Addition of Grignard Reagents to Quinolinium Salts: Evidence for a Unique Redox Reaction between a 1,4- and a 1,2-Dihydroquinoline

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Addition of nucleophilic reagents to quinolines and acylquinolinium salts has proven to be a useful method for the synthesis of substituted quinoline derivatives.[1] In the case of organometallic reagents such as organolithiums and Grignard reagents, these additions are known to occur predominantly at the 2-position to form 2-substituted 1,2-dihydroquinolines,[2] which can then be transformed in situ to 2-substituted quinolines by oxidation[3] or to the corresponding 1,2,3,4-tetrahydroquinolines by reduction.[4] A limitation to the broader versatility of this approach, however, is the lack of a suitable complimentary method to regioselectively direct the attack to the 4-position. In the context of our interest in exploring convenient access to substituted 1,2,3,4-tetrahydroquinolines as useful intermediates for preparing pharmacologically active heterocyclic systems,[5] we desired an efficient entry into 4-substituted 1,2,3,4-tetrahydroquinolines through regioselective functionalization of quinoline at the 4-position. We wish to report herein our observations on the addition of Grignard reagents to quinolinium salts.

In the closely related case of pyridines and acylpyridinium salts, addition of organometallic nucleophiles appears to take place preferentially at the 2-position.[6] However, several successful attempts have been reported in which nucleophilic attack at the 4-position of 1-acylpyridinium salts was predominant when softer nucleophiles such as organocopper (R_2CuLi; RMgX, cat. CuI; RCu·BF_3)[7] and titanium reagents[8] were employed. In a conceptually different approach, Katritzky,[9] and subsequently Akiba,[10] have shown that by using pyridinium salts containing bulky substituents that can shield the 2- and 6-positions the attack of Grignard reagents can be forced to occur preferentially at the 4-position. To the best of our knowledge, studies on the prospects of such an approach in the case of quinolinium salts have not been previously reported.[11]

Though the extended conjugation in quinolines makes nucleophilic attack at the 4-position a considerably more difficult task, we felt that quaternized quinolinium salts with steric shielding at the 2-position might promote preferential attack at the 4-position. We reasoned that the use of trialkylsilyl triflates as tunable quaternizing agents might be suitable in this capacity mainly due to their ease of formation (perhaps as a result of the longer Si−N bond that reduces the peri hydrogen interaction)[12] and, more importantly, due to their reduced reactivity toward Grignard reagents.[13] Thus, treatment of quinoline with TMSOTf in dichloromethane at room temperature afforded the quinolinium triflate **1**. Treatment of this quinolinium triflate with ethylmagnesium bromide followed by an aqueous workup yielded a mixture of four products (Scheme 1). These products were identified as 4-ethylquinoline (**2**), 2-ethylquinoline (**3**), 4-ethyl-1,2,3,4-tetrahydroquinoline (**4**), and 2-ethyl-1,2,3,4-tetrahydroquinoline (**5**) using ^{1}H NMR and mass spectrometry. Structural assignments were confirmed by comparison of spectral data with those of authentic samples.

The effect of steric bulk of silyl groups on the regioselectivity was examined using several silyl triflates (Table 1). In the case of trimethylsilyl triflate, 2-ethylquinoline resulting from attack of the Grignard reagent at the 2-position was the predominant product. In the cases of triethylsilyl and triphenylsilyl triflates, attack at the 4-position was clearly more favorable, leading to much better yields of **2** and **4**. Interestingly, the 2-ethyl adduct (**5**) was detected only in the case of trimethylsilyl triflate. The bulkier triisopropylsilyl triflate reacted sluggishly to form the quinolinium salt as was observed by TLC analysis, and the resulting quinolinium gave much poorer

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Scheme 1

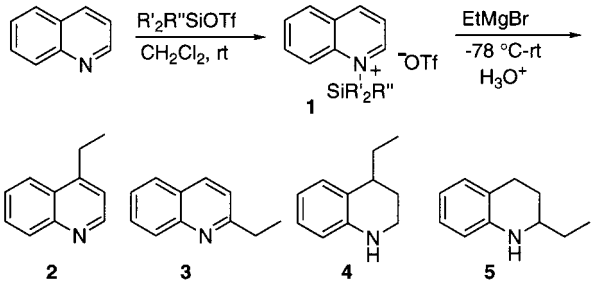
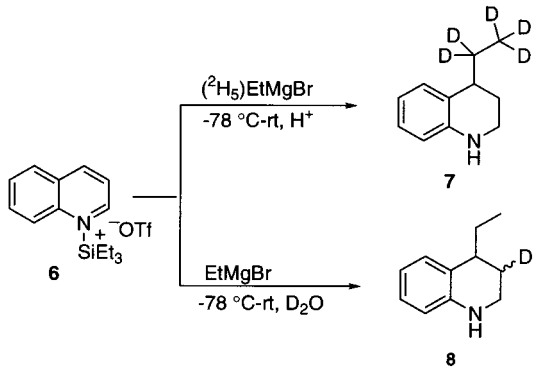


Table 1. Reaction of Ethylmagnesium Bromide with Quinolinium Triflates

			yield[b] (%)			
entry	silyl triflate	conversion[a] (%)	**2**	**3**	**4**	**5**
1	Me_3SiOTf	100	8	51	14	7
2	TBDMSOTf	72	7	34	30	0
3	Et_3SiOTf	100	4	37	31	0
4	Ph_3SiOTf	100	8	29	42	0
5	*i*-Pr_3SiOTf	10	57	43	trace	0

[a] Percent conversions are based on recovered quinoline. [b] Isolated yields are based upon the recovered quinolines.

Scheme 2



yields of products when reacted with the Grignard reagent.

The formation of the tetrahydroquinolines was quite unexpected. Intriguingly, some of the 4-ethyl-1,4-dihydroquinoline and 2-ethyl-1,2-dihydroquinoline intermediates had undergone further reduction to the corresponding tetrahydroquinolines. The results in the case of triphenylsilyl triflate eliminate the possibility of the alkyl groups on the silyl group participating in a hydride-transfer reduction to form the observed tetrahydroquinolines.

Another possible reductant could be the Grignard reagent itself, which was used in slight excess (1.25 equiv). To rule out this possibility, the reaction was carried out with perdeuterated ethylmagnesium bromide (Scheme 2).[14] Mass spectral analysis[15] of the products indicated incorporation of only five deuterium atoms corresponding to the pentadeuterated 4-ethyl-1,2,3,4-tetrahydroquinoline **7**, clearly obviating the possibility of the Grignard reagent participating as a reducing agent.

Alternatively, quenching the reaction after nondeuterated EtMgBr addition with D_2O followed by proton NMR and mass spectral analysis of the products clearly indicated formation of 4-ethyl-1,2,3,4-tetrahydroquinoline **8** with incorporation of one deuterium at the 3-position (Figures 1b and 2b), suggesting that the initial protonation of the 4-ethyl-1,4-dihydroquinoline intermediate occurs at the 3-position. No deuterium incorporation was detected in the 2- and 4-ethylquinolines isolated. The 4-ethyl-3,4-dihydroquinolinium derivative (**12**) obtained by protonation (Scheme 3) could act as a hydride acceptor and undergo an intermolecular redox reaction with the 2-ethyl-1,2-dihydroquinoline (**10**) already present in the reaction mixture to form the observed tetrahydroquinoline **4**. 1,2-Dihydroquinolines obtained by regiocontrolled reduction of quinoline using LAH or DIBAH have been known to disproportionate to some extent, and the intermediacy of 1,4-dihydroquinoline in the redox process has been suggested.[16] To verify this possibility, quinoline deuterated at the 2-position (**9**) was synthesized[17] and subjected to the same reaction conditions (Scheme 3). Analysis of mass spectra of the products formed showed that the 4-ethyl-1,2,3,4-tetrahydroquinoline **13** formed incorporated two deuterium atoms (Figure 1c), whereas the 2-ethylquinoline (**3**) formed had no deuterium incorporation. Proton NMR clearly showed that the deuterium incorporated was only at the 2-position (Figure 2c). Incorporation of two deuterium atoms at the 2-position thus unambiguously proved the redox reaction mechanism in which the more reactive 2-ethyl-1,2 dihydroquinoline transfers a hydride to the iminium species **12** generated by the protonation of the 4-ethyl-1,4 dihydroquinoline **11**.

In summary, our studies indicate that the addition of Grignard reagents to quinolinium salts involving trialkyl/arylsilyl triflates occurs at both the 2- and 4-positions. With bulkier silyl groups, the 4-position is favored. Protic workup of the resultant mixture of 1,2- and 1,4-dihydroquinolines leads to an intermolecular redox reaction leading to 4-alkyl-1,2,3,4-tetrahydroquinoline and 2-alkylquinoline. In the case of the smaller trimethylsilyl triflate, attack at the 2-position is favored, and the resultant 2-ethyl-1,2-dihydroquinoline (**10**) undergoes disproportionation under protic conditions to yield small amounts of **5**. Although the intermediacy of 1,4-dihydroquinoline in disproportionation mechanisms has been suggested in previous studies,[18] our findings for the first time definitively establish the regiospecificity of this intermolecular redox process between a 1,4- and a 1,2-dihydroquinoline. The substituted tetrahydroquinoline formed can be easily separated from the more polar quinoline byproducts by flash column chromatography. This reaction thus offers a one-pot method for synthesis of 4-alkyl-1,2,3,4-tetrahyroquinolines from inexpensive commercially available quinolines and may prove to be of preparative utility relative to otherwise multistep

(14) ($^2H_5$)ethylmagnesium bromide was readily prepared from commercially available ($^2H_5$)ethyl bromide by standard methods.

(15) Mass spectral fragmentation patterns clearly show that deuterium incorporation is on the ethyl group on the hydroaromatic system of 1,2,3,4-tetrahydroquinoline. For mass spectra of tetrahydroquinolines, see: Draper, P. M.; MacLean, D. B. *Can. J. Chem.* **1968**, *46*, 1499−1505.

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(17) (2-^2H)Quinoline was prepared in good yields (85% after purification) by reduction of 2-chloroquinoline using zinc metal and ($^2H_4$)-acetic acid−D_2O at 0 °C. See the Supporting Information for experimental details or ref 18 for an alternate method.

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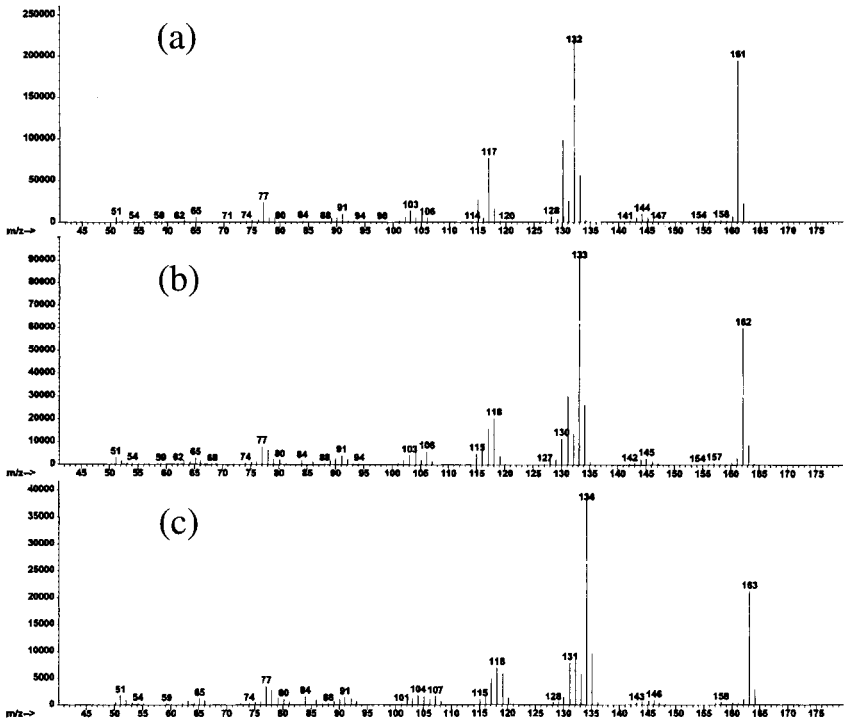


Figure 1. Mass spectra from deuterium substitution experiments: (a) 4-ethyl-1,2,3,4-tetrahydroquinoline (**4**); (b) (3-^2H)-4-ethyl-1,2,3,4-tetrahydroquinoline (**8**) obtained when the reaction was quenched with deuterium oxide; (c) 2-($^2H_2$)-4-ethyl-1,2,3,4-tetrahydroquinoline (**13**) obtained when 2-deuterium substituted quinoline was used as a substrate for the reaction.

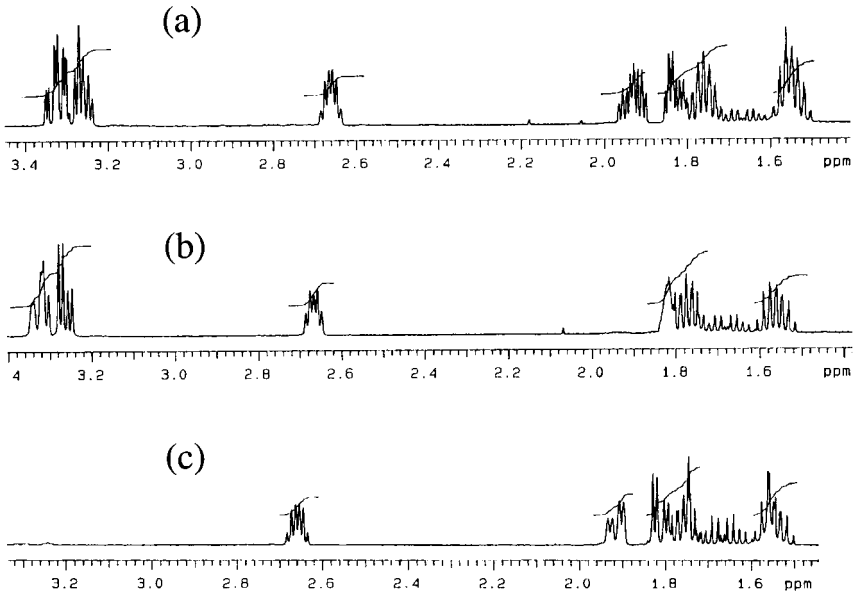


Figure 2. Portions of proton NMR spectra from deuterium substitution experiments: (a) 4-ethyl-1,2,3,4-tetrahydroquinoline (**4**); (b) (3-^2H)-4-ethyl-1,2,3,4-tetrahydroquinoline (**8**) obtained when the reaction was quenched with deuterium oxide; (c) 2-($^2H_2$)-4-ethyl-1,2,3,4-tetrahydroquinoline (**13**) obtained when 2-deuterium substituted quinoline was used as a substrate for the reaction.

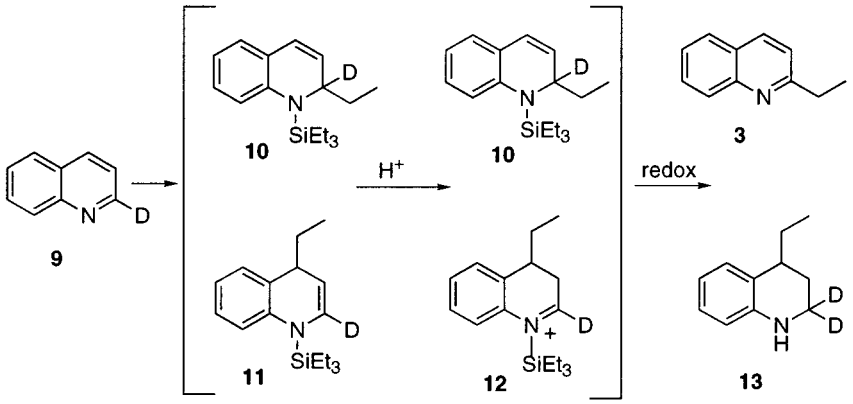
strategies. Our studies in this direction will be the subject of future publications.

Experimental Section

General Methods. CH_2Cl_2 was distilled over calcium hydride and quinoline over KOH. The remaining commercially available reagents and solvents were used without further purification and were handled by using standard syringe techniques. ^{1}H NMR spectra were recorded at 400 or 500 MHz using $CDCl_3$ as solvent and TMS (0.00 ppm ^{1}H) or $CHCl_3$ (7.26 ppm ^{1}H) as internal standards. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in hertz (Hz). GC−MS analyses were carried out using a Hewlett-Packard 6890 series instrument, and mass spectra were recorded at an ionizing voltage of 70 eV. Analytical TLC was carried out on silica gel plates. Flash column chromatography was conducted using silica gel 60 (EM Science, 230−400 mesh).

General Procedure for the Addition of Grignard Reagent to Quinolinium Triflates. Trialkyl/arylsilyl triflate (12.5 mmol) was added to a magnetically stirred solution of quinoline (10 mmol) in dry CH_2Cl_2 (20 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred until TLC showed consumption of quinoline (24−48 h). The

Scheme 3



solution was then cooled to −78 °C, and a 1 M solution of ethylmagnesium bromide (12.5 mL) was added dropwise. After 1−2 h, the cooling bath was removed, and the reaction mixture was stirred for another 8−10 h while warming to room temperature. The reaction mixture was then quenched by adding water (25 mL) or dilute acid (1 N HCl, 25 mL), and the resulting mixture was stirred for 2−4 h. The acidic mixture was neutralized with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography (silica, 1:20 EtOAc/hexanes) to afford the following, in order of elution: (i) 2-ethyl-1,2,3,4-tetrahydroquinoline (**5**) (observed only in the case of TMSOTf), (ii) 4-ethyl-1,2,3,4-tetrahydroquinoline (**4**), (iii) 2-ethylquinoline (**3**), and (iv) 4-ethylquinoline (**2**). All of the above products are known compounds[5] and are easily identified by their ^{1}H NMR and mass spectra.

Deuterium Substitution Experiments. (3-^{2}*H*)4-Ethyl-1,2,3,4-tetrahydroquinoline (8). In an experiment similar to the one described above, triethylsilyl triflate was used as the quaternizing agent, and the reaction was quenched with D_2O (25 mL). The products were isolated in the usual manner to obtain the deuterium-incorporated 4-ethyl-1,2,3,4-tetrahydroquinoline **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 5.6), 1.51−1.82 (3H, m), 2.66 (1H, ddd, J_1 = 4.0, J_2 = 6.8), 3.2−3.34 (2H, m), 3.85 (1H, br), 6.5 (1H, d, J = 6.4), 6.63 (1H, t, J = 5.6), 6.98 (1H, t, J = 5.6), 7.03 (1H, d, J = 6.4); MS (70 eV) m/z 162 M^+, 133 $(M - CH_3CH_2^-)^+$.

(2-^{2}*H*$_2$)4-Ethyl-1,2,3,4-tetrahydroquinoline (13). In an experiment similar to the one described in the general procedure, (2-^{2}*H*)quinoline was used as the substrate and triethylsilyl triflate as the quaternizing agent. The products were isolated in the usual manner to obtain the deuterated 4-ethyl-1,2,3,4-tetrahydroquinoline **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 5.6), 1.51−1.94 (4H, m), 2.66 (1H, m), 3.84 (1H, br), 6.5 (1H, d, J = 6.4), 6.63 (1H, t, J = 5.6), 6.98 (1H, t, J = 5.6), 7.03 (1H, d, J = 6.4); MS (70 eV) m/z 163 M^+, 134 $(M - CH_3CH_2)^+$.

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Supporting Information Available: Experimental procedure for the preparation of (2-^{2}*H*)quinoline (**9**), ^{1}H NMR spectra, and mass spectra for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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