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AROMATIC SUBSTITUTION VIA ORGANOBORANES 3. SIMULTANEOUS REGIOSPECIFIC FUNCTIONALIZATION OF THE INDOLE NUCLEUS AT THE 2- AND 3-POSITIONS

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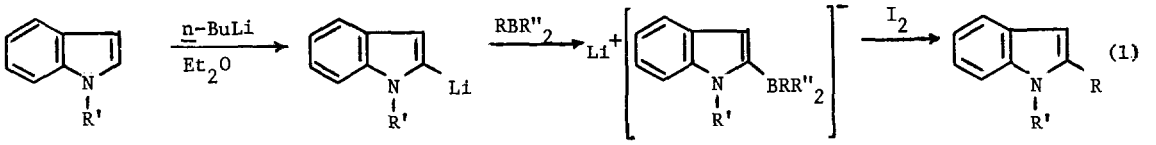
Summary: Reaction of 1-methyl-2-lithioindole with trialkylboranes leads to a borate salt. Treatment with carbon electrophiles leads to regiospecifically substituted 2,3-dialkylindoles.

Simple functionalized indoles are of interest[1] because of their biological properties, their industrial uses, and their potential as intermediates in the synthesis of biologically active indole alkaloids. Since its discovery in 1883, the Fisher indole synthesis[2] has remained the most versatile approach to the indole nucleus. Yet it and various related approaches to substituted indoles are based on specifically substituted benzene derivatives as starting materials. In contrast to the many well known aromatic substitution reactions of benzene and its derivatives there are relatively few synthetically useful substitution reactions for the indole nucleus. Our recent interest in aryltrialkylborate salts[3-5] derived from 2-lithioindoles[5a] has led to a novel method for functionalizing the indole nucleus at the 2-position (eq 1). We now wish to report



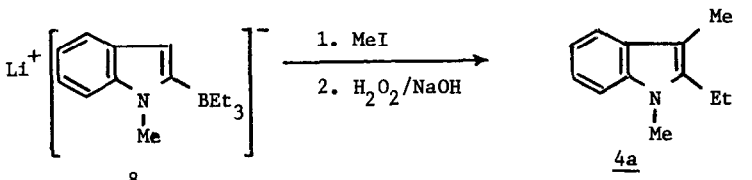
(1)

1 2 3

1a R' = Me R" = R or 9-BBN
1b R' = SO_2Ph

that the intermediate salt 2a is extremely nucleophilic. For example treatment of 2a (R=R"=Et) with methyl iodide at room temperature leads upon oxidation to an 82% yield of 1,3-dimethyl-2-ethylindole (eq 2). Furthermore, in some cases the B-alkyl-9-BBN[6] derivatives may be useful. In view of the ready availability of 2-lithioindoles[7] and the ease of carrying out this reaction we have investigated a number of boranes and electrophiles. The results are summarized in Table I.

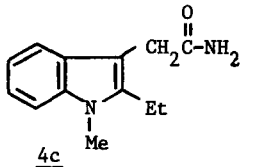
Many indole alkaloids contain as a basic part of their skeleton the indole nucleus with a β-aminoethyl unit at the 3-position. Therefore the regiospecific formation of 4c by treatment of



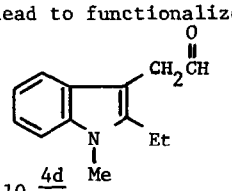
(2)

4a

2a with iodoacetonitrile[8] or iodoacetamide are particularly important. Reduction with LAH should lead to β-aminoethylindoles.[9] Similarly, 4d should lead to functionalized derivatives by

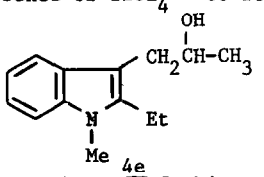


4c

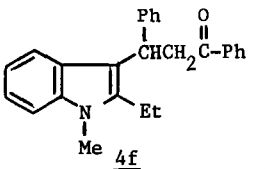


4d

reductive amination with amines and sodium cyanoborohydride.[10] As final indications of the reactivity of 2a we note its ability to open epoxides and add in 1,4-fashion to α,β-unsaturated ketones in the presence of $TiCl_4$[11] to form 4e and 4f respectively.



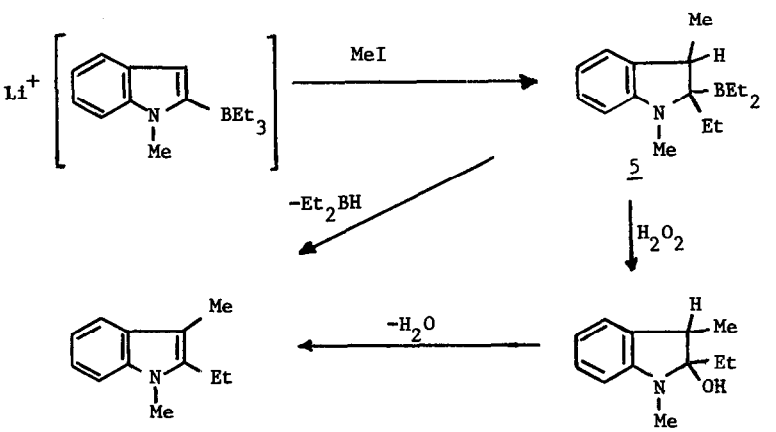
4e



4f

Presumable the mechanism of this reaction is analogous to the alkylation of alkynl-[12] and aryltrialkylborate salts. A rationale is outlined in Scheme I for 2a (R=R"=Et) and methyl iodide. Thus alkylation of 2a, by methyl iodide with migration of an alkyl group from boron to carbon leads to 5. Two paths are available for conversion of 5 to 4a. Oxidation leads to the 2-hydroxyindoline which is expected to rearomatize by loss of water. Alternately, dehydroboration leads directly to the desired product. We presently favor the former path because of the absence of hydrogen evolution upon quenching with aqueous media.

Scheme I



4a

In summary, the present development provides a unique one-pot reaction for functionalizing the 2- and 3- positions of N-aklylindoles. To be generally useful, however, one requires a

Table I. Regiospecific 2,3-Dialkylation of 1-Methyl-2-lithioindole[a] via Organoboranes[15]

Organoborane[b]	Electrophile[c]	Product[d,e]	Yield,[f] %
triethylborane	methyl iodide	1,3-dimethyl-2-ethylindole (4a)	80
	allylbromide	1-methyl-2-ethyl-3-allylindole (4b)	94
	iodoacetamide	1-methyl-2-ethylindol-3-yl-acetamide (4c)	(53)
	iodoacetonitrile		(61)[h]
	bromoacetaldehyde diethylacetal	1-methyl-2-ethylindol-3-yl-acetaldehyde (4d)[g]	(54)
	propylene oxide	1-methyl-2-ethyl-3-(2-hydroxy-prop-1-yl)-indole (4e)	(66)
	chalcone/$TiCl_4$	β-(1-methyl-2-ethylindol-3-yl)-β-phenylpropiophenone (4f)[i]	(50)
triisobutylborane	methyl iodide	1,3-dimethyl-2-isobutyl-indole (4g)	85
B-isobutyl-9-BBN[j]			64
tri-sec-butylborane		1,3-dimethyl-2-sec-butyl-indole (4h)	30,50[k]
B-sec-butyl-9-BBN[j]			-
tricyclopentylborane		1,3-dimethyl-2-cyclopentyl-indole (4i)	84
B-cyclopentyl-9-BBN[j]			26

[a] 5 mmol in 10mL of ether. [b] 5 mmol added neat or as a 0.5M-1.0M solution in THF at -80°C. [c] 5.25 mmol added neat or as a ca. 1M solution in THF. [d] Reactions are allowed to warm to room temperature and stirred for 16-20 hours unless otherwise noted. [e] Workup involves washing 3 times with 5 ml of 3N NaOH and oxidation with 2 ml of 30% H_2O_2 and 5 ml of 3N NaOH. [f] Analysis by GLC vs. an internal standard. Isolated yields are in parenthesis. [g] After hydrolysis with 5% HCl in THF for 24 hours. [h] The nitrile is hydrolyzed by the basic hydrogen peroxide. [i] Washed with water instead of 3N NaOH then oxidized in the usual manner. [j] Reactions involving B-alkyl-9-BBN derivatives were run on a 2.5 mmol scale. [k] Stirred for 36 hours at R.T. before oxidation.

suitable protecting group for nitrogen. Unfortunately, salts derived from 2-lithio-N-benzenesulfonylindole (1a)[7] fail to undergo this reaction. We are therefore exploring a variety of N-protected 2-lithioindoles in this sequence. Finally, in the light of our recent successful halogen-mediated coupling of pyrryl- and furanylborate salts,[5c] this alkylation procedure may be applicable to a variety of aromatic heterocycles.

The following procedure is representative.[13] A dry 50-mL round-bottom flask equipped with a septum-capped side arm and reflux condenser was connected to an oil bubbler. The system was purged and maintained under nitrogen until after oxidation. To this flask was added sequentially 5 mL of THF, 0.66 mL (5 mmol) of N-methylindole and 3.43 mL (5.25 mmol) of n-butyllithium. The solution was heated under reflux for 5 hours, cooled to -80°C, and 0.71 mL

(5 mmol) of triethylborane added. The mixture was stirred for 10 min, and 0.398 mL (5 mmol) of iodoacetonitrile added. The solution was warmed to room temperature and stirred overnight, then washed three times with 5 mL of 3N NaOH under nitrogen.[14] The solvent is removed by water aspirator, and 5 mL of THF, 5 mL of ethanol, and 5 mL of 3N NaOH added. The borane is oxidized by the addition of 5 mL of 30% hydrogen peroxide and heating under reflux for 1 h. The organic layer was diluted with 1:1 THF/ether, washed with water, dried ($MgSO_4$) and the solvent removed under vacuum to give 0.82 g of a crude yellow solid. Recrystallization from 95% ethanol gave 0.66 g (61%) of analytically pure 1-methyl-2-ethylindol-3-ylacetamide (mp 154-5°C).

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13. All reactions were handled under an inert nitrogen atmosphere using techniques described in: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M., "Organic Synthesis via Boranes", Wiley-Interscience, New York, N.Y., 1975; Chapter 9.
14. Alkylations with unhindered alkylating agents and boranes (i.e., triethylborane) were oxidized at this point by the addition of 5 mL of 3N NaOH and 2 mL of 30% hydrogen peroxide.
15. All compounds exhibited spectral data (IR, NMR) in accordance with their structures and gave satisfactory elemental composition by elemental analysis or high resolution mass spectrometry.

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