3-Alkylation of the Pyrrole Ring. III[1]

Sir:

With the exception of nitrosation of pyrroles[2] and the formation of 2-methyl-3-selenocyanatopyrrole from 2-methylpyrrole and selenocyanogen,[3] preferential substitution at the 3 position of the pyrrole ring is unknown, although widely investigated.[4] We find that pyrrolylmagnesium chloride in ethyl ether is alkylated with ethylene oxide at predominantly the 3 position yielding (39%)[5] 2-pyrrol-2-ylethanol (I) and 2-pyrrol-3-ylethanol (II) in a ratio of 1:3 (vpc).[6] Moreover, in tetrahydrofuran II is the only monoalkyl product (16%) that we have been able to isolate. The isomeric hydroxyethylpyrroles were identified by elemental analysis and spectral properties.[7] Also, lithium aluminum hydride reduction of II-tosylate gave 3-ethylpyrrole, which was identical with the Wolff–Kishner reduction product from 3-acetylpyrrole.[1]

The preference for 3-alkylation indicates that the reaction takes place *via* the epoxide and not by way of the possible intermediate di-2-chloroethoxymagnesium, from the reaction of the epoxide and magnesium–chlorine bond breaking in the Grignard reagent,[10] for the chlorohydrin derivative would be expected to favor 2-alkylation.[8] A rationale for our results, albeit not the only one, can be offered in terms of the relative solvating power of the ethers: tetrahydrofuran > ethylene oxide > ethyl ether,[11] and steric hinderance to intermolecular alkylation at the 2 position of the pyrrole ring due to ether molecules complexed with magnesium, which is bonded at the ring nitrogen.[8a,12] In ethyl ether, replacement of the solvent ligands by ethylene oxide and reaction of the complexed epoxide with the nearby 2 position of the pyrrole ring yield I. Models[13] show that the 3 position is too far away to become involved in this way, and instead reaction occurs at this position by a separate intermolecular mechanism to form II. The stronger solvent tetrahydrofuran is not displaced from coordination with magnesium by ethylene oxide and as a result substitution does not occur at the 2 position, but takes place solely at the 3 position in this solvent.

Pyrrolylmagnesium bromide reportedly[14] reacts with ethylene oxide in ethyl ether–benzene to form I. Similarly, in the first step of the first claimed synthesis of the alkaloid hygrine, the same Grignard reagent with propylene oxide in ethyl ether was thought to yield 1-pyrrol-2-yl-2-propanol.[15] Both of these earlier reports now seem questionable.[16] However, pyrrolylmagnesium chloride apparently reacts with trimethylene oxide in ethyl ether to form 3-pyrrol-2-yl-1-propanol and 3-pyrrol-3-yl-1-propanol in a ratio of 4:1.[17]

(1) For the preceding report in this series see A. J. Castro, J. R. Lowell, Jr., and J. P. Marsh, Jr., *J. Heterocyclic Chem.*, **1**, 207 (1964).
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(5) Uncorrected for recoverable pyrrole.
(6) Carbowax 20M, Varian Aerograph Co., Walnut Creek, Calif.
(7) Isomeric pair, bp 161° (2 mm). *Anal.* Calcd for C_6H_9NO: C, 64.8; H, 8.16; N, 12.60. Found: C, 65.01; H, 8.30; N, 12.70. For I (vpc) ir: OH and NH 3.02, ring H in-plane deformations[8a,9] 8.96, 9.15 μ; nmr ($CDCl_3$, internal TMS): NH τ 1.00 (broad singlet), ring H-5 3.55 (multiplet), ring H-4 3.90 (multiplet), ring H-3 4.05 (multiplet), carbinol CH_2 6.20 (triplet), ring-bonded CH_2 7.20 (triplet), OH 7.95 (singlet), expected integrals. For II (vpc) ir:[9] OH and NH 2.99 μ; nmr: NH 1.70 (broad singlet), ring H-2 and H-5 3.30 (multiplet), ring H-4 3.90 (multiplet), carbinol CH_2 6.23 (triplet), ring-bonded CH_2 7.27 (triplet), OH 7.97 (singlet), expected integrals.
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(11) R. J. Gritter, "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1967, pp 378–380.
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(13) Framework Molecular Models, Prentice-Hall, Inc., Englewood Cliffs, N. J.
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(16) After this communication was accepted for publication, the recent paper by F. Moll and H. Thoma, *Arch. Pharm. (Weinheim)*, **301**, 872 (1968), became available to us. These workers have found that the reaction with ethylene oxide in the Hess procedure does indeed yield I and II, in approximately equal amounts, as the major product and a small amount of the third possible isomer, 2-pyrrol-1-ylethanol.
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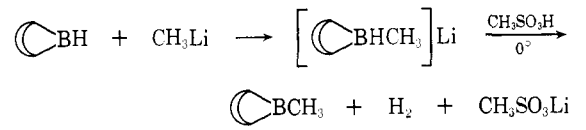
The Reaction of Ethyl Haloacetates and α-Bromo Ketones with B-Aryl-9-borabicyclo[3.3.1]nonanes under the Influence of Potassium *t*-Butoxide. A New Convenient Procedure for the α Arylation of Ketones and Esters

Sir:

Under the influence of potassium *t*-butoxide organoboranes react with ethyl bromoacetate,[1] ethyl dihaloacetates,[2] and various α-bromo ketones[3] to give the corresponding esters, α-halo esters, ethyl dialkylacetates, and α-alkyl ketones. Application of the B-alkyl-9-borabicyclo[3.3.1]nonane derivatives[4] (B-alkyl-9-BBN) circumvented some of the difficulties encountered with the more hindered trialkylboranes[2,3] and greatly improved the utilization of the alkyl groups.[5,6]

We now wish to report that B-alkyl- and B-aryl-9-BBN may be readily synthesized from the corresponding organolithium derivatives and 9-BBN (eq 1 and 2).



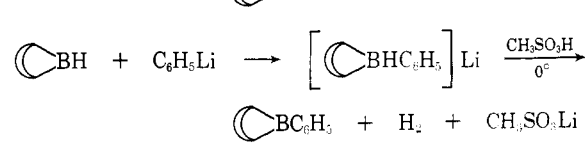


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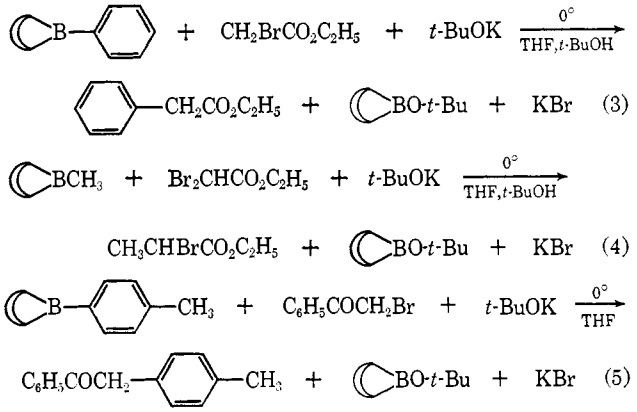
Table I. Reaction of B-Aryl- and B-Alkyl-9-borabicyclo[3.3.1]nonanes with Ethyl Bromoacetate, Ethyl Dibromoacetate, and Various α-Bromo Ketones under the Influence of Potassium *t*-Butoxide

B-R-9-BBN	mmoles	α-Halo compound	*t*-BuOK, mmoles	mmoles	Solvent	Product	Yield, %[a]
Methyl	10	$C_6H_5COCH_2Br$	10	10	THF	$C_6H_5COCH_2CH_3$	40[b]
	10	$CHBr_2CO_2C_2H_5$	10	10	THF, *t*-BuOH	$CH_3CHBrCO_2C_2H_5$	40[b]
n-Butyl	10	$C_6H_5COCH_2Br$	10	10	THF	$C_6H_5CO(CH_2)_4CH_3$	80
Phenyl	10	$CH_2BrCO_2C_2H_5$	10	10	THF, *t*-BuOH	$C_6H_5CH_2CO_2C_2H_5$	50
	10	$CHBr_2CO_2C_2H_5$	10	10	THF, *t*-BuOH	$C_6H_5CHBrCO_2C_2H_5$	65
	10	$C_6H_5COCH_2Br$	10	10	THF	$C_6H_5COCH_2C_6H_5$	93
	10	$(CH_3)_3CCOCH_2Br$	10	10	THF	$(CH_3)_3CCOCH_2C_6H_5$	92
p-Tolyl	10	$CH_2BrCO_2C_2H_5$	10	10	THF, *t*-BuOH	*p*-$CH_3C_6H_4CH_2CO_2C_2H_5$	73
	10	$C_6H_5COCH_2Br$	10	10	THF	$C_6H_5COCH_2C_6H_4CH_3$-*p*	95[c]

[a] Yields are by glpc analysis. [b] There was present about 40% of unreacted B-methyl-9-BBN in the reaction mixture. [c] Isolated after oxidation of the reaction mixture with alkaline hydrogen peroxide, extraction with pentane, and washing with water. Removal of solvents gave 95% of the product, mp 94–96°. After one recrystallization from ethanol, it exhibited mp 95.5–96° (A. McKenzie, A. K. Mills, and J. R. Myles, *Ber.*, **63**, 1904 (1930), report mp 94–96°).

These derivatives readily participate in these new alkylation reactions. Consequently, the synthesis is now extended to alkyl groups not available *via* hydroboration, and especially to aryl groups, also not available *via* hydroboration (eq 3–5). This facile introduction of



aryl groups into the α positions of ketones and esters should provide a convenient new route to such structures.

The following procedure for the preparation of B-*p*-tolyl-9-BBN is illustrative. *p*-Tolyllithium was prepared in ether solution in the usual manner from excess lithium, 1.53 g (220 mg-atom), and *p*-bromotoluene, 11.6 ml (100 mmol). This solution of *p*-tolyllithium was taken up in a hypodermic syringe and added to a solution of 9-BBN (100 mmole) in 165 ml of THF at 0°. This was immediately followed by dropwise addition of 6.5 ml of methanesulfonic acid (100 mmol), and approximately 100 mmol of hydrogen was rapidly evolved.[7] The salt was allowed to settle, and the clear solution was transferred under nitrogen to a dropping funnel attached to a small distilling flask. The solvents were removed at atmospheric pressure and the residue (containing lithium bromide) was distilled under vacuum. There was obtained 18.0 g (85% yield) of B-*p*-tolyl-9-borabicyclo[3.3.1]nonane as a colorless liquid, bp 155–160° (5.5 mm), whose purity by glpc was approximately 95%.

Similarly, phenyllithium gave an 85% yield of B-phenyl-9-BBN, bp 108° (1.2 mm), methyllithium gave a 75% yield of B-methyl-9-BBN, bp 67–68° (14 mm), and B-*n*-butyl-9-BBN was obtained in 80% yield. The latter substance was identical in every respect with the *n*-butyl derivative synthesized *via* reaction of 1-butene with 9-BBN.[4]

Glpc analysis of the crude reaction mixture, immediately following addition of the methanesulfonic acid, revealed the presence of approximately 10% of toluene. Subsequent experiments revealed that the B-aryl-9-BBN derivatives are very sensitive toward water and other efficient protonolysis agents. Thus the addition of water to a solution of B-phenyl-9-BBN in THF caused 50% hydrolysis of the phenyl group in 5 min. After 30 min the reaction was essentially complete. Consequently, it is essential that both moisture and oxygen be carefully excluded during the preparation and isolation of the intermediate. Moreover, the addition of methanesulfonic acid should be carried out at low temperature, with vigorous stirring. Finally, it is essential to avoid the use of excess methanesulfonic acid.

The reactions of B-aryl-9-BBN and B-alkyl-9-BBN with ethyl bromoacetate, ethyl dibromoacetate, and various α-bromo ketones were carried out under the same experimental conditions described previously.[4,5] The results of these experiments are summarized in Table I.

The reactions involving B-phenyl-9-BBN and B-*p*-tolyl-9-BBN proceeded quite satisfactorily and gave good yields of the α-aryl derivatives. On the other hand, the yields with B-methyl-9-BBN were lower and a considerable quantity of the boron derivative was present in the reaction mixture following addition of the stoichiometric quantity of base. This is contrary to the behavior of the higher alkyl derivatives and may be the result of the unusual openness of the boron atom in this derivative. Thus this compound may compete effectively with the α-halo compound for the base. If so, use of a more hindered base should overcome this difficulty. This question is under examination.

This development opens up the possibility of the simple introduction of aryl groups into activated α positions of a large variety of derivatives. We are currently exploring this possibility.

(7) The reaction of methanesulfonic acid with the parent compound, 9-BBN, is relatively slow under these conditions, requiring almost 1 hr for complete hydrogen evolution. On the other hand, the intermediate borohydride reacts rapidly, hydrogen being evolved almost instantly as the acid is added.

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