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CONVENIENT SYNTHETIC EQUIVALENTS OF 2-LITHIOPYRROLE AND 2,5-DILITHIOPYRROLE

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Summary: Bromination of pyrrole by 1,3-dibromo-5,5-dimethylhydantoin, followed by direct reaction with BOC anhydride and DMAP, affords the stable N-BOC dervatives of 2-bromopyrrole and 2,5-dibromopyrrole. Lithium-halogen exchange of the latter with n-butyllithium generates the N-BOC derivatives of 2-lithiopyrrole, 2,5-dilithiopyrrole or 5-bromo-2-lithiopyrrole, which react with various electrophiles to give substituted N-BOC pyrroles in excellent yield.

The direct metal-hydrogen exchange of the α-hydrogens of pyrrole is not possible due to the presence of the acidic proton of the pyrrole nitrogen. Monolithiation of N-benzenesulfonylpyrrole and of N-BOC pyrrole have been reported, but the former proceeds with partial loss of the protecting group while the latter requires the use of the expensive base lithium tetramethylpiperidide.[1]

2-Bromopyrrole (**1**) and 2,5-dibromopyrrole (**2**) are formed by the reaction of pyrrole with NBS, but these compounds have seen no use in synthesis due to their great tendency to autodecomposition upon attempted isolation.[2] We now report that bromopyrroles **1** and **2**, prepared advantageously from pyrrole and 1,3-dibromo-5,5-dimethylhydantoin, may be converted *in situ* and in good yield into their stable N-BOC (t-butyloxycarbonyl) derivatives **3** and **4**,[3] which are valuable intermediates for the synthesis of a wide variety of α-substituted pyrroles.

Bromides **3** and **4** undergo halogen-lithium exchange readily with one equivalent n-butyllithium (THF, -78°, 5 min) to give the lithio derivatives **5** and **6**, respectively; using two equivalents of n-butyllithium under the same conditions, dibromide **4** affords the dilithio derivative **7**.

Table I shows a number of N-BOC substituted pyrroles which we have obtained in good to excellent yield by reaction of the lithio derivatives **5-7** with various electrophiles. Since the N-BOC protecting group is easily removed in the pyrrole series either by thermolysis[4] or by methoxide in methanol,[1] the protocol illustrated above offers a new and convenient route to many 2-substituted and 2,5-disubstituted pyrroles starting with the parent heterocycle.

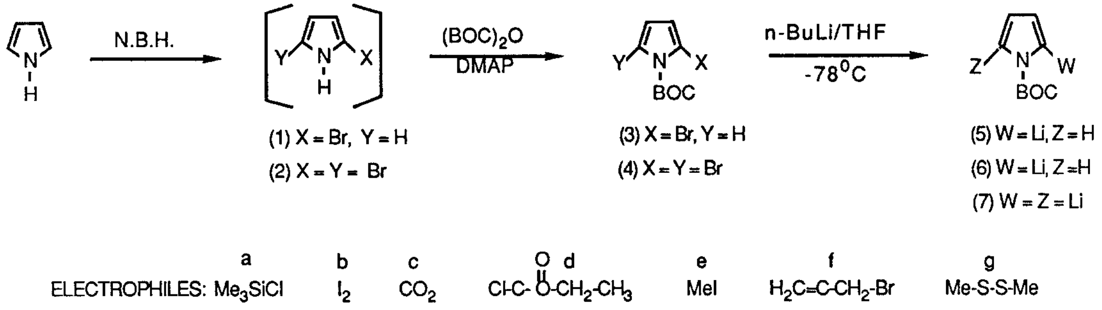

Table I

Entry	Starting material	Products	Yield(%)
1	5	5a : W = TMS	84
2	5	5b : W = I	86
3	5	5c : W = CO_2H	70
4	6	6c : W = CO_2H	68
5	6	6d : W = CO_2Et	90
6	7	7a : W = Z = TMS	81
7	7	7b : W = Z = I	78
8	7	7c : W = Z = CO_2H	70
9	7	7e : W = Z = Me	95
10	7	7f : W = Z = CH_2-CH = CH_2	72
11	7	7g : W = Z = SMe	98

REFERENCES AND NOTES

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3. Hexane solutions (~20-25%) of bromopyrroles 1 and 2 were reacted with BOC anhydride in the presence of catalytic amounts of DMAP and a couple of drops of triethylamine. The overall yields of 3 (oil) and 4 (m.p. 80^{0}C) from pyrrole were 88% and 81%, respectively.

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