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단신 (Notes)

Formation of 4-*tert*-Butyl-1,2,3,4-tetrahydroquinoline from One-pot Reactions of Quinoline/organoaluminum Complex with *tert*-Butyllithium

Hye Jin Jeong and Sung Keon Namgoong*
Department of Chemistry, Seoul Women's University, Seoul 01797, Korea.
**E-mail: sknam@swu.ac.kr*
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Quinoline derivatives are key structural units in many important natural products[1,2] and pharmaceuticals.[3,4] Nucleophilic addition reaction of quinoline with an organometallic reagent, such as organolithium and Grignard reagent, is a good method to obtain a 2-homologated quinoline or its 1,2-dihydroquinoline.[5-7]

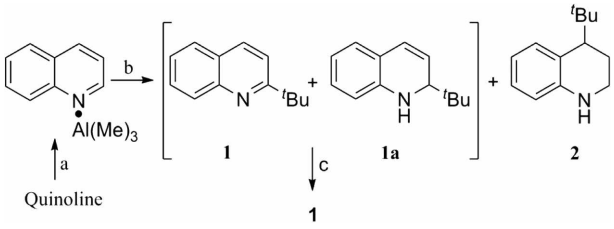
One of those homologation results was the example for the *t*-butyl ligand working as a nucleophile in quinoline chemistry: a conversion of quinoline (Q) to 2-*t*-butyl-1,2,3,4-tetrahydrolquinoline, proceeding through two step reactions.[7] Our result[8] previously reported was the other example: a boron-Lewis acid-induced conversion of **Q** to 2-*t*-butylquinoline **1** by one-pot reaction.

Treatment of **Q** with RLi (R: alkyl or aryl)/*N*-acylating agent,[9] to enhance the reactivity of quinoline at 2- or 4-position, also did afford the corresponding 1,2-dihydroquinoline derivative exclusively, except the reaction for benzyl ligand. None of the homologation strategies mentioned above is practically successful in the formation reactions of 4-homologated quinoline or its reduced derivative. The extended conjugation in **Q** makes nucleophilic attack at the 4-position a considerably more difficult task.

A continuous effort was then initiated to develop an effective one-pot method to yield 4-homologated quinoline derivative. The quinoline/organoaluminum complex with steric shielding at the 2-position might be suitable for preferential attack at the 4-position. Thus, the presented strategy began with the reaction of **Q**·$AlMe_3$ pre-complex with *t*-butyllithium (*t*-BuLi). This 1:1 complex is prepared *in situ* from the reaction of **Q** with $AlMe_3$ and directly used without purification. In our experience, $AlMe_3$ was generally less susceptible to nucleophilic attack by alkyl (or aryl) ligand than boron-Lewis acids,[8,9] such that its quinoline complex preferentially underwent homologation reaction with *t*-BuLi prior to decomposition of **Q**·$AlMe_3$ complex (*Scheme* 1).

The corresponding reaction initially produced an inseparable mixture of 2-*t*-butylquinoline **1**[8,10] and 2-*t*-butyl-1,2-dihydroquinoline **1a**[11], which is then practically transformed into the product **1** in 83% yield. Such a transformation was entirely achieved by open-vessel air oxidation[12] of the water-quenched reaction mixture and subsequent chromatographic purification. The other minor product **2** was isolated in 12% yield from the presented reaction (*Scheme* 1).

The ^{1}H NMR spectrum of the product **2** is shown in *Fig.* 1. The H-2, H-3 and H-4 signals of **Q** are typically found from 7.4 to 8.9 ppm, whereas those proton signals are not



***Scheme* 1.** The reaction of quinoline·$AlMe_3$ pre-complex with *t*-BuLi. Reagents and conditions: (a) $AlMe_3$ (1 equiv, 2.0 M in hexane), THF, 0 °C; (b) *t*-BuLi (1.1 equiv), THF, -78 °C, 12 h; (c) quenching with excess H_2O at -78 °C, additional stirring for 4 h at 25 °C, chromatographic purification; **1**: 83% yield; **2**:12% yield.

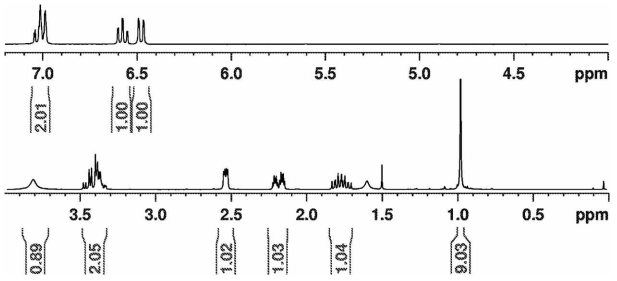


***Figure* 1.** The ^{1}H NMR spectrum of the product **2**.

observed in this spectrum. Therefore, it is indicated that the nitrogen-bearing ring of **Q** is fully reduced. In addition, a broad singlet signal (NH proton) at 3.8 ppm was not reproducibly detected through repeated NMR experiments.

The other issue was where the *t*-butyl group is introduced at the structure of the product **2**. As for the case of 2-*t*-butyl-1,2.3.4-tetrahydrolquinoline,[11] the one axial H-2 signal (dd, $J = 2.6$ and 11 Hz) is detected at 3.05 ppm. Instead, the two H-2 signals (m) and one *pseudo*-axial H-4 signal (dd, $J = 2.4$ and 5.4 Hz) of the product **2** are observed at 3.4 and 2.5 ppm, respectively. The two H-3 signals (m) are displayed at 2.2 and 1.8 ppm, representing the diastereotopic protons. Accordingly, it suggests that the *t*-butyl group (proton signals at 0.98 ppm) is attached at C-4 of the 1,2,3,4-tetrahydroquinoline backbone.

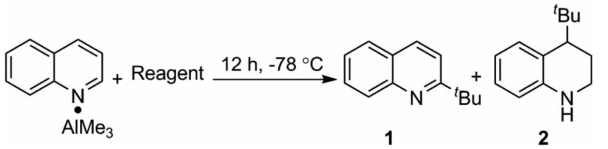
As a consequence of ^{1}H NMR structural analysis, the product **2** is considered as 4-*t*-butyl-1,2,3,4-tetrahydroquinoline (*Fig.* 1). The formation reaction of the product **2** is extremely rare. It is the only example[13] previously published by Degrand and Lund: a conversion reaction of **Q** to the reductive *t*-butylated quinoline derivatives. The electrochemical reaction of **Q** with *t*-butyl chloride, *via* an electron transfer reaction and formation of t-butyl radical, allowed to give 4-*t*-butyl-1,2,3,4-tetrahydroquinoline **2** in 9.5% yield. Although the ^{1}H NMR spectral data for the reported compound was not clearly assigned, both the chemical shift for each of the protons and the coupling constants (dd, $J =$ 2.5 and 5.0 Hz)[13] of H-4 matched with those of the resulting product **2**. The molecular weight of the product was also confirmed by its mass spectroscopic analysis.

This result is of particular interest as the reductive *t*-butylation product is hardly obtained through one-pot reaction without use of proper reducing agent. A curious question arise from production of the product **2**: how is this conversion possible from **Q**?. This question is addressed later by the reaction mechanism illustrated in *Scheme* 3.

The reductive *t*-butylation reactions of **Q** were examined to improve the yield of the product **2** under the reaction conditions employed several different solvents and organoaluminum reagents. The other homologation reactions of **Q** with Grignard reagents were also investigated. The subsequent results are summarized in *Tables* 1 and 2.

Initially, the reactions of **Q**·$AlMe_3$ complex with *t*-BuLi were investigated in three different solvents (*Table* 1). The result for solvent variation study showed that THF is considered as the most efficient solvent to record optimum yield of the products **1** and **2** without generation of side product among the solvents used (entry 1, *Table* 1). Instead, the rest of the products **1** and **2** was a side product which

***Table* 1.** The results for the formation of the products **1** and **2** in different solvents



Entry	Reagent[b]	Solvent	T (°C)	Yield (%)[a]	
				1	2
1	*t*-BuLi	THF	−78	83	12
2	*t*-BuLi	Toluene	78	47	14
3	*t*-BuLi	Benzene[c]	−10	76	11
4	EtMgBr	THF	−78	NR[d]	
5	PhMgCl	THF	78	NR[d]	

[a]Isolated yield based on the recovered quinoline. [b]1.1 equiv of reagent used. [c]The freezing point of benzene: 5.5 °C. [d]No reaction occurred.

remains unknown in toluene and benzene (entry 2 and 3, *Table* 1). Its ^{1}H NMR spectral data suggests that this side product presumably exists as a dimeric form of *t*-butylquinoline derivative.

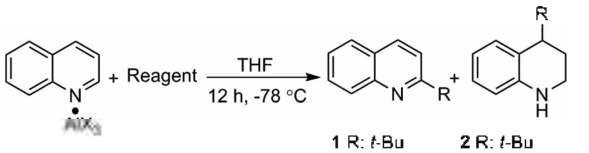
On the other hand, a replacement of *t*-BuLi with either EtMgBr or PhMgCl in THF solvent did not affect formation of the corresponding quinolines or tetrahydroquinolines at all (entry 4 and 5, *Table* 1). It is not clear why these reactions did not work at all. However, $AlMe_3$, as a Lewis acid, was a good reagent to produce the product **1**, whereas it was not an efficient reagent to obtain the product **2**. Its low yield is probably due to sterically not hindered and sufficiently reactive nature at 2-position of **Q**·$AlMe_3$ complex, thereby generating the compound **1** as the major product.

Therefore, the other strategy to improve the yield of the product **2** began with the reactions of sterically more hindered **Q**·AlX_3 (X: octyl, *t*-Bu and Ph) complexes with several organometallic reagents in THF (*Table* 2).

The use of Al(octyl)$_3$ was increased about three-fold in the formation of the product **2** as compared to that of $AlMe_3$ (entry 1, *Table* 2). A side product was also produced in this application and its yield was 19%. As for the case of Al(*t*-Bu)$_3$, it rather reduced the formation of the product **2**, unlike the case of Al(octyl)$_3$ (entry 2, *Table* 2). Al(*t*-Bu)$_3$ which is not commercially available was prepared by the previous literature procedure.[14] This result was unusual since Al(*t*-Bu)$_3$ is expected to behave as a sterically more hindered Lewis acid than Al(octyl)$_3$.

The preparation method employing $AlPh_3$ considerably improved the yield of the product **2** comparable to that of the product **1** (entry 3, *Table* 2). According to the reaction mechanism (*Scheme* 3) illustrated later, the theoretical

***Table* 2.** The results for the formation of the products **1**-**6**



1 R: *t*-Bu **2** R: *t*-Bu
3 R: 4-MeOPh **4** R: 4-MeOPh
5 R: Et **6** R: Et

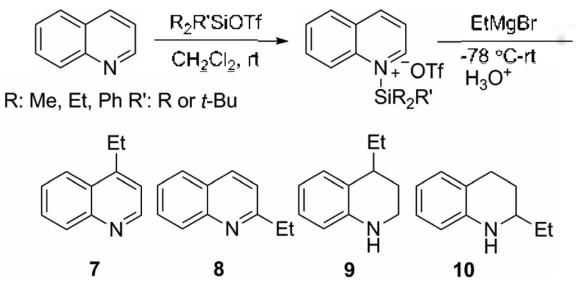
Entry	X[b]	Reagent[c]	Yield (%)[a]		
			1/2	3/4	5/6
1	octyl	*t*-BuLi	46/33	–	–
2	*t*-Bu	*t*-BuLi	73/21	–	–
3	Ph	*t*-BuLi	43/43	–	–
4	Ph	4-MeOPhMgBr[d]	–	78/0	–
5	Ph	EtMgBr		NR[e]	

[a]Isolated yield based on the recovered quinoline. [b]1.0 equiv of reagent used. [c]1.1 equiv of reagent used. [d]3.0 equiv of reagent used. [e]No reaction occurred.

maximum yield of the product **2** depends on that of the product **1** and must be equally 50% under the presented reaction condition. In fact, the 43% yield for each of the products is considered as the excellent yield in this application. 4% and 10% of the reactant **Q** were only recovered, respectively from the latter two reactions instead of a side product. A small amount of **Q** seems to be regenerated during additional stirring of the quenched reaction mixture for 4 h (*Scheme* 1) even though the reaction was completed.

Another reaction replaced $AlMe_3$/PhMgCl by $AlPh_3$/4-MeOPhMgBr proceeded as the previous reaction (entry 5, *Table* 1) was unsuccessful. The use of more nucleophilic 4-MeOPhMgBr resulted in formation of the product **3**[15] as a major product without formation of the corresponding tetrahydroquinoline derivative **4**[16] (entry 4, *Table* 2). In this case, **Q** was recovered in 9% yield. Finally, the reaction of **Q**·$AlPh_3$ complex with EtMgBr failed to produce any of the products **5**[17] and **6**[17] (entry 5, *Table* 2).

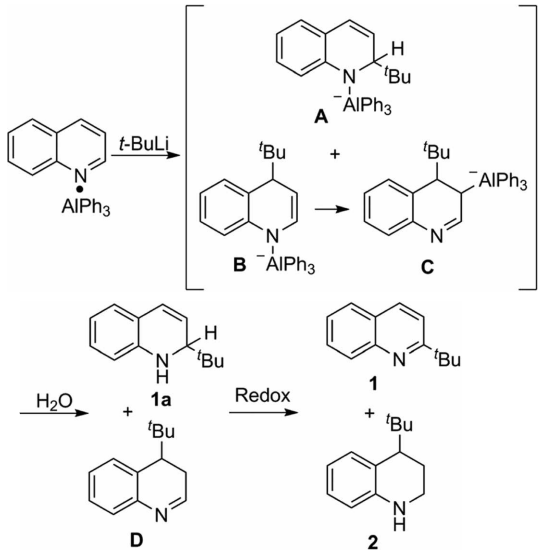
As for the specific formation reaction mechanism of 4-homologated tetrahydroquinoline derivative, there was the only example previously reported by Mani and collaborators.[17] The quinolinium triflates derived from the reactions of **Q** with trialkyl (or aryl)silyl triflates were converted to the products **7**-**10** (*Scheme* 2). The one-pot reactions of these salts with EtMgBr in CH_2Cl_2 allowed to generate the products **8** and **9** in the range of 29-51% and 14-42% yields as the major products. The identical reaction of 2-deuterioquinoline with EtMgBr and subsequent ^{1}H NMR analysis clearly proved that the products **8** and **9** were formed by the redox[18] reaction mechanism.



***Scheme* 2.** Reaction of ethylmagnesium bromide with quinolinium triflates.

However, this homologation strategy was not successful when it was applied to the formation reaction of the product **2**. A number of side products were observed in this application and the only product **1** was isolated in 20% yield. Addition of *t*-BuLi to CH_2Cl_2 may generate either deprotonated or dechlorinated species that can react with quinolinium triflates and leads to production of unknown side products. The same reaction of this quinolinium salt (R and R′: Me) did not work in THF and allowed to exclusively recover **Q** from the reaction mixture.

The one-pot reaction mechanism for the formation of products **1** and **2** is unambiguously proposed in *Scheme* 3, proceeding through 4-step process from **Q**·$AlPh_3$ complex: (1) 1,2- and 1,4-nucleophilic addition of *t*-BuLi to the complex; (2) rapid migration of the $AlPh_3$ group to a 3-carbon of the adduct **B**; (3) protonation of the adducts **A** and the more stable, conjugated imine **C**; (4) redox reaction between the imine **D** and the 1,2-dihydrointermediate **1a**.



***Scheme* 3.** The redox reaction mechanism for the formation of the products **1** and **2** from **Q**·$AlPh_3$ complex.

In the final step, the compounds **1** and **2** are formed through the redox reaction mechanism in which the more reactive 2-*t*-butyl-1,2-dihydroquinoline **1a** transfers a hydride to the imine species **D**.

It is noted that the formation of the product **1** affects the yield of the product **2** according to this redox reaction mechanism. Therefore, the maximum yield of the product **2** cannot exceed 50%.

In conclusion, one-pot homologation reaction of quinoline was achieved in the presence of $AlPh_3$/*t*-BuLi and recorded optimum yield of the products **1** and **2**. The structure of the product **2** was confirmed by ^{1}H NMR spectroscopic analysis and a literature search. The specific redox reaction mechanism for formation of the compounds **1** and **2** was also proposed.

EXPERIMENTAL

Materials

All the organometallic and organoaluminum reagents used in this work, except Al(*t*-Bu)$_3$, were purchased from Aldrich. THF solvent was freshly distilled and used.

General Procedure

The solution of AlX_3 (1.0 mmol) was added to the solution of quinoline (1.0 mmol) in THF (2 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was then cooled to -78 °C and the organometallic reagent (1.1 mmol) was added dropwise to the reaction mixture. After THF solution was stirred for another 12 h at -78 °C, the reaction was then quenched with water (2 mL) at -78 °C. The resulting mixture was stirred for additional 4 h at room temperature. THF was evaporated under reduced pressure and CH_2Cl_2 (2 mL) was added to the resulting mixture. The organic layer was separated and dried over $MgSO_4$. The dichloromethane solution was filtered and evaporated. The crude reaction mixture was purified column chromatography (ethyl acetate:hexane, 1:20) to give the homologated product as a either colorless oil or white solid.

2-*t*-Butylquinoline 1[10]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.5 (s, 9H, $(CH_3)_3$),7.5 (m, 2H, Ar-H), 7.7 (m, 1H, Ar-H), 7.8 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.1 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 38.1, 118.2, 125.6, 126.4, 127.2, 129.0, 129.4, 135.9, 147.4, 169.2 ppm.

4-*t*-Butyl-1,2,3,4-tetrahydroquinoline 2[13]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (s, 9H $(CH_3)_3$), 1.8 (m, 1H, H-3), 2.2 (m, 1H, H-3′), 2.5 (dd, *J* = 2.4 and 5.4 Hz, 1H, H-4), 3.4 (m, 2H, H-2), 3.8 (s, 1H, NH), 6.5 (d, *J* = 7.8 Hz, 1H, Ar-H), 6.6, (m, 1H, Ar-H), 7.0 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6, 29.1, 35.0, 39.4, 45.3, 113.4, 115.1, 122.4, 127.0, 131.2, 144.8 ppm; m/z (EI): 189 (M^+, 20%), 132 ((M-*t*-Bu)$^+$, 100%).

2-(4-Methoxyphenyl)quinoline 3[15]

White solid; mp: 122-123 °C (lit[15]: 122-124 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.9 (s, 3H, OMe), 7.1 (m, 2H, Ar-H), 7.5 (m, 1H, Ar-H), 7.7 (m, 1H, Ar-H), 7.8 (m, 2H, Ar-H), 8.2 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 114.2, 118.6, 125.9, 126.9, 127.4, 128.9, 129.5, 132.3, 136.6, 148.3, 156.9, 160.8 ppm.

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REFERENCES

1. Kayser, O.; Kiderlen, A.; Croft, S. *Parasitol. Res.* **2003**, *90*, S55.
2. Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 697.
3. Fetzner, S. *Appl. Microbiol. Biotechnol.* **1998**, *49*, 237.
4. Cragg, G. M.; Newman, D. J. *J. Ethnopharmacol.* **2005**, *100*, 72.
5. Crawforth, C.; Meth-Cohn, O.; Russell, C. *J. Chem. Soc., Chem. Commun.* **1972**, 259.
6. Eisch, J. J.; Comfort, D. R. *J. Organomet. Chem.* **1972**, *38*, 209.
7. Eisch, J. J.; Comfort, D. R. *J. Organomet. Chem.* **1972**, *43*, C17.
8. Seo, H. J.; Yoon, S. J.; Jang, S. H.; Namgoong, S. K. *Tetrahedron Lett.* **2011**, *52*, 3747.
9. Seo, H. J.; Namgoong, S. K. *Tetrahedron Lett.* **2012**, *53*, 3594.
10. Parekh, V.; Ramsden, J. A.; Wills, M. *Tetrahedron: Asymmetry.* **2010**, *21*, 1549.
11. Goldstein, S. W.; Dambek, P. J. *Synthesis.* **1989**, 221.
12. Louërat, F.; Fort, Y.; Mamane, V. *Tetrahedron Lett.* **2009**, *50*, 5716.
13. Degrand, C.; Lund, H. *Acta Chem. Scand.* **1977**, *31*, 593.
14. Hamdemir, I. K.; Özkar, S.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2013**, *378*, 333.
15. Su, W.; Yu, J.; Li, Z.; Zheng, B. *Synlett.* **2010**, *8*, 1281.
16. Rueping, M.; Theissmann, T.; Stoeckel, M.; Antonchick, A. P. *Organic & biomolecular chemistry.* **2011**, *9*, 6844.
17. Mani, N. S.; Chen, P.; Jones, T. K. *J. Org. Chem.* **1999**, *64*, 6911.
18. Minter, D. E.; Stotter, P. L. *J. Org. Chem.* **1981**, *46*, 3965.