Tetrahedron Letters,Vol.25,No.43,pp 4913-4916,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SUBSTITUENT EFFECTS ON THE REDUCTIONS OF QUINOLINE-N-BORANES

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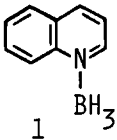
Abstract: Reductions of 2-substituted quinoline-N-boranes by sodium *bis*-(2-methoxyethoxy)aluminum dihydride lead to 1,2,3,4-tetrahydroquinolines by hydride attack at C-4 and subsequent reduction of the resulting enamine.

When carried out under conditions of kinetic control, reductions of quinoline-N-borane (1) and other substrates of the general type 2 by sodium *bis*(2-methoxyethoxy)aluminum dihydride (3) generally give products resulting from exclusive hydride attack at C-2.[1] While strict adherence to specific reaction parameters[2] is critical to assure clean 1,2-reductions of these compounds, our current study confirms that such precautions are much less important when substituents are present at position 4. For example, 1 can be converted to 4 or mixtures of 4 and 5 depending on reaction conditions and the molar quantity of 3. On the other hand, amine-boranes 6 and 7 give only 8 and 9 respectively even when the reduction step is performed at room temperature for relatively lengthy reaction times.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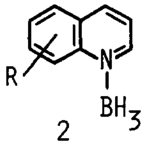
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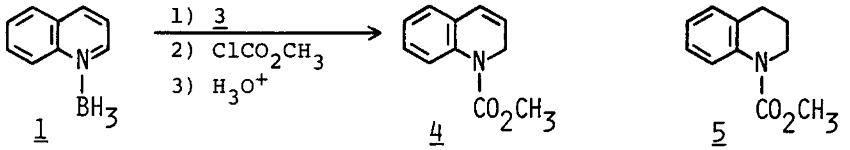
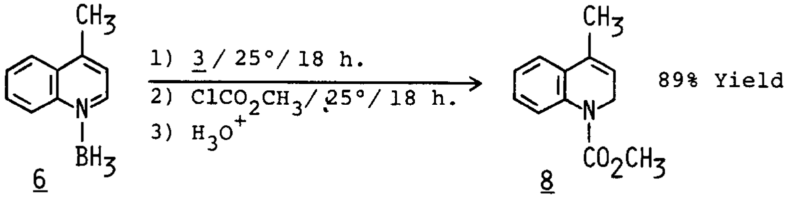
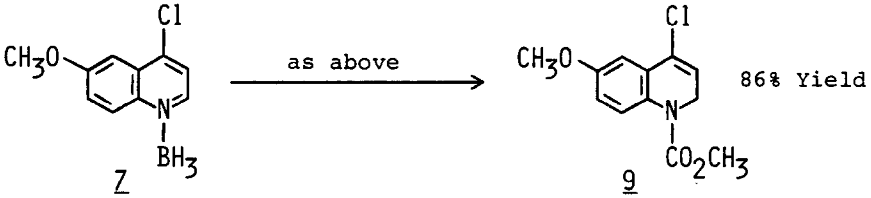
$NaAl(OCH_2CH_2OCH_3)_2H_2$

3

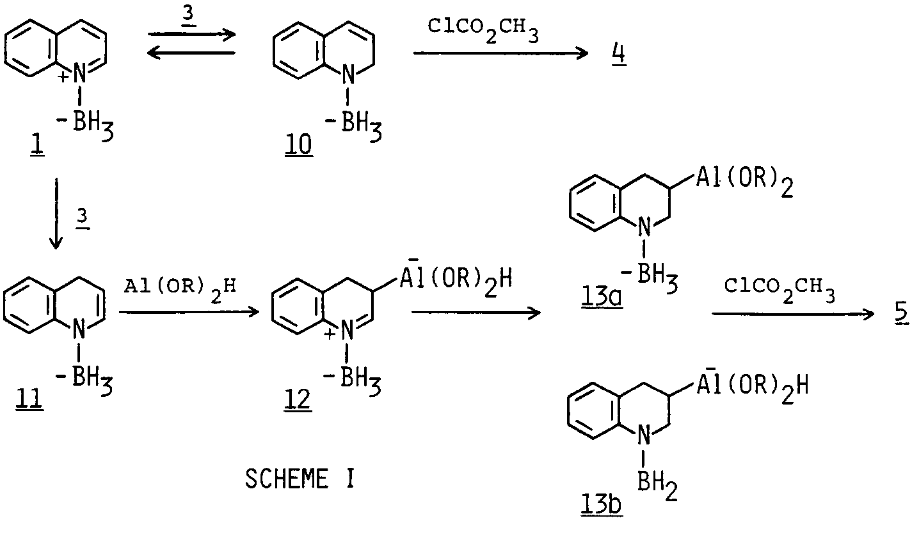


Conditions for step 1	% 4	% 5	% Yield
2.0 molar equiv. 3 / -78° C / 20 min.	100	-	90
1.1 molar equiv. 3 / +25° C / 1.75 h.	45	55	87
1.1 molar equiv. 3 / +25° C / 18 h.	38	62	92
2.0 molar equiv. 3 / +25° C / 18 h.	44	56	85





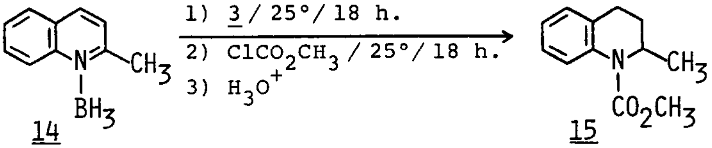
Mechanistically, these reactions may be rationalized as shown in Scheme I. Kinetic hydride attack at C-2 (1 $\rightleftarrows$ 10) is rapid and reversible at -78° C, but apparently the concentration of 10 is sufficiently high at short reaction times to afford good yields of the acylated 1,2-dihydroquinoline. Under more severe conditions,[3] hydride attack at C-4 becomes competitive and leads to 5 *via* 11, 12, and 13. The formation of 12 is envisioned as the reaction of an enamine with a Lewis acid and may be facilitated by the requirement that $Al(OR)_2H$ be generated from 3 in the proximity of C-3. Reduction of the imine-borane 12 could occur by hydride migration from aluminum and/or boron to give 13a and/or 13b respectively.[4] According to this interpretation, tetrahydroquinolines will be produced only if hydride attacks at C-4. Since no 1,4-dihydroquinoline adducts are obtained, the reaction of 11 with $Al(OR)_2H$ must be quantitative. The reductions of 6 and 7 are consistent with this mechanism



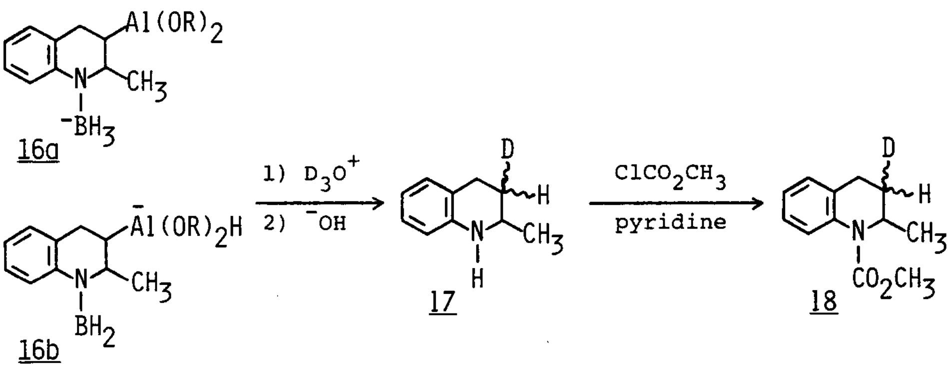
SCHEME I

if the substituents at C-4 interfere sterically with bimolecular reduction at that position.

Likewise, it should be possible to block C-2; and to demonstrate this, quinaldine-N-borane (14) was chosen for study.[5] No reduction at all occurred at -78° C (30 minutes), but at 0° C (45 minutes) for the reduction step, the conversion to 15 was approximately 50%. When the reduction conditions were extended to 18 hours at 25° C, 15 was produced as the sole product in 75% yield.

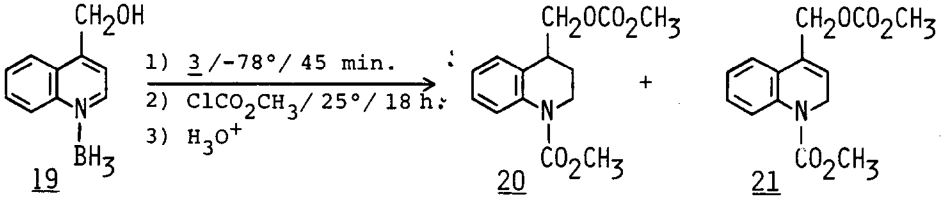


According to Scheme I, the intermediate after step 1 of this sequence should be 16a or 16b.[6] When the reaction was quenched by addition of D_3O^+ at that stage, the secondary amine 17 could be isolated in 70% crude yield. Acylation of 17 produced 18 which was clearly monodeuterated at C-3 as indicated by the appearance of the C-4 methylene hydrogens as a broadened doublet at 2.64 ppm δ (90 MHz). The multiplets at 1.36 - 1.73 ppm δ and 2.10 - 2.44 ppm δ for the non-equivalent methylene hydrogens at C-3[7] were each reduced in integrated area by 50% for an equimolar mixture of *cis* and *trans*-18-3d.



Finally, the reduction/acylation of quinoline-4-methanol-N-borane (19) provided evidence that even 4-substituted substrates can be forced to give tetrahydroquinoline products if hydride attack is directed circuitously at C-4. Addition of 3 to 19 at -78° C was accompanied by vigorous evolution of gas and the characteristic color change to yellow-brown. The standard "one-pot" sequence indicated below produced 20 contaminated with approximately 5% of 21. Since no other 4-substituted substrates gave tetrahydroquinoline products, this process must have involved reaction of 3 with the hydroxyl of

19 prior to intramolecular hydride attack at C-4.



These data suggest strongly that bimolecular hydride reductions of quinoline-N-boranes are highly susceptible to the steric effects of substituent groups at positions 2 and 4. Nucleophilic attack at C-4, which is manifest in the generation of tetrahydroquinoline products when 3 is the reducing agent, can be achieved under thermodynamic conditions if that position is unsubstituted. Except for special cases such as 19, kinetic control is possible regardless of substituents at C-4. However, clean 1,2-reductions of type 2 substrates require low temperature and a large excess of 3. Apparently, these conditions impede the formation of 11 by increasing the equilibrium concentration of 10.[8]

ACKNOWLEDGMENT. This work was supported by the Texas Christian University Research Fund (Grant 5-23717).

REFERENCES AND FOOTNOTES

1. Minter, D. E.; Stotter, P. L. J. Org. Chem. *1981*, 46, 3965.
2. Experimental details can be found in ref. 1 under Reduction Method B.
3. Kinetic control in the reduction of type 2 substrates requires the regulation of three parameters—temperature, reaction time, and concentration of 3—the last being perhaps most important. Detectable amounts of 5 are present in the final product when only one equivalent rather than two equivalents of 3 is used at -78° C / 30 minutes.
4. Hydride migration from boron to carbon at -78° C has been observed in these laboratories with imine-boranes similar to 12 in connection with an unrelated study in progress.
5. 2-Chloroquinoline-N-borane also does not reduce with 3 at -78° C / 30 min.
6. a) Intermediates 16a and 16b as well as 13a and 13b may be interconvertible through a series of intermolecular hydride transfers. The observed stereochemistry of the deuteron at C-3 of 18 does not imply necessarily that 16a and/or 16b are 50:50 mixtures of geometric isomers with respect to C-2,C-3 substituents. While it has been shown that hydrolysis of C-Al bonds in the ether-stabilized trialkylalanes proceeds with retention of configuration,[6b] we have found no evidence from literature that dialkoxyalanes behave similarly.

   b) Eisch, J. J.; Fichter, K. C. J. Amer. Chem. Soc. *1974*, 96, 6815.
7. Nagarajan, K.; Nair, M. D.; Pillai, P. M. Tetrahedron *1967*, 23, 1683.
8. For additional information regarding 1,2 *vs* 1,4-additions of nucleophiles to quinolines, see: Zoltewicz, J. A.; Helmick, L. S.; Oestreich, T. M.; King, R. W.; Kandetzki, P. E. J. Org. Chem. *1973*, 38, 1947, 1949.

(Received in USA 6 July 1984)