Tetrahedron Letters,Vol.29,No.45,pp 5725-5728,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES AND 1,2,3,4-TETRAHYDRO-1,6-NAPHTHYRIDINES BY A DIRECTED LITHIATION REACTION [1]

J. Norman Reed,* Judy Rotchford,[2] and Dean Strickland[3]

Department of Chemistry, Memorial University of Newfoundland and

Sir Wilfred Grenfell College

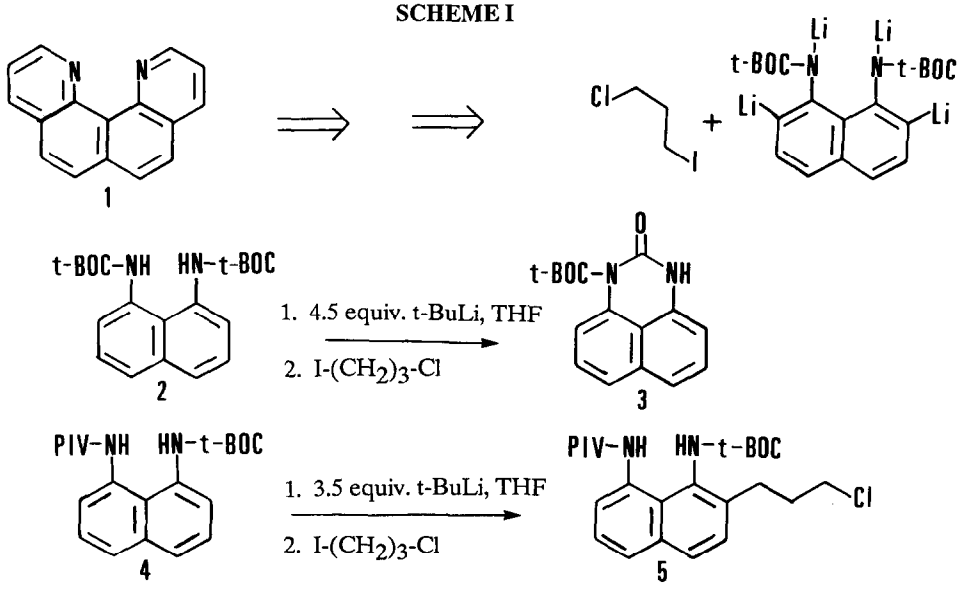
Corner Brook, Newfoundland, Canada A2H 6P9

Summary: N-(tert-butoxycarbonyl)anilines (**7**), are easily converted in a one pot reaction sequence into the N-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolines (**8**), by directed ortho lithiation followed by reaction with 1-chloro-3-iodopropane, hence providing a new versatile quinoline ring nucleus synthesis. In an analogous reaction 2-N-(tert-butoxycarbonyl)- and an 2-N-(pivaloylamino)pyridine are converted to 1,2,3,4-tetrahydro-1,6-naphthyridines.

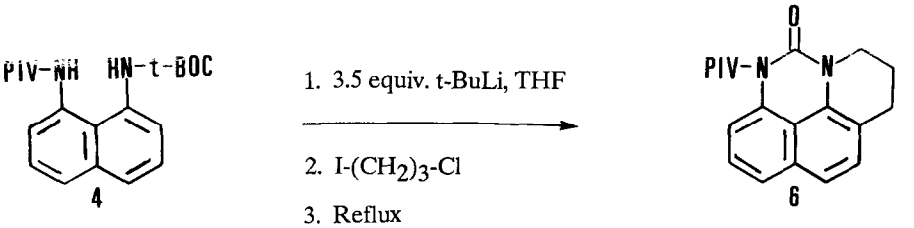
There are a large number of classical synthetic routes for the preparation of substituted quinolines,[4] but to date there have been only a few reports of the synthesis of the quinoline ring nucleus via a directed lithiation approach;[5] all of which involve more than one independent step. As part of a research effort aimed at the synthesis of the interesting "proton sponge" type molecule quino[7,8-h]quinoline (**1**),[6] we have developed a general synthesis of 5-, 6-, and 8- monosubstituted N-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolines (**8**) that is based on the ortho lithiation of the substituted N-(tert-butoxycarbonyl)anilines (**7**),[7] and is accomplished in a one pot procedure.

As shown in **SCHEME I**, our initial retrosynthetic plan for compound (**1**) involved the concept of a novel simultaneous double lithiation of the N,N'-di-(tert-butoxycarbonyl) derivative of 1,8-diaminonaphthalene (**2**), followed by quenching with two equivalents of 1-chloro-3-iodopropane so that the desired ring system might be formed in a one pot sequence. Unfortunately lithiation of (**2**) under standard

SCHEME I

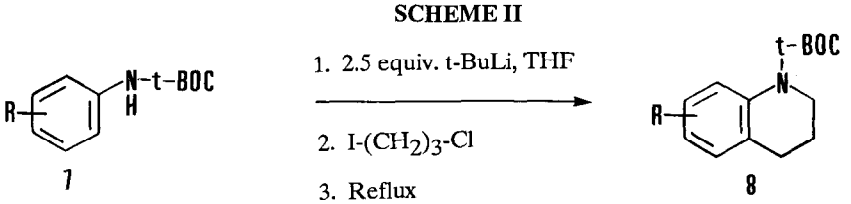


conditions[7a] gave an intramolecular cyclization leading to the formation of the urea-carbamate (**3**). We turned our attention to compound (**4**) in which one nitrogen was substituted with an N-pivaloyl (PIV) group,[8] and the other with the N-(tert-butoxycarbonyl) (t-BOC) group. Under standard lithiation conditions for the N-t-BOC group[7a] compound (**5**) was indeed obtained in 50% yield (40% recovered starting material) if the reaction mixture was quenched at -20 °C. If instead of quenching, the reaction mixture was warmed to the minimum temperature required to effect the desired ring formation, compound (**6**) was formed in 50% yied. Hence, the desired one pot quinoline ring nucleus synthesis was again plagued by urea formation in this special case.



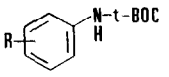
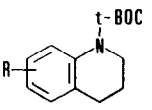
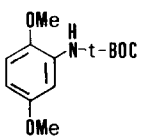
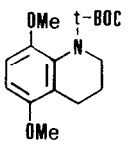
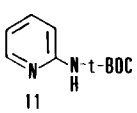
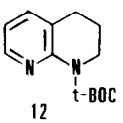
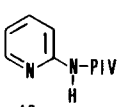
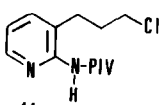
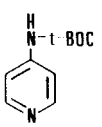
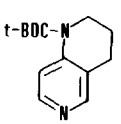
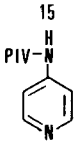
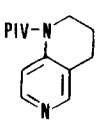
The simple idea of forming a quinoline ring by the cyclization of a an o-(3-chloropropyl)-aromatic amine is a very old one, however it has not been used as a general method of quinoline ring synthesis, due to the difficulty in obtaining the appropriately substituted aromatic rings.[9] Having now in hand a directed metalation approach to this type of quinoline ring nucleus construction, we decided to first generalize this reaction for simple substituted anilines before persuing compound (**1**). The general reaction is shown in **SCHEME II** and the specific examples are indicated in the **TABLE**. Several important points are worth noting. The reaction is versatile in that not only does it provide an alternate synthesis of unusually substituted tetrahydroquinolines, but also will provide direct access to a variety of substituted quinolines via simple aromatization of the de-protected derivatives of compounds (**8**).[10] Entries **6** and **7** in the **Table** indicate that there is a limitation to this reaction when there is steric crowding of the N-(t-BOC) group by an ortho substituent.[11] Entries **8, 9, 10** and **11** are of special note since they represent an attempt to synthesize the 1,6- and 1,8-naphthyridine ring systems by metalation of the appropriate N-(t-BOC)aminopyridines and N-(pivaloylamino)pyridines.[12,13] In the case of the N-(t-BOC)aminopyridines (entries **8** and **10**) the results were poor, so the N-(pivaloylamino)pyridines were attempted (entries **9** and **11**). The yield of the initial alkylation product (**14**) in the 2-(pivaloylamino)pyridine case was good. The failure of the cyclization in this case is likely a result of interaction between the pyridine nitrogen lone pair and the pivaloyl group.

SCHEME II



The obvious utility of the N-(t-BOC) group as an aromatic ortho metalation director demonstrated here needs to be explored further so that its full usefullness, particularly for the synthesis of new "proton sponges" may be realized. To this end we are continuing a full generalization of the reaction described here, as well as an investigation of the ability of the N-(t-BOC) group to effect ortho lithiation in larger fused aromatic ring systems, such as outlined in the approach to compound (1).[14]

Table. Synthesis of N-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydroquinoline and -1,2,3,4-tetrahydro-1,6-naphthyridine Derivatives

Entry	Aromatic N-(*t*-BOC) Derivative[a]	Product[b]	Yield (%)[c]	mp (bp, mmHg)[d]
	 7	 8		
1	7a (R = 4-Me)	8a (R = 6-Me)	51	(108-110, 0.5)
2	7b (R = 4-Cl)	8b (R = 6-Cl)	81	(128-130, 1.7)
3	7c (R = 2-F)	8c (R = 8-F)	85	(95-98, 0.3)
4	7d (R = 4-F)	8d (R = 6-F)	55	(105-108, 0.4)
5	7e (R = 4-OMe)	8e (R = 6-OMe)	44	(124-126, 0.3)
6	7f (R = 3-OMe)	8f (R = 5-OMe)	26	(118-120, 0.4)
7	 9	 10	0 (90% recovered starting material)	
8	 11	 12	0 (a number of unidentified products obtained)	
9	 13	 14	74	(135-138, 0.5)
10	 15	 16	28	(130-132, 0.5)
11	 17	 18	23	120-122, Ethyl acetate - Hexane

a. Obtained by reaction of the corresponding amine with di-tert-butyldicarbonate.[7a]
b. All compounds show spectral (IR, NMR, MS) data consistent with the assigned structure.
c. All yields are of chromatographically pure materials.
d. Kugelrohr air bath temperature.

Typical Procedures. The N-t-BOC compounds were lithiated according to the procedure described in refernce **7a** and the N-pivaloyl compounds were lithiated according the procedures described in reference **13c**. The resulting solutions of ortho lithiated species were then quenched at the appropriate temperature with 1.1 equiv. of 1-chloro-3-iodopropane, stirred a further 20 min, and then refluxed overnight. A typical reaction mixture was then quenched with water and partitioned between CH_2Cl_2 and water. The organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated and the residue was then purifired by flash chromatography using ethyl acetate-hexane as eluant to afford the pure product.

References and Footnotes

1. This paper is dedicated to the memory of Gerald I. Connelly in rememberance of his enduring love and support.

2. Second year undergraduate student at MUN-SWGC and holder of a Challenge '87 Canadian Student Employment and Education Development Grant.

3. Second year undergraduate student at MUN-SWGC and holder of a Challenge '88 Canadiana Student Employment and Education Development Grant.

4. Jones, G. **In** Jones, G. Ed. "Quinolines, Pt I. The Chemistry of Heterocyclic Compounds," Vol. 32, Wiley, New York, **1977.**

5. (a) Chong, R. J.; Siddiqui, M. A. and Snieckus V. Tetrahedron Lett. **1986**, 27, 5323. (b) Fishwick, C. W. G.; Storr, R. C.; Manley, P. W. J. Chem. Soc., Chem. Commun. **1984**, 1304. (c) Tamura, Y.; Chen, L. C.; Fujita, M.; Kita, Y. Chem. Pharm. Bull. Jpn. **1982**, 30, 1257.

6. This molecule was recently synthesized by a classical route, see Zirnstein, M. A.; Staab, H. A. Angew. Chem. Int. Ed. Engl. **1987**, 27, 460.

7. The aromatic N-(tert-butoxycarbonyl) group is a well established effecient ortho lithiation directing group. See for example (a) Muchowski, J. M.; Venuti, M. C. J. Org. Chem. **1980**, 45, 4798. (b) Saa, C.; Guitian, E.; Castedo, L. J. Org. Chem. **1986**, 51, 2781. (c) Sharp, M. J.; Cheng, W.; Snieckus, V. Tetrahedron Lett. **1987**, 28, 5093.

8. The N-pivaloyl group is also a well known aromatic directing group for ortho lithiation, but it can require more vigorous metalation conditions than the N-t-BOC group, and it is more difficult to remove by acid hydrolysis than the N-t-BOC group, see Fuhrer, W.; Gschwend, H. W. J. Org. Chem. **1978**, 44, 1133.

9. Reference 4, page 222.

10. For an example of this type of aromatization see: Tanga, M.J.; Reist, E.J. J. Heterocycl. Chem. **1986**, 23, 747.

11. Macdonald, J. E.; Poindexter, G. S. Tetrahedron Lett. **1987**, 28, 1851.

12. For a recent general review of the synthesis and importance of naphthyridines see Noravyan, A. S.; Paronikyan, E. G.; Vartanyan, S. A. Pharm. Chem. J. **1985**, 19, 439. (Chem. Abs. 104: 186324c).

13. For previous examples of lithiations of these pyridine derivatives see for example (a) Reference 5b. (b) Roland, D. M.; Macchia, W. 10th International Congress of Heterocyclic Chemistry, August 11-16, 1985. Waterloo, Canada. Abstract P1-10. (c) Turner, J. A. J. Org. Chem. **1983**, 48, 3401.

14. We are very grateful to NSERC Canada, the Department of Chemistry of Memorial University and the Department of Chemistry of Sir Wilfred Grenfell College for financial support of our research programs. We would also like to thank Michelle Simms (first year undergraduate student MUN-SWGC) for her help with experimental aspects of the work, as well as Mr. William Layden, Ms. Wanda Ellsworth and Mr. Wade Goulding for technical support.

(Received in USA 24 June 1988)