Efficient Conversions of Quinolines to N-(Carboalkoxy)-1,2-dihydroquinolines

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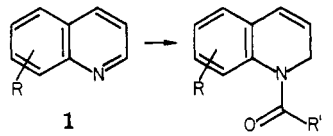
Two efficient preparations of *N*-(carboalkoxy)-1,2-dihydroquinolines have been demonstrated. The first method involves direct acylation of the 1,2-hydroalumination adducts derived from quinolines and DIBAH. Overall yields range from 59% to 82% for reduction/acylation of simple quinolines including those with alkyl substituents at C-2. This method can be readily applied to large-scale reactions; however, it does not appear to be compatible with acid-sensitive functionalities. The second method is a complementary procedure involving reduction of quinoline–*N*-boranes (generated by addition of BH_3·THF to quinolines) with sodium dialkoxyaluminum dihydride at −78 °C followed by in situ acylation of the intermediate aminoborohydride. Overall yields of products derived by this method are quite high (87–92%) for a number of examples including very electron-rich quinolines and systems containing Lewis acid labile groups such as acetals. However, quinoline–*N*-boranes with C-2 alkyl substituents fail to undergo 1,2-reduction. Both methods generate *N*-(carboalkoxy)-1,2-dihydroquinolines which are uncontaminated by impurities derived from 1,4-dihydroquinoline and 1,2,3,4-tetrahydroquinoline byproducts.

Recent studies in these laboratories required facile preparations of *N*-(carboalkoxy)-1,2-dihydroquinolines **2**



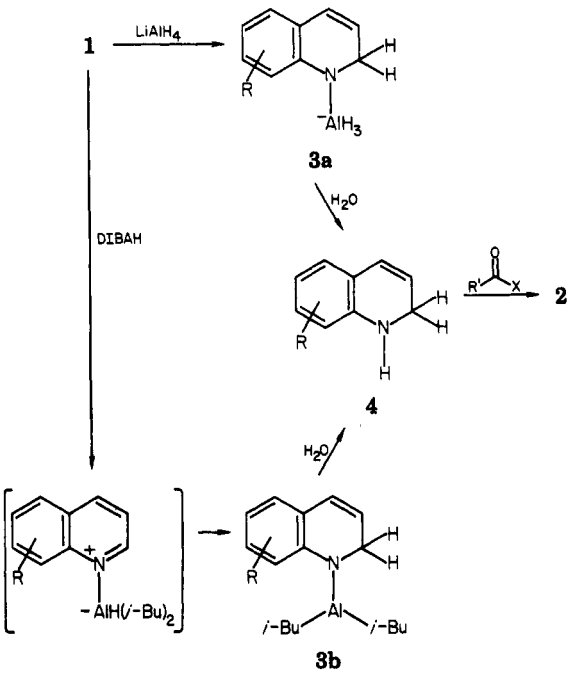
(1)

1 **2**

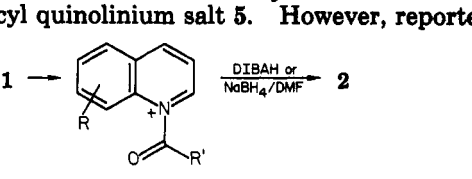
for use as intermediates in alkaloid synthesis. In particular, N-acylated 1,2-dihydroquinoline-4-carboxaldehydes were sought. Because a number of methods which convert quinolines **1** to **2** by reduction/acylation have already been reported,[2-7] it seemed likely that one or more of these would prove amenable to the specific transformations that we required. However, conspicuously absent among reported conversions of **1** to **2** are simple, direct procedures which generate pure products **2** in consistently high yields without contamination either by isomeric *N*-acyl-1,4-dihydroquinolines or by overreduced *N*-acyltetrahydroquinolines.

As reported, both lithium aluminum hydride[2] and diisobutylaluminum hydride (DIBAH)[3] are effective reagents for regiocontrolled reduction of a variety of quinolines. Protonation of the respective aluminum intermediates (aminoaluminum hydride **3a** and aminoalane **3b**) produces 1,2-dihydroquinolines **4** (Scheme I) as unprotected secondary amines in excellent yield (80–95%). Unfortunately, compounds **4** are air sensitive and easily oxidized to regenerate **1**; they are also susceptible to facile disproportionation which leads to a mixture of **1** and 1,2,3,4-tetrahydroquinolines.[4] As a consequence, *N*-acyl-1,2-dihydroquinolines **2** derived from acylations of **4** are usually contaminated[4] with N-acylated tetrahydroquinolines which may prove difficult to separate. Under optimal conditions, yields of isolated products **2** from this multistep sequence generally do not exceed 60–70%. We have noted no reports describing syntheses of **2** directly from either **3a** or **3b**. In these laboratories, attempts to acylate **3a** led to complex mixtures containing less than 20% of **2**. Acylations of **3b**, however, proved more effective and will be discussed presently.

Scheme I



Of currently available routes to **2**, the most straightforward are modifications of the Reissert reaction[5] that call for either DIBAH[3] or sodium borohydride[6] to reduce a preformed acyl quinolinium salt **5**. However, reported



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conversions of **5** to **2** via these reactions rarely exceed 55–65%, a consequence of competitive hydride attack at

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(2) (a) F. Bohlmann, *Chem. Ber.*, 85, 390 (1952); (b) K. W. Rosenmund and F. Zymalkowski, *ibid.*, 86, 37 (1953); (c) K. W. Rosenmund, F. Zymalkowski, and N. Schwarte, *ibid.*, 87, 1229 (1954); (d) E. A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, 3249 (1960); (e) R. F. Collins, *ibid.*, 3641 (1954).

(3) W. P. Neumann, *Justus Liebigs Ann. Chem.*, 618, 90 (1958); *Angew. Chem.*, 70, 401 (1958).

(4) J. F. Muren and A. Weissman, *J. Med. Chem.*, 14, 49 (1971).

(5) F. D. Popp, *Adv. Heterocycl. Chem.*, 24, 187 (1979), and references cited therein.

(6) (a) Bristol-Myers Co., Netherlands, Appl. 6 614 408 (1967); *Chem. Abstr.*, 68, 49468 (1968); (b) B. Belleau, R. Martel, G. Lacasse, M. Menard, N. L. Weinberg, and Y. G. Perron, *J. Am. Chem. Soc.*, 90, 823 (1968).

(7) M. Natsume, S. Kumadaki, Y. Kanda, and K. Kiuchi, *Tetrahedron Lett.*, 2335 (1973).

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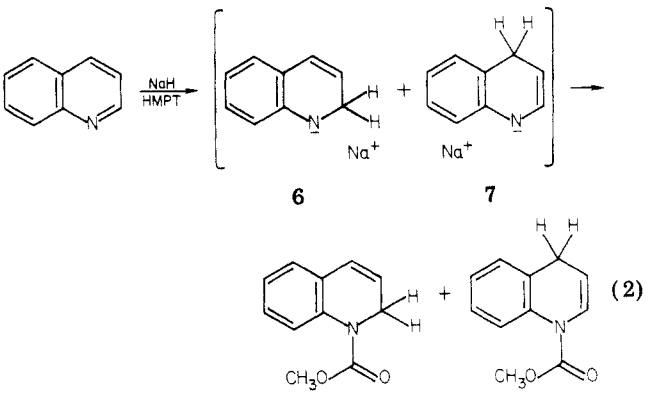
Table I. Reaction Parameters and Yield Data for Reduction/Acylation of Quinolines 8

					method A			method B			
quinoline	product	R_1	R_2	R_3	reaction time (DIABH), h	temp, °C	% yield[a]	molar equiv of 11	reaction time	temp, °C	% yield[a]
8a	9a	H	H	H	1.0	0	78	2.0	20 min	−78	90
8b	9b	H	CH_3	H	1.0	0	82	2.0	30 min	−78	87
								1.0	60 min	−78	89
8c	9c	OCH_3	Cl	H	1.5	0	78	2.0	30 min	−78	88
								0.5	60 min	−78	90
								0.1	60 min	25	86
8d	9d	H	H	CH_3	10	25	59	2.0	30 min	−78	*b*
8e	9e	OCH_3	CH_3	H	1.75	0	69	2.0	30 min	−78	92
								2.0	24 h	25	95
								1.0	60 min	−78	89
8f	9f	H		H	1.0	0	<25	2.0	30 min	−78	85
8g	9g	OCH_3		H				2.0	30 min	−78	90
8h	9h	OCH_3	H	H				2.0	20 min	−78	89

[a] Yields included in this table represent isolated products after distillation or rapid-elution chromatography. [b] A mixture of 8d and its amine-borane was recovered.

either the activated carbonyl of 5 or at the desired C-2 of the quinoline ring. Thus, substantial amounts of starting quinoline and reduced acylating agent are isolated along with 2. Our attempts to utilize this procedure were generally unsatisfactory (yields 10–60%), particularly with electron-rich systems.

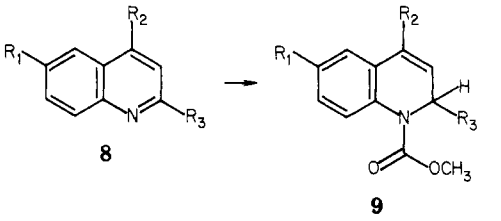
Other hydride reagents such as sodium hydride[7] have also been used for reduction of 1, and the intermediate sodium amides (e.g., 6) have been acylated directly. However, the reactions are not highly regioselective. Treatment of quinoline with NaH in hexamethylphosphoric triamide (HMPT) at 30–60 °C for several hours followed by addition of methyl chloroformate produces an 81.5% yield of a 2:3 mixture[7] of the *N*-(carbomethoxy)-1,2- and -1,4-dihydroquinolines, respectively (eq 2). The loss



(2)

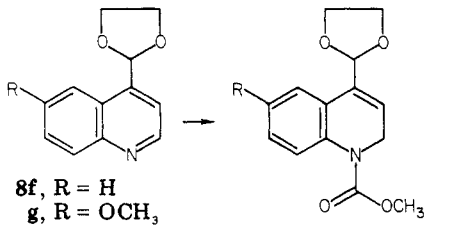
of regioselectivity for hydride addition may be attributed to the high reactivity of 6 as a hydride source when group 1 metal gegenions and strongly ionizing solvents are employed; i.e., the dissociated ion pair 6 is less stable than associated species such as 3. If one assumes that formation of 6 is not only kinetic but also reversible or that 6 itself may serve as a hydride donor to starting quinoline, it is not surprising that the thermodynamically more stable intermediate 7 predominates in reactions carried out at elevated temperature and extended reaction time.[8]

In this study, a series of quinolines 8, having various substituents R_1, R_2, and R_3, were converted to the corresponding *N*-(carbomethoxy)-1,2-dihydroquinolines 9 (eq 3) by using modifications of some of the methods described



(3)

above. Of particular interest to us were conversions of acetals 8f and 8g to the corresponding products 9f and 9g (eq 4; see Table I). Because of the lack of regioselectivity[7]



(4)

for reductions using NaH/HMPT, this method seemed unattractive; and the modified Reissert procedures[3,6] gave relatively low yields in several initial studies. Since direct acylation of the mixture of sodium amides 6 and 7 reportedly[7] avoided the problems of reoxidation and/or disproportionation in generating *N*-acyldihydroquinolines, we attempted comparable direct acylations of regiospecific intermediates 3a and 3b. Although acylation of 3a proved unsatisfactory, as noted above, reactions of 3b with alkyl chloroformates[9] were generally quite successful. Thus, we have achieved superior yields of 9 (as indicated in Table I) by method A: an "inverse" sequence involving addition of DIBAH *followed by* methyl chloroformate[9] rather than the "normal" modified Reissert reaction sequence.[3]

Method A was not amenable, however, to the transformations 8f → 9f and 8g → 9g since the allylic acetal moiety is not compatible with alane hydride donors which are also

(8) F. W. Fowler, *J. Org. Chem.*, 37, 1321 (1972).

(9) Both methods described in this paper are compatible with methyl, ethyl, and other alkyl chloroformates as acylating agents.

strong Lewis acids. This synthetic problem has been solved by a new reductive acylation procedure, method B: a sequence utilizing basic hydride reduction of quinoline–*N*-boranes at low temperature, *followed by* direct acylation of the resulting intermediates. This method appears to be highly regioselective and allows isolation of the desired *N*-acyl-1,2-dihydroquinolines[9] in the highest yields yet reported.

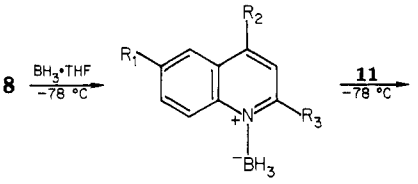
Results and Discussion

Method A: Reduction/Acylation Using DIBAH Followed by Methyl Chloroformate. The reaction of DIBAH with quinolines is one of the most convenient ways to synthesize simple 1,2-dihydroquinolines **4**.[3] We have taken advantage of the efficacy of this reaction to produce urethanes **9** in good yield by method A, which involves direct acylation of **3b**. Reactions of quinolines with DIBAH were accomplished by addition of 1.1 equiv of DIBAH (1.1 M in hexane) to the quinoline **8** (1.0 M in ether) at 0 °C. Reductions were normally complete in less than 2 h except in the case of **8d**, which has a 2-alkyl substituent (see Table I). Methyl chloroformate[9] (3.3 equiv) served as both an acylating agent and a quenching agent for excess hydride. Although no attempts have been made to determine the minimum satisfactory time for this acylation step, 18 h at room temperature was sufficient for all compounds investigated. Short-path distillation or rapid-elution chromatography on silica gel using methylene chloride provided pure compounds **9a–e** in yields ranging from 59% to 82%.[10] The data in Table I indicate that quinolines **8a–c** underwent reduction/acylation in approximately 80% yield. For **8e**, a very electron-rich substrate, the yield was slightly less. Of several hydride reagents investigated in these laboratories, only DIBAH effected a clean 1,2-addition to quinolines having a C-2 alkyl substituent, as in the case of **8d**.

However, when the quinoline acetal **8f** was subjected to the reduction conditions described above, an insoluble black oil formed within a few minutes after addition of 0.9 equiv of DIBAH. Subsequent treatment with methyl chloroformate followed by neutral aqueous workup gave a brown oil which proved to be a complex mixture containing only about 25% of the desired *N*-(carbomethoxy)-1,2-dihydroquinoline **9f**.

In the case of **8f**, it appears that hydroalumination was sufficiently slow that reaction of residual DIBAH with the benzylic acetal moiety of **8f** (or with the allylic acetal of the intermediate aminoalane) led to extensive decomposition. This result suggested that at least two modifications would be essential in formulating a milder reduction procedure compatible with quinolines such as **8f** and **8g** which possess acid-sensitive functionality: (a) the use of an activated quinoline which would cleanly accept hydride at C-2 at low temperature and (b) the use of a basic hydride donor whose conjugate Lewis acid is only weakly acidic. These objectives have been met by method B, which utilizes highly electrophilic quinoline–*N*-boranes as hydride acceptors and **11**, a sodium dialkoxyaluminum dihydride, as the reducing agent.

Method B: Reduction/Acylation Using Quinoline–*N*-Boranes 10 and Sodium Bis(2-methoxyethoxy)aluminum Hydride (11) Followed by Methyl Chloroformate. Quinoline–*N*-boranes **10** were generated quantitatively in situ by addition of 1.0 equiv of BH_3·THF to tetrahydrofuran solutions of quinolines **8** at −78 °C (eq 5). Subsequent treatment of **10** with 1.0–2.0 molar equiv[11]



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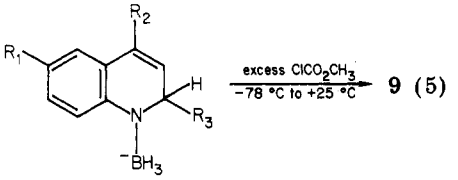


12

of **11** at −78 °C produced an intense yellow-brown solution, the color of which we attribute to the presence of aminoborohydride **12**. After 20–60 min[11] at −78 °C, the reaction was quenched at that temperature by addition of excess methyl chloroformate[9,12] (to effect both acylation and quenching of aluminum and boron hydrides) and allowed to warm to ambient temperature. Acylation was complete after 18 h. Conventional workup and purification procedures (see Experimental Section) afforded pure products **9a–c,e–h** in very high yields as summarized under method B in Table I.

The most obvious limitation of this procedure is exemplified by the failure of **8d**, having a 2-alkyl substituent, to undergo 1,2-reduction under the conditions described above. All other examples without a C-2 substituent were converted quite efficiently to **9**. Acetals **9f** and **9g**, which could not be prepared satisfactorily by any other reduction method, were produced in 85% and 90% yields, respectively, by this new procedure. Apparently, **11** is an ideal hydride source. Its hydride activity is sufficiently high to allow rapid and complete reductions of quinoline–*N*-boranes at −78 °C; and the dialkoxyalane, generated after hydride delivery, is a relatively weak Lewis acid toward Lewis bases such as acetals.

Strict adherence to specified reaction conditions[13] was absolutely essential for reduction/acylation of **8a** and **8h**,

(10) The highly colored crude products isolated from the method A procedure after acidic workup (see Experimental Section) were spectrally pure by ^1H NMR in most cases. However, the use of an internal integration standard indicated the presence of ^1H NMR inactive material. Colored byproducts remained in the distillation pot residue or at the top of the column during the chromatographic separation and constituted less than 10% of the total mass. The side reactions responsible for these impurities were apparently oxidation processes and could be minimized, but not totally eliminated, by the use of degassed solvents and reagents and by rigorous exclusion of air during both the two-stage reaction and the workup procedures.

(11) Sodium bis(2-methoxyethoxy)aluminum dihydride (**11**) as a solution in benzene or toluene is commercially available as either Redal or Vitride. See Table I for specific quantities of **11** and the corresponding reaction times.

(12) Alkyl chloroformates proved to be superior to acyl chlorides such as acetyl chloride for the acylation step in method B. Use of acetyl chloride results in a 10–15% recovery of the starting quinoline and/or its quinoline–*N*-borane. Apparently, highly electrophilic acylating agents can also function as hydride acceptors from C-2 of **12**, thus regenerating **10**.

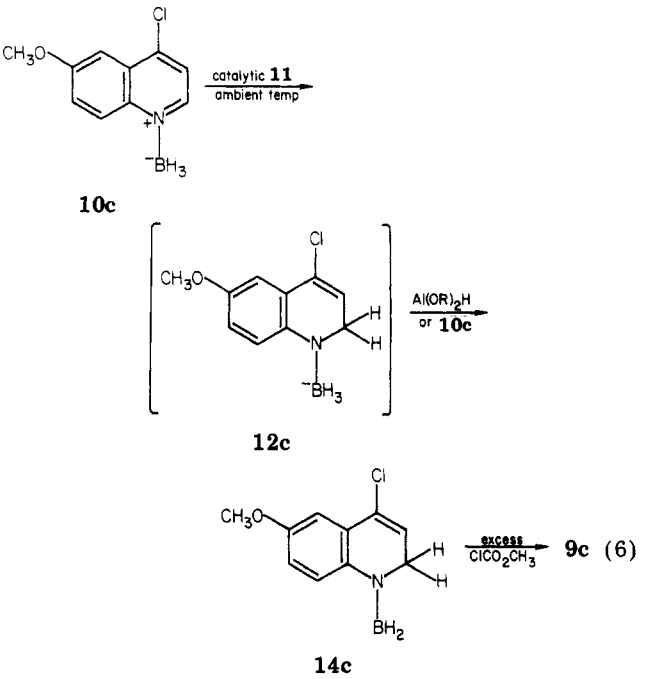
(13) The standard procedure given in the Experimental Section under Reduction Method B specifies the use of a 0.05 M solution of the quinoline in THF (1 mmol/20 mL) for these reactions. This concentration appears to be critical in the reduction/acylation of **8a** and **8h**. At higher concentrations, the reaction solution became dark brown rather than yellow-brown when **11** was added to the quinoline–*N*-borane at −78 °C. The yield of desired product decreased, and a significant quantity of the 1,2,3,4-tetrahydroquinoline urethane was produced even at very short reaction times prior to quenching with methyl chloroformate. However, the concentration factor is apparently less important for other substrates. Both **8c** and **8e** underwent reductive acylation without complication at concentrations as high as 0.12 M, which approaches a saturated solution of the corresponding quinoline–*N*-boranes in THF at −78 °C.

where R_2 = H. Reaction time for the reduction step should be minimized to 30 min or less at −78 °C; this short reaction time necessitated the use of excess (2 molar equiv) 11. When only 1 equiv of the reducing agent was added, reaction times of 45 min to 1 h were required to assure complete reduction at −78 °C; but with these longer reaction times, the corresponding 1,2,3,4-tetrahydroquinoline urethanes were observed as byproducts in up to 15% yield.[13,14] In contrast, reductions of quinoline–*N*-boranes having C-4 substituents were uncomplicated by this side reaction and could be accomplished in 1 h at −78 °C with 1 molar equiv of 11. Even at the relatively drastic conditions of 24 h at room temperature for the reduction step, **8e** was converted cleanly to **9e** in 95% yield. For very reactive substrates such as **8c**, which has an electron-withdrawing C-4 substituent, reduction of the corresponding quinoline–*N*-borane was complete in 1 h at −78 °C with only 0.5 molar equiv (1.0 hydride equiv) of 11.

The use of excess reducing agent to facilitate rapid and complete hydride transfer presents no problems provided that the reaction is quenched with sufficient alkyl chloroformate[9] both to destroy excess hydride and to acylate the alkoxide ligands on aluminum, as well as to acylate nitrogen. The removal of methyl or ethyl methoxyethyl carbonate in vacuo was not difficult. When higher molecular weight alkyl chloroformates were used, removal of the mixed carbonate required distillation or preparative column chromatography.

To determine whether or not **12** itself can function as a hydride source for reduction of **10**, we carried out reduction/acylation of **8c** using a variant of method B with catalytic 11 (eq 6). When 10 mol % of 11 was added to quinoline–*N*-borane **10c** at −78 °C, the reaction mixture remained virtually colorless. As the temperature was raised to ambient, the characteristic yellow-brown color developed, and 1,2-reduction of the quinoline ring was complete after 1 h. Standard acylaton and workup procedures afforded pure **9c** in 86% yield.

For this "catlytic reduction" to occur in high overall yield, tautomerization of **10c** to aminoborane **14c** must be



complete prior to addition of the acylating agent. Since **10c** is stable in tetrahydrofuran at ambient temperature in the absence of 11, aminoborohydride **12c** (formed in small quantities from **10c** and catalytic 11) must facilitate this tautomerization. Thus, **12c** contains at least one reactive hydride which is capable of transfer from boron to C-2 of **10c** in a chain-reaction process. It is not known whether the transfer is a direct reaction between **12c** and **10c** (i.e., **12c** + **10c** → **14c** + **12c**) or whether dialkoxyalane serves as a transfer agent (eq 7 and 8). Mechanistic

$$\mathbf{12c} + (RO)_2AlH \rightarrow \mathbf{14c} + \mathbf{11} \quad (7)$$

$$\mathbf{11} + \mathbf{10c} \rightarrow (RO)_2AlH + \mathbf{12c} \quad (8)$$

studies of this hydride transfer reaction as well as other reactions involved in the method B procedure are under investigation.

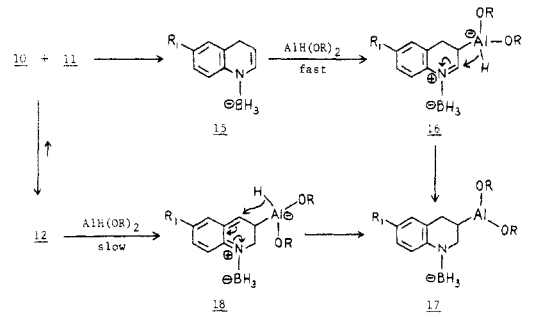
Conclusions

The results described in this study indicate that use of DIBAH followed by acylation of the resulting aminoalane **3b** is normally an excellent method for converting simple quinolines to *N*-(carboalkoxy)-1,2-dihydroquinolines. This reaction sequence is particularly well-suited for quinolines with C-2 substituents as well as for large-scale preparations since only a small amount of solvent and a small excess of DIBAH are required. However, best yields for reduction/acylation of quinoline systems (excluding those having C-2 substituents) are obtained via the reactions of quinoline–*N*-boranes with 11 followed by (oxidative) acylation of aminoborohydride intermediates. This latter procedure is the method of choice for acid-sensitive and electron-rich substrates. Continuing investigations of "catalytic reductions" of quinoline–*N*-boranes using limited amounts of 11 (as already demonstrated in this study for **10c** → **9c**) may lead to even more convenient and economical procedures.

Experimental Section

General Methods. Quinolines **8a,b,d,h** and quinoline-4-carboxaldehyde were obtained from Aldrich Chemical Co. and were purified by vacuum distillation. Quinoline **8c** was obtained from Saber Laboratories, Inc., and used directly. Quinoline **8e** was prepared according to the procedure of Campbell and

(14) Possible mechanistic explanations for the formation of tetrahydroquinolines from **8a** and **8h** at long reaction time involve the intermediacy of organoaluminum species **17**. Thus, formation of **15** via 1,4-addition of hydride to **10** (R_2 = R_3 = H) may be postulated if the observed kinetic 1,2-reduction (**10** → **12**) is slowly reversible. If produced, the highly nucleophilic enaminoborohydride **15** would react rapidly with dialkoxyalane to produce **16**. Alternatively, **12** may undergo slow addition of dialkoxyalane to form **18** directly. Both **16** and **18** are ideally suited to undergo intramolecular hydride migration yielding **17**. Intermediate **17** would generate the observed tetrahydroquinoline byproduct after acylation of nitrogen and hydrolysis of the C–Al bond (see below). These



mechanisms are analogous to that proposed[15] for the reduction of isoquinolinium salts to tetrahydroisoquinolines by sodium borohydride and are consistent with the observation that reduction/acylation of quinoline–*N*-boranes having C-4 substituents was unaccompanied by side reactions even under forcing conditions. Current mechanistic studies will be delineated in a future manuscript.

(15) R. E. Lyle and P. S. Anderson, *Adv. Heterocycl. Chem.*, **6**, 46, 68, 73 (1966).

Schaffner.[16] Oxidation of 8e according to the method of Bender and Coffen[17] gave 6-methoxyquinoline-4-carboxaldehyde. Sodium bis(2-methoxyethoxy)aluminum dihydride,[11] 70% in benzene (Redal), and BH_3·THF complex were purchased from Aldrich Chemical Co. and standardized by measurement of hydrogen evolved from aqueous quench. DIBAH (diisobutylaluminum hydride) was obtained from Texas Alkyls and was standardized by analysis of the mixture of benzaldehyde and benzyl alcohol from reaction of DIBAH with excess aldehyde at −78 °C. Anhydrous tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. All reactions were carried out by using degassed solvents under an argon atmosphere. ^{1}H NMR spectra were recorded with a Varian T60A spectrometer using $CDCl_3$ solutions with Me_4Si as an internal standard. IR spectra were recorded with a Beckman IR 4220 spectrophotometer using a thin-film of the neat liquid between NaCl plates. Combustion analyses were obtained from Galbraith Laboratories, Inc., and Chemalytics, Inc. All new compounds gave satisfactory analyses for carbon and hydrogen.

Preparation of Acetals 8f and 8g. Acetal 8f[18] from Quinoline-4-carboxaldehyde. A solution of 0.424 g (2.7 mmol) of the aldehyde and 0.250 g (4.0 mmol) of ethylene glycol in 30 mL of CH_2Cl_2 was cooled to 0 °C, and 5.4 mmol of BF_3·Et_2O was added. The yellow reaction mixture (not homogeneous) was stirred at room temperature for 22 h and then poured into 45 mL of 5% NaOH at 0 °C with rapid stirring. The CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). Extracts were combined with the original organic layer and washed with 5% NaOH (20 mL), H_2O (20 mL), and finally with brine (20 mL). The product was dried over Na_2SO_4, and the solvent was removed by rotary evaporation. Residual volatiles were removed in vacuo [25 °C (0.1 mm), 24 h]. The product (0.465 g, 86%) as directly isolated was suitable for use in reduction reactions. Spectral data for 8f were in agreement with those reported by Wang.[18b]

Acetal 8g from 6-Methoxyquinoline-4-carboxaldehyde.[16,17] Acetal 8g was prepared from the reaction of 0.430 g (2.3 mmol) of aldehyde, 0.222 g (3.6 mmol) of ethylene glycol, and 5.0 mmol of BF_3·Et_2O in 30 mL of CH_2Cl_2 by using the procedure described above for the preparation of 8f. The pale yellow oil (0.473 g, 89%) isolated after removal of residual solvents was pure as shown by the ^{1}H NMR spectrum and combustion analysis. ^{1}H NMR δ 3.87 (3 H, s, OCH_3), 4.05 (4 H, s, OCH_2CH_2O), 6.30 (1 H, s, OCHO), 7.16–7.57 (3 H, m, H3,5,7), 8.02 (1 H, d, J = 10.0 Hz, H8), 8.73 (1 H, d, J = 4.2 Hz, H2). Anal. ($C_{13}H_{13}NO_3$): C, H.

Reduction Method A: DIBAH Followed by Methyl Chloroformate. Methyl 1,2-Dihydroquinoline-1-carboxylate (9a) from Quinoline (8a). To 0.258 g (2.0 mmol) of 8a in 2 mL of ethyl ether at 0 °C was added 2.0 mL of 1.08 M DIBAH in hexane (2.16 mmol). The resulting red solution was stirred for 1 h at 0 °C, during which time the color faded to yellow. Methyl chloroformate (0.614 g, 6.5 mmol) was added all at once, and the ice bath was removed. After 18 h at room temperature, the reaction mixture (red) was transferred with 20 mL of ether to a flask containing 50 mL of water at 0 °C. The resulting emulsion was stirred vigorously (under argon) for 30 min and then acidified by dropwise addition of 6 N HCl until a well-defined interface was obtained (approximately pH 4). The ethereal layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). Extracts were combined with the original ether layer, dried over Na_2SO_4/Na_2CO_3, and rotary evaporated. Remaining volatiles were removed at 0.1 mm (25 °C; 4 h). Bulb to bulb distillation [110–115 °C (0.1 mm)] of the residual oil gave 0.310 g (78%) of pale yellow liquid [lit.[6a] bp 86 °C (0.04 mm)]: ^{1}H NMR δ 3.75 (3 H, s, OCH_3), 4.37 (2 H, dd, J = 4.0, 1.8 Hz, H2), 5.90 (1 H, dt, J = 9.7, 4.0 Hz, H3), 6.43 (1 H, dt, J = 9.7, 1.8 Hz, H4), 6.90–7.32 (3 H, m, H5–7), 7.53 (1 H, m, H8); IR (major bands) 755, 786, 1051, 1126, 1226, 1248, 1342, 1366, 1434, 1483, 1706 cm^{-1}. Anal. ($C_{11}H_{11}NO_2$): C, H.

Methyl 1,2-Dihydro-4-methylquinoline-1-carboxylate (9b) from 4-Methylquinoline (8b). Method A as described for the preparation of 9a was used to obtain 0.401 g of crude 9b (brown oil) from 0.333 g of 8b. Rapid-elution chromatography on 60/200-mesh silica gel with CH_2Cl_2 gave 0.387 g (82%) of pure 9b as a pale yellow oil: ^{1}H NMR δ 2.00 [3 H, unresolved td (appearing as a quartet), J = 1.9, 1.6 Hz, C4 CH_3], 3.73 (3 H, s, OCH_3), 4.27 (2 H, dq, J = 4.5, 1.9 Hz, H2), 5.74 (1 H, tq, J = 4.5, 1.6 Hz, H3), 6.87–7.37 (3 H, m, H5–7), 7.53 (1 H, m, H8); IR (major bands) 762, 805, 1032, 1062, 1147, 1191, 1220, 1240, 1255, 1341, 1355, 1382, 1440, 1489, 1718 cm^{-1}. Anal. ($C_{12}H_{13}NO_2$): C, H.

Methyl 1,2-Dihydro-4-chloro-6-methoxyquinoline-1-carboxylate (9c) from 4-Chloro-6-methoxyquinoline (8c). Method A was used to obtain 0.472 g of crude 9c (brown oil) from 0.415 g of 8c. Rapid-elution chromatography on 60/200-mesh silica gel with CH_2Cl_2 gave 0.425 g (78%) of pure 9c as a pale yellow oil: ^{1}H NMR δ 3.77 (3 H, s, C6 OCH_3), 3.81 (3 H, s, CO_2CH_3), 4.41 (2 H, d, J = 4.8 Hz, H2), 6.15 (1 H, t, J = 4.8 Hz, H3), 6.83 (1 H, dd, J = 9.0, 2.8 Hz, H7), 7.12 (1 H, d, J = 2.8 Hz, H5), 7.47 (1 H, d, J = 9.0 Hz, H8); IR (major bands) 761, 873, 1035, 1056, 1136, 1164, 1192, 1230, 1249, 1266, 1285, 1344, 1381, 1449, 1493, 1571, 1607, 1719 cm^{-1}. Anal. ($C_{12}H_{12}ClNO_3$): C, H, Cl.

Methyl 1,2-Dihydro-2-methylquinoline-1-carboxylate (9d) from 2-Methylquinoline (8d). To 0.286 g (2.0 mmol) of 8d in 2 mL of ethyl ether at 0 °C was added 2.16 mmol of DIBAH in hexane, and the resulting yellow solution was stirred at room temperature for 10 h. The reaction mixture was then cooled to 0 °C, and 6.5 mmol methyl chloroformate was added. After 18 h at room temperature, the workup procedure of method A was used to obtain 0.268 g of crude 9d (green oil). Rapid-elution chromatography on 60/200-mesh silica gel with CH_2Cl_2 gave 0.239 g (59%) of pure 9d as a pale yellow oil: ^{1}H NMR δ 1.08 (3 H, d, J = 7.0, C2 CH_3), 3.78 (3 H, s, OCH_3), 5.10 [1 H, unresolved qd (appearing as a quintet), J = 7.0, 5.5 Hz, H2], 5.95 (1 H, dd, J = 9.5, 5.5 Hz, H3), 6.40 (1 H, d, J = 9.5 Hz, H4), 6.90–7.33 (3 H, m, H5–7), 7.53 (1 H, m, H8); IR (major bands) 744, 758, 772, 1125, 1243, 1273, 1310, 1328, 1377, 1390, 1434, 1485, 1702 cm^{-1}. Anal. ($C_{12}H_{13}NO_2$): C, H.

Methyl 1,2-Dihydro-4-methyl-6-methoxyquinoline-1-carboxylate (9e) from 4-Methyl-6-methoxyquinoline (8e). Method A as described for the preparation of 9a was used to obtain 0.179 g of crude 9e (brown oil) from 0.176 g of 8e. Rapid-elution chromatography on 60/200-mesh silica gel with CH_2Cl_2 gave 0.164 g (69%) of pure 9e as a pale yellow oil: ^{1}H NMR δ 2.01 [3 H unresolved td (appearing as a quartet), J = 1.8, 1.5 Hz, C4 CH_3], 3.72 (3 H, s, C6 OCH_3), 3.75 (3 H, s, CO_2CH_3), 4.25 (2 H, dq, J = 4.4, 1.8 Hz, H2), 5.76 (1 H, tq, J = 4.4, 1.5 Hz, H3), 6.72 (2 H, m, H5, H7), 7.42 (1 H, d, J = 9.5 Hz, H8); IR (major bands) 757, 794, 1027, 1054, 1142, 1174, 1198, 1235, 1253, 1281, 1350, 1379, 1440, 1486, 1698 cm^{-1}. Anal. ($C_{13}H_{15}NO_3$): C, H.

Reduction Method B: Sodium Bis(2-methoxyethoxy)-aluminum Dihydride (11) Followed by Methyl Chloroformate. Methyl 1,2-Dihydro-4-chloro-6-methoxyquinoline-1-carboxylate (9c) from 4-Chloro-6-methoxyquinoline (8c). To 0.194 g (1.0 mmol) of 8c in 20 mL of anhydrous THF at −78 °C was added 1.0 mL of 1.0 M BH_3·THF complex in THF (1.0 mmol). After 30 min, 0.57 mL (2.0 mmol) of 11 (3.5 M in benzene) diluted with 2 mL of THF was added. The resulting deep yellow reaction mixture was stirred at −78 °C for 30 min. Methyl chloroformate (1.14 g, 12.0 mmol) was then added all at once, and the dry ice bath was removed. After 18 h at room temperature, the reaction mixture (pale yellow) was cooled to 0 °C and 2 mL of H_2O was added. The solvent was decanted from the aluminum salts into a separatory funnel containing 100 mL of H_2O, and the product was extracted into CH_2Cl_2 (3 × 20 mL). The extracts were combined, dried over Na_2SO_4, and rotary evaporated. The crude product was dissolved in CH_2Cl_2 (approximately 5 mL/mmol) and filtered through a small plug of silica gel to remove aluminum salts carried into the organic layer during extraction. Methylene chloride was removed by rotary evaporation, and residual solvent and volatile carbonates were removed at 0.1 mm (room temperature, 12 h). Bulb to bulb distillation of the crude material [145–150 °C (0.1 mm)] gave 0.225

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g (88%) of pure **9c**, identical in all respects to purified **9c** prepared by method A.

Methyl 1,2-Dihydro-4-[(ethylenedioxy)methyl]-quinoline-1-carboxylate (9f) from 4-[(Ethylenedioxy)-methyl]quinoline (8f). Method B as described above for preparation of **9c** was used to obtain 0.279 g of crude **9f** (brown oil) from 0.215 g of **8f**. Rapid-elution chromatography on 60/200-mesh silica gel with CH_2Cl_2 gave 0.237 g (85%) of pure **9f** as a pale yellow oil: ^{1}H NMR δ 3.75 (3 H, s, OCH_3), 3.98 (4 H, br s, OCH_2CH_2O), 4.37 (2 H, dd, J = 4.4, 0.8 Hz, H2), 5.66 (1 H, dt, J = 1.0, 0.8 Hz, OCHO), 6.28 (1 H, td, J = 4.4, 1.0 Hz, H3), 6.87-7.25 (2 H, m, H6, H7), 7.25-7.65 (2 H, m, H5, H8). Anal. ($C_{14}H_{15}NO_4$): C, H.

Methyl 1,2-Dihydro-4-[(ethylenedioxy)methyl]-6-methoxyquinoline-1-carboxylate (9g) from 4-[(Ethylenedioxy)-methyl]-6-methoxyquinoline (8g). Method B as described above for preparation of **9c** was used to obtain 0.230 g of crude **9g** (brown oil) from 0.204 g of **8g**. Rapid-elution chromatography on 60/200-mesh silica gel with CH_2Cl_2 gave 0.217 g (90%) of pure **9g** as a pale yellow oil: ^{1}H NMR δ 3.74 (3 H, s, C6 OCH_3), 3.77 (3 H, s, CO_2CH_3), 4.01 (4 H, br s, OCH_2CH_2O), 4.37 (2 H, br d, J = 4.4 Hz, H2), 5.65 (1 H, br s, OCHO), 6.30 (1 H, br t, J = 4.4 Hz, H3), 6.75 (1 H, dd, J = 9.0, 2.9 Hz, H7), 7.04 (1 H, d, J = 2.9 Hz, H5), 7.43 (1 H, d, J = 9.0 Hz, H8). Anal. ($C_{15}H_{17}NO_5$): C, H.

Methyl 1,2-Dihydro-6-methoxyquinoline-1-carboxylate (9h) from 6-Methoxyquinoline (8h). Method B as described above for preparation of **9c** was used to obtain 0.254 g of crude **9h** (red-brown oil) from 0.185 g of **8h**. Bulb to bulb distillation of the crude material [140-143 °C (0.5 mm)] gave 0.228 g (89%) of pure **9h**: ^{1}H NMR δ 3.75 (6 H, s, C6 OCH_3 and CO_2CH_3), 4.35 (2 H, dd, J = 4.0, 1.8 Hz, H2), 5.96 (1 H, dt, J = 9.4, 4.0 Hz, H3), 6.42 (1 H, dt, J = 9.4, 1.8 Hz, H4), 6.53-6.87 (2 H, m, H5, H7), 7.44 (1 H, d, J = 8.8 Hz, H8). Anal. ($C_{12}H_{13}NO_3$): C, H.

Other dihydroquinoline urethanes prepared by this method include **9a** (90%), **9b** (87%), and **9e** (92%). See Table I for precise reaction conditions.

Variant of Method B: Reduction of 8c Using Catalytic 11. Quinoline-*N*-borane **10c** (1.0 mmol) was prepared from **8c** at -78 °C as described above. A catalytic amount of **11** (0.10 mmol) was added and the dry ice bath was removed. As the solution warmed above -20 °C, the characteristic deep yellow color began to develop. After 1 h at room temperature, the dry ice bath was replaced; and the reaction was quenched by addition of 4.0 mmol of methyl chloroformate. The workup procedure described above gave pure **9c** in 86% yield.

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Registry No. 8a, 91-22-5; **8b**, 491-35-0; **8c**, 4295-04-9; **8d**, 91-63-4; **8e**, 41037-26-7; **8f**, 56503-48-1; **8g**, 78513-88-9; **8h**, 5263-87-6; **9a**, 17718-14-8; **9b**, 78513-89-0; **9c**, 78513-90-3; **9d**, 78513-91-4; **9e**, 78513-92-5; **9f**, 78513-93-6; **9g**, 78513-94-7; **9h**, 78513-95-8; **10c**, 78529-62-1; **11**, 22722-98-1; quinoline-4-carboxaldehyde, 4363-93-3; 6-methoxyquinoline-4-carboxaldehyde, 4363-94-4.

Cyclization of Phenyl Azides with Homoallylic or Allylic Ortho Substituents and the Consequences of Triazoline Fragmentation

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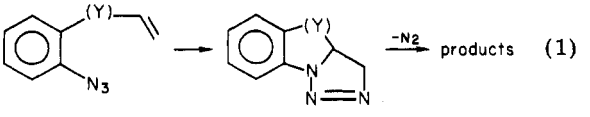
o-(Allyloxy)phenyl azide (**1**) and 14 derivatives substituted on the allyl group were thermolyzed at 110-120 °C to form benzoxazines (**16**), dihydroazirinobenzoxazines (**17**), or 3-alkenylbenzomorpholines (**18**, **19**) through fragmentation of intermediate triazolines. With substituted allyl groups, the geometrical isomers gave the same products in the same ratio, except in the case of *o*-(β,γ-dimethylallyl)phenyl azide. Rearrangement by phenyl migrations occurred with the β-phenylallyl compound. *o*-Allylphenyl azide (**27a**), (*o*-azidophenyl)acetaldehyde (**27b**), and *o*-[(*cis*-1-propenyl)oxy]phenyl azide (**27c**) required temperatures of 155-200 °C for thermolysis and yielded 2-methylindole, oxindole, and 2-ethylbenzoxazole, respectively, by nitrene insertion.

Thermolysis or photolysis of ortho-substituted aryl azides commonly leads to cyclization with loss of molecular nitrogen.[2] This may take place through formation of a nitrene intermediate, which may insert in an adjacent bond (generally C-H), or it may occur by addition of the azido group or nitrene to an adjacent unsaturated atom. Loss of nitrogen may thus precede ring closure, be synchronous with it, or follow it. Those azides that thermolyze more difficultly have been thought to form discrete nitrenes in the rate-determining step, whereas those that thermolyze at lower temperatures (<100 °C) and have lower activation energies (<28 kcal/mol) undergo loss of nitrogen synchronously with or subsequent to ring closure.[3-5]

Anchimerically assisted fragmentation of the azido group might require only a suitably placed nucleophilic center, in the form of an unshared electron pair or the π electrons of a multiple bond, or might additionally require the possibility of continuous conjugation embracing the azido group and the site of ring closure in an electrocyclic process.[4]

A further possibility is initial intramolecular 1,3-dipolar cycloaddition to form a stable intermediate (eq 1) that could subsequently lose nitrogen[5] to form the ultimate products in intermediate zwitterions or diradicals.



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