrogen peroxide (1 ml). The product thus obtained was extracted three times with ether and the combined organic layer was dried over magnesium sulfate. VPC analysis (15% Silicone DC-550 on Uniport B, 120 °C) indicated that 2.73 mmol (91%, based on tri-*s*-butylborane) of 3-*s*-butylfuran had been obtained. An analytically pure material was obtained by preparative VPC (15% Silicone DC-550 on Uniport B, 3 m) with Varian Autoprep Model-2800.

Identification of the Products. *3-Butylfuran*: n_D^{20} 1.4705. Found: C, 77.02: H, 9.85%. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74%. Mass; *m/e*=124 (M^+). IR(neat); 3150, 1520, 885, 780 cm^{-1}. NMR(CCl_4): δ, 0.95 (3H, t, *J*=7.0 Hz), 1.50 (4H, m), 2.42 (2H, t, *J*=7.0 Hz), 6.20—7.30 (3H, m).

3-Isobutylfuran: n_D^{20} 1.4580. Found: C, 77.26; H, 9.68%. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74%. Mass; *m/e*=124 (M^+). IR(neat); 3150, 1515, 885, 780 cm^{-1}. NMR(CCl_4); δ, 0.95 (6H, d, *J*=6.0 Hz), 1.90 (1H, m), 2.34 (2H, d, *J*=7.0 Hz), 6.20—7.30 (3H, m).

*3-*s*-Butylfuran*: n_D^{20} 1.4595. Found: C, 77.14; H, 9.86%. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74%. Mass; *m/e*=124 (M^+). IR(neat); 3150, 1515, 885, 785 cm^{-1}. NMR(CCl_4); δ, 0.95 (3H, t, *J*=7.0 Hz), 1.20 (3H, d, *J*=7.0 Hz), 1.57 (2H, m), 2.58 (1H, m), 6.25—7.30 (3H, m).

3-Cyclopentylfuran: n_D^{20} 1.4660. Found: C, 79.19; H, 8.71%. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88%. Mass; *m/e*=136 (M^+). IR(neat); 3150, 1510, 885, 780 cm^{-1}. NMR(CCl_4); δ, 1.35—2.18 (8H, m), 2.87 (1H, m), 6.22—7.30 (3H, m).

3-Hexylfuran: n_D^{20} 1.4820. Found: C, 78.73; H, 10.61%. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59%. Mass; *m/e*=152 (M^+). IR(neat); 3150, 1515, 885, 780 cm^{-1}. NMR (CCl_4); δ, 0.90 (3H, t, *J*=6.0 Hz), 1.17—1.78 (8H, m), 2.30 (2H, t, *J*=7.0 Hz), 6.20—7.30 (3H, m).

3-Butylthiophene: n_D^{20} 1.5680. Found: C, 68.45; H, 8.70%. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.51%. Mass; *m/e*=140 (M^+). IR(neat); 3120, 1460, 850, 680 cm^{-1}. NMR(CCl_4); δ, 0.90 (3H, t, *J*=7.0 Hz), 1.30—1.72 (4H, m), 2.63 (2H, t, *J*=7.0 Hz), 6.80—7.22 (3H, m).

3-Isobutylthiophene: n_D^{20} 1.5475. Found: C, 68.38; H, 8.37%. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.51%. Mass; *m/e*=140 (M^+). IR(neat); 3120, 1465, 855, 690 cm^{-1}. NMR(CCl_4); δ, 0.93 (6H, d, *J*=6.0 Hz), 1.93 (1H, m), 2.52 (2H, d, *J*=7.0 Hz), 6.80—7.25 (3H, m).

*3-*s*-Butylthiophene*: n_D^{20} 1.5490. Found: C, 68.66; H, 8.72%. Calcd for $C_8H_{12}S$; C, 68.51; H, 8.51%. Mass; *m/e*=140 (M^+). IR(neat); 3120, 1460, 850, 680 cm^{-1}. NMR(CCl_4); δ, 0.83 (3H, t, *J*=6.0 Hz), 1.22 (3H, d, *J*=7.0 Hz), 1.57 (2H, m), 2.73 (1H, m), 6.80—7.25 (3H, m).

3-Cyclopentylthiophene: n_D^{20} 1.5642. Found: C, 70.84; H 7.90%. Calcd for $C_9H_{12}S$: C, 71.00; H, 7.94%. Mass; *m/e*=152 (M^+). IR(neat); 3120, 1450, 860, 680 cm^{-1}. NMR(CCl_4); δ, 1.47—2.23 (8H, m), 3.05 (1H, m), 6.80—7.25 (3H, m).

3-Hexylthiophene: n_D^{20} 1.5790. Found: C, 71.43; H, 9.48%. Calcd for $C_{10}H_{16}S$: C, 71.36; H, 9.60%. Mass; *m/e*=168 (M^+). IR(neat); 3120, 1460, 855, 680 cm^{-1}. NMR(CCl_4); δ, 0.90 (3H, t, *J*=6.0 Hz), 1.15—1.78 (8H, m), 2.63 (2H, t, *J*=7.0 Hz), 6.80—7.25 (3H, m).

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