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AROMATIC SUBSTITUTION VIA ORGANOBORANES 2. REGIOSPECIFIC ALKYLATION OF THE FURAN AND PYRROLE NUCLEUS

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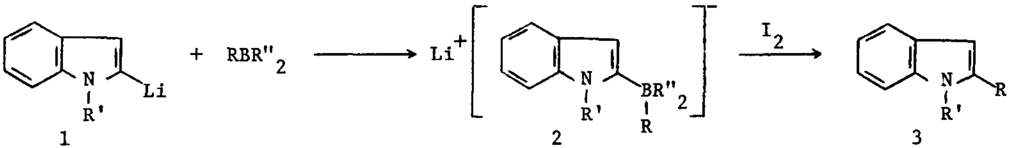
Summary: Reaction of 2-lithiofuran or 1-methyl-2-lithiopyrrole with trialkylboranes leads to a borate salt. Subsequent treatment with an appropriate electrophile such as NCS leads to the 2-alkylfuran or 1-methyl-2-alkylpyrrole.

Electrophilic substitution is among the most important methods known for the functionalization of benzene and related aromatic derivatives.[1] In sharp contrast, heteroaromatics show variable response in electrophilic substitution reactions.[2] Furans and pyrroles, in particular, respond poorly to typical Friedal-Crafts conditions. Instead, nonselective substitution, polymerization or ring destruction is usually observed.

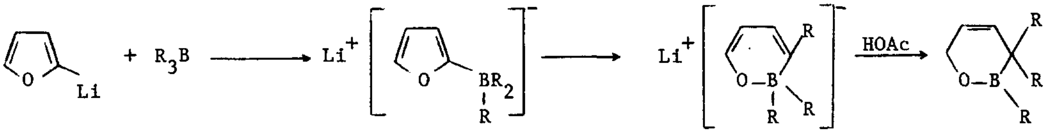
We have recently demonstrated[3] a novel method for regiospecifically substituting the indole nucleus at the two-position via organoboranes (eq 1). In principle, this methodology should be applicable to a variety of aromatic systems.[4,5] Suzuki[6] has reported, however, that 2-lithiofuran reacts with trialkylboranes to give ring fragmentation, followed by transfer of a second alkyl group, presumably in the workup (eq 2).[7]



1 2 3

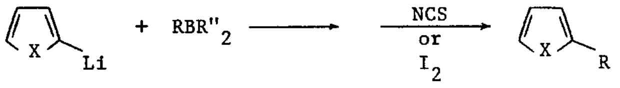
(1)

1a: R' = Me $R''_2 = R_2$ or 9-BBN
1b: R' = SO_2Ph



(2)

In light of our recent results with the indole system, we have investigated the reaction of 2-lithiofuran[8] and 1-methyl-2-lithiopyrrole[9] with trialkylboranes. We wish to report that these salts are stable at low to moderate temperatures. Subsequent treatment with iodine or NCS leads to moderate to excellent yields of the 2-alkylated heterocycle (eq 3). Furthermore, B-alkyl-9-BBN derivatives[10] selectively transfer the alkyl group. The results are summarized in Table I.



(3)

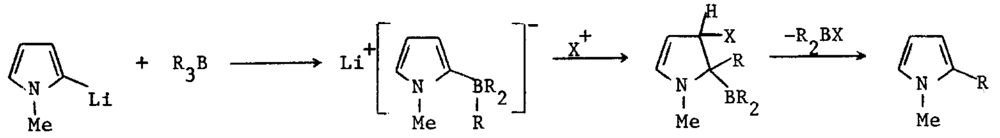
4

4a: X = O $R''_2 = R_2$ or 9-BBN

4b: X = N-Me

It is interesting that in contrast to the indole and pyrrole borate salts, the furan derivatives give only low yields of alkylated products on treatment with halogens. Thus, in this case, the choice of electrophile is crucial. Of those tested, only NCS provides satisfactory results.[11]

In principle, one can rationalize these results via attack of an electrophile at the 2-, 3-, or 5-positions. However, in view of the related reactions of alkenyl-[12], indolyl-[3] and arylborate salts[4], we tend to prefer initial attack at the 3-position. Our rationale is outlined for the pyrrole case. Initial complexation leads to an "ate" complex. Subsequent attack by the electrophile followed by alkyl group migration leads to 5. β-Haloboranes similar to 5 are known to eliminate R_2BX under a variety of conditions.[13] Thus, a thermal syn elimination or a base catalyzed anti elimination upon workup leads directly to the 2-alkylated pyrrole (eq 4).



(4)

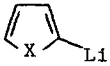
X = I_2 or NCS

5

In summary, we have now demonstrated that these arylborate salts are stable thermally and may be used to regiospecifically substitute the heterocyclic nucleus. This type of reaction circumvents the problems encountered in S_n2 reactions of aryllithiums and in typical electrophilic substitution reactions. Thus, it should have important implications for the synthesis of these heterocycles. In view of the similarity of these intermediates to the alkynlborate salts,[14] we are presently exploring the reactivity of these and other heterocyclic borates with a variety of electrophiles, including simple alkylating agents. In addition, we are exploring the use of a protecting group for nitrogen in the pyrrole derivative. These results will be the subject of a forthcoming publication.

The following procedure is representative.[15] A dry 50 mL round bottom flask equipped with a magnetic stirring bar and septum capped inlet is assembled hot and allowed to cool under a nitrogen purge. A static pressure of nitrogen is maintained in the system until after the oxidation. The flask is charged with 5 mL of THF and cooled to -25°C. To the flask is added 2.08 mL (5 mmol) of n-butyllithium in hexane followed by 0.36 mL (5 mmol) of furan.[9] The solution is allowed to warm to 15°C, stirred for 0.5 h and then cooled to -15°C. To this solution is added 9.97 mL (5 mmol) of a solution of B-n-hexyl-9-BBN in THF and the mixture stirred for 10 min. To this solution 0.702 g (5.25 mmol) of NCS dissolved in 18 mL of THF is added slowly.

Table I. The Regiospecific Alkylation of 2-Lithiated Pyrroles[a] and Furans[b] *via* Organoboranes.

Organoborane[c,d]	 X =	Electrophile[e,f]	Product[g]	Yield,[h,i] %
tri-*n*-hexyl	0	NCS	2-*n*-hexylfuran	82
B-*n*-hexyl-9-BBN	0	NCS		72 (51)
triisobutylborane	0	NCS	2-isobutylfuran	76
B-isobutyl-9-BBN	0	NCS		82
tri-*sec*-butylborane	0	NCS	2-*sec*-butylfuran	70
B-*sec*-butyl-9-BBN	0	NCS		67
tricyclopentylborane	0	NCS	2-cyclopentylfuran	73
B-cyclopentyl-9-BBN	0	NCS		73
tricyclohexylborane	0	NCS	2-cyclohexylfuran	74
B-cyclohexyl-9-BBN	0	NCS		74
tri-*n*-hexylborane	N-Me	NCS	1-methyl-2-*n*-hexylpyrrole	59
	N-Me	I_2		41
B-*n*-hexyl-9-BBN	N-Me	NCS		44
	N-Me	I_2		39
tri-2-methyl-1-pentylborane	N-Me	NCS	1-methyl-2-(2-methyl-1-pentyl)-pyrrole	66
	N-Me	I_2		72
B-2-methyl-1-pentyl-9-BBN	N-Me	NCS		39
	N-Me	I_2		41
tri-*sec*-butylborane	N-Me	I_2	1-methyl-2-*sec*-butylpyrrole	75
B-*sec*-butyl-9-BBN	N-Me	I_2		53
tricyclopentylborane	N-Me	I_2	1-methyl-2-cyclopentyl-pyrrole	59
B-cyclopentyl-9-BBN	N-Me	I_2		45
tricyclohexylborane	N-Me	NCS	1-methyl-2-cyclohexylpyrrole	63
	N-Me	I_2		86
B-cyclohexyl-9-BBN	N-Me	NCS		42
	N-Me	I_2		52

[a] Prepared by addition of 6 mmol of *t*-butyllithium to 5 mmol of *N*-methylpyrrole in 5 mL of THF at -30°C. The solution is allowed to stir at 15°C for 1 h. Lithiation is greater than 90%. [b] Prepared by addition of 5 mmol of furan to 5 mmol of *n*-butyllithium dissolved in 5 mL of THF at -25°C. The solution is stirred for 0.5 h at 15°C. [c] 5 mmol of the borane added at -15°C to the furanyllithium and stirred 10 min. [d] 5 mmol of the borane added at -78°C to the pyrryllithium and stirred 10 min. [e] 5.0 mmol of NCS added as a ca. 0.25 M solution in THF. [f] 5.0 mmol of I_2 as a ca. 1 M solution in THF. [g] All compounds exhibited spectral data in accordance with their structure and gave satisfactory elemental composition by elemental analysis or high resolution mass spectrometry. [h] Analysis by GLC vs. an internal standard. [i] Isolated yields in parenthesis.

The solution is stirred for 1 h. For isolation[16] the mixture is warmed to room temperature and poured into 140 mL of pentane, and 0.36 g (6.0 mmol) of 2-aminoethanol added. After stirring for 0.5 h the precipitate is gravity filtered and the solvent removed in vacuo. The resultant oil is separated on an 80 g column of activity IV neutral alumina. Elution of 60-100 mL of hexane results in 0.428 g of crude furan. Kugelrohr distillation gives 0.39 gms (51%) of 2-*n*-hexylfuran (pot temperature 100-122° @ 16 mm Hg).

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8. V. Ramanathan and R. Levine, J. Org. Chem., 27, 1216 (1962).
9. We have used a modification of the procedure of: S. Gronowitz and N. Gjos, Acta Chemica Scandinavia, 22, 2596 (1971); see Table I, footnote a.
10. 9-BBN is commercially available from Aldrich Boranes, a division of Aldrich Chemical Company.
11. Electrophiles investigated include, I_2, Br_2, Cl_2, NCS, NBS, NIS, and 2,5-dinitrobenzenesulfenylchloride.
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15. All reactions were handled under an inert nitrogen atmosphere using techniques described in: H. C. Brown, G. W. Kramer, A. B. Levy and M. M. Midland, "Organic Synthesis via Boranes," Wiley-Interscience, New York, N.Y., 1975, chapter 9.
16. For analysis by GLC the mixture is washed three times with 5 mL of 3N NaOH, then oxidized by addition of 5 mL of 3N NaOH and 2 mL of 30% H_2O_2.

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