Tetrahedron Letters 51 (2010) 3876–3878

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 5-hydroxyquinolines

Jianke Li, Daniel W. Kung, David A. Griffith *

Department of Cardiovascular, Metabolic and Endocrine Diseases, Pfizer Global Research and Development, Groton, CT 06340, United States

ARTICLE INFO

Article history:
Received 7 April 2010
Revised 12 May 2010
Accepted 13 May 2010
Available online 21 May 2010

ABSTRACT

A series of 5-hydroxyquinolines has been prepared via the Skraup reaction. Several regioisomers were made either by selective displacement of a leaving group or by using a bromo substituent as a blocking group. The bromo group was found to be an excellent blocking group due to its stability during the Skraup reaction and easy removal thereafter. Halides at the 5-position of quinoline were found to be much more reactive than those at the 7- and 8-positions. Finally, we have also found a unique method to reduce the pyridyl ring on quinolines, leaving a halogen substituent untouched.

Quinolines are important building blocks for pharmaceutical agents. They exist in many drugs, such as the antimalarial drugs Chloroquine, Quinine, Mefloquine, and Primaquine, and the antiarrhythmic drug Quinidine.[1] Quinolines have also proven useful for targeting antiviral, antibacterial, anti-inflammatory, and anticancer drugs.[2] Although a large number of methods to make quinolines have been developed, the synthesis of highly substituted quinolines is still a formidable task. We report herein the syntheses of some 5-hydroxyquinoline derivatives.

A series of methyl- and chloro-substituted 5-hydroxyquinolines was needed for the systematic exploration of SAR during a recent project (Fig. 1). Among the well-established methods for preparing quinolines, such as the Combes,[3] Conrad–Limpach,[4] Friedlander,[5] Gould–Jacobs,[6] Meth-Cohn,[7] Pfizinger,[8] and Skraup quinoline syntheses,[9] the Skraup quinoline synthesis was attractive because the readily available aniline and crotonaldehyde starting materials were expected to enable the synthesis of most of our desired compounds.

The synthesis of methyl-substituted 8-chloro-5-hydroxyquinoline derivatives is outlined in Scheme 1.

The Skraup quinoline synthesis, 'the worse witch's brew',[10] is notorious for the difficult purification that follows the reaction. Typical reported yields are around 50%. In our hands, provided that the mixture of compound **3** in hydrochloric acid was homogeneous before compound **4** was added, the cyclization between anilines **3** and crotonaldehydes **4** proceeded cleanly as determined by LC–MS. However, analysis by thin-layer chromatography showed multiple impurities, and purification by flash column chromatography was inefficient.

Purification was greatly simplified by forming the quinoline's zinc chloride complex.[11] After the cyclization reaction was complete, the mixture was cooled to room temperature and 2 equiv of solid zinc chloride was added in one portion, and the resulting mixture was stirred at room temperature for 30 min and then at 0 °C for 1.5 h. The precipitate was collected by filtration and was washed sequentially with 1 N HCl, isopropanol, and water. Finally, the zinc chloride quinoline complex was broken by treatment with NH_4OH and extraction with ether to afford the desired Skraup products.

For the synthesis of the methyl-substituted isomers of 8-chloro-5-hydroxyquinoline, the requisite anilines and crotonaldehydes

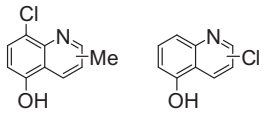

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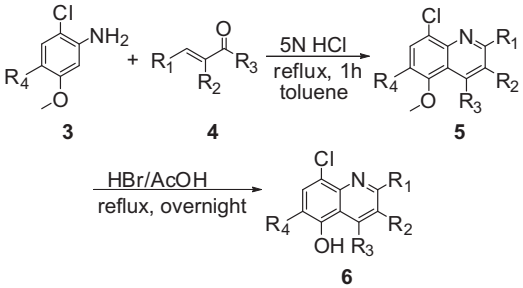
Figure 1. Methyl- and chloro-substituted 5-hydroxyquinoline targets.



3 4 5 6

Scheme 1. Synthesis of **6** via the Skraup reaction.

* Corresponding author. Tel.: +1 860 441 6215; fax: +1 860 715 8324.
E-mail address: david.a.griffith@pfizer.com (D.A. Griffith).

0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.05.058

Table 1
The isolated yields of **5** and **6**

R_1	R_2	R_3	R_4	Yield of **5**[a] (%)	Yield of **6** (%)
Me	H	H	H	23	22
H	Me	H	H	27	77
H	H	Me	H	35	88
H	H	H	Me	30	79

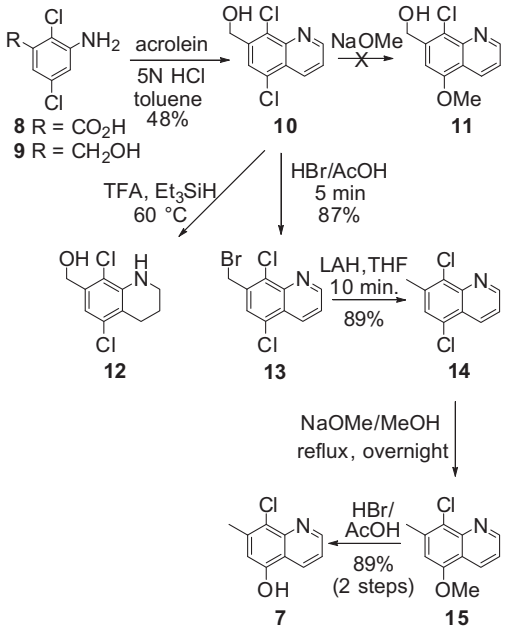
[a] No attempt was made to recover additional desired product from the filtrate after isolation of the zinc complex.

were readily available. 5-Methoxyquinolines **5** were selected as the penultimate intermediates based on the expectation that the methyl ether would be a suitable protecting group for the harsh Skraup conditions. The isolated yields of intermediates **5** from unoptimized reaction conditions are shown in Table 1.

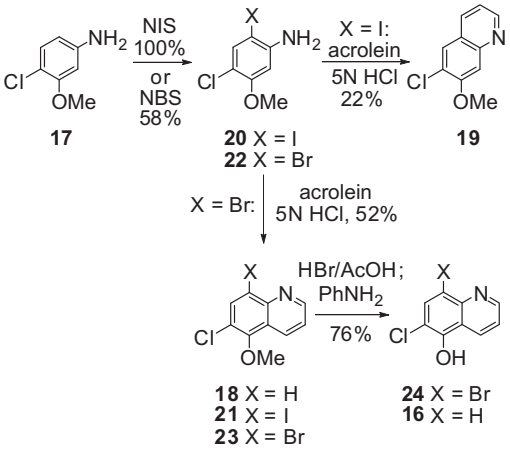
Initial attempts to cleave the methyl ether by treating the 5-methoxyquinolines with BCl_3 (0 °C) or diethylaminoethanethiol/NaOEt (160 °C) afforded no detectable conversion. However, heating the methyl ether **5** in a refluxing mixture of 1:1 acetic acid and 49% hydrobromic acid afforded the desired 5-hydroxyquinoline **6** after purification by column chromatography. In general the demethylation was very sluggish, especially for R_3 = methyl, likely due to steric hindrance, although the yields were generally reasonable (Table 1).

The synthesis of 8-chloro-7-methyl-5-hydroxyquinoline (**7**) using the procedure outlined in Scheme 1 was not pursued because the required aniline was not readily available. An alternate approach to **7** is outlined in Scheme 2. Complete reduction of the acid was envisioned to provide the desired 7-methyl group. Based on a few literature examples suggesting that 5-halo-quinolines are more reactive to nucleophilic substitution than 7- or 8-halo-quinolines[12], the selective reaction at one of the chlorine-bearing carbons was expected to allow the introduction of the 5-hydroxy group.

The reduction of compound **8** with lithium aluminum hydride gave compound **9**, which underwent Skraup cyclization to afford compound **10**. Attempted displacement of the 5-chloro group from **10** with sodium methoxide afforded a complex product mixture. We reasoned that the benzylic alcohol was interfering with the desired transformation and therefore attempted to remove the



Scheme 2. Synthesis of compound **7**.



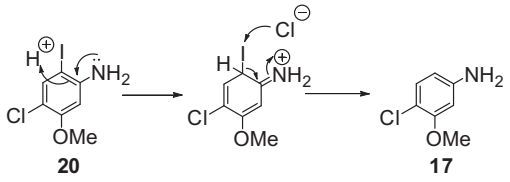
Scheme 3. Synthesis of **16** using blocking group.

hydroxyl group prior to NaOMe displacement. Treatment of compound **10** with TFA/Et_3SiH at room temperature afforded no detectable reaction. However, when the reaction was heated at 60 °C overnight, compound **12** was isolated in 60% yield. The selective reduction of the pyridine ring in the presence of the halogens and the benzylic alcohol is an uncommon transformation that may be of significant synthetic utility. Further studies will be conducted to explore its scope.

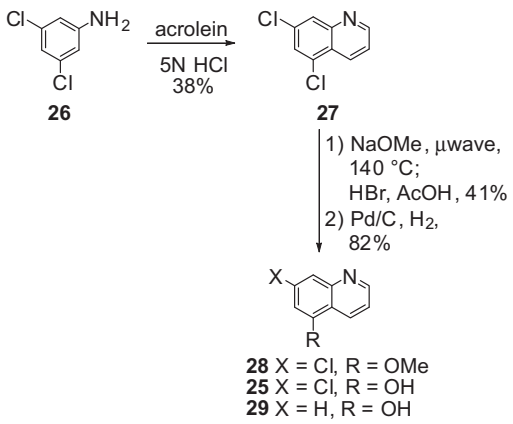
Activating the benzylic alcohol for reduction by conversion to the corresponding bromide was accomplished by treatment of **10** with HBr/AcOH. Attempts to remove the bromide from **13** with Zn/HBr/AcOH and Zn/NaOH were not successful,[13] however, lithium aluminum hydride readily cleaved the bromide to afford compound **14** in high yield. Selective displacement of one chloro group was achieved by heating compound **14** with NaOMe in methanol at reflux for 18 h to afford compound **15**. The assigned 8-chloro-5-methoxy structure was verified by observation of NOE enhancements between the methoxy and adjacent aromatic protons. The methyl ether protecting group was removed with HBr/AcOH to afford compound **7**.

The synthesis of the 6- and 7-chloro-5-hydroxyquinoline isomers via the Skraup reaction afforded challenges in achieving the desired regiochemistry. The synthesis of 6-chloro derivative **16** is outlined in Scheme 3. To avoid the probability that compound **17** used directly in the Skraup reaction would form both the desired isomer **18** and its isomer **19**, an iodo substituent was placed para to the methoxy group to act as a removable blocking group. Treatment of compound **17** with *N*-iodosuccinimide gave a quantitative yield of compound **20**. The subsequent Skraup reaction, however, did not give desired compound **21**, but exclusively compound **19**, whose structure was confirmed by COSY NMR. Assessment of the stability of compound **20** under the Skraup reaction conditions demonstrated that 60% of compound **20** decomposed to compound **17** within 10 min at 100 °C, likely by the mechanism outlined in Scheme 4.

A bromo, rather than iodo, substituent was expected to be less labile to reductive cleavage during the Skraup reaction (Scheme 3).



Scheme 4. Mechanism for conversion of **20** to give **17**.



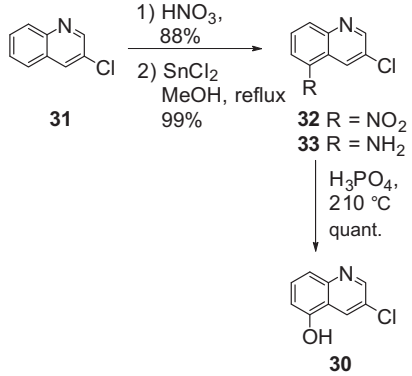
Scheme 5. Synthesis of compound **25**.

Compound **22** underwent Skraup cyclization to provide the desired compound **23**, without evidence of debromination. Heating methoxyquinoline **23** in HBr/AcOH afforded the expected compound **24**, with trace amounts of compound **16** also observed.

Although it has been reported that bromo groups para or ortho to an amino group are readily removed with HBr/AcOH,[14] extended heating time did not further promote debromination of **24**. We hypothesized that the addition of a reagent to scavenge any Br_2 produced might further promote the debromination reaction. In the presence of aniline (3 equiv) as bromine-scavenger, compound **23** was completely transformed to the desired compound **16** after heating at 120 °C with HBr/AcOH overnight. Upon cooling to room temperature, the solid was removed by filtration and the filtrate was then treated with saturated aqueous Na_2CO_3 solution to give a brown precipitate. Rinsing the isolated precipitate with ether followed by drying gave compound **16**, as determined by ^{1}H NMR.

The planned synthesis of 7-chloro derivative **25** was based on the belief that regioselective chloride displacement from **27** could be achieved (Scheme 5).[12] Compound **27** was readily prepared by the Skraup reaction. Treatment of compound **27** with NaOMe at 140 °C in a microwave reactor for 4 h afforded an inseparable mixture of compounds **28** and **25**. Pure compound **25** was isolated after demethylation with HBr/AcOH. Unfortunately ^{1}H NMR analysis could not exclude the possibility that 5-chloro-7-hydroxyquinoline had been formed rather than the desired compound **25**. Confirmation of the desired and expected regioselectivity was achieved by hydrogenolysis to produce the known compound **29**.

Synthesis of 3-chloro derivative **30** using the Skraup reaction would require the starting material 2-chloroacrolein. The literature preparation of 2-chloroacrolein reports the reaction of acrolein with



Scheme 6. Synthesis of compound **30** via the Bucherer reaction.

chlorine gas and subsequent distillation.[15] To avoid safety hazards with this route, an alternative to the Skraup synthesis was employed (Scheme 6). Regioselective nitration of compound **31** with fuming nitric acid gave compound **32**, which was then reduced with tin dichloride to afford compound **33** in nearly quantitative yield.

The conversion of aniline **33** into phenol **30** proved to be problematic. The stepwise conversion, treating compound **33** first with sodium nitrite in sulfuric acid and then with aqueous NaOH gave only trace amounts of the desired product. The Bucherer reaction with sodium hydrogensulfite,[16] a direct conversion from aniline to phenol, failed to give the desired result. We reasoned that sodium hydrogensulfite might not be sufficiently acidic for the quinoline substrate and therefore heated compound **33** at 210 °C for 2 h in a microwave reactor in the presence of phosphoric acid resulting in complete transformation of compound **33** to 5-hydroxyquinoline **30**.

In summary, a series of 5-hydroxyquinolines has been prepared. Several regioisomers were made either by selective displacement of a leaving group or by using a bromo substituent as a blocking group in the Skraup reaction. The bromo group was found to be an excellent blocking group due to its stability during the Skraup conditions and easy removal thereafter. Halides at the 5-position of quinoline were found to be much more reactive than those at the 7- and 8-positions. Finally, we have also found a unique method to reduce the pyridyl ring on quinolines, leaving a halogen substituent untouched.

References and notes

1. (a) Chauhan, P. M.; Srivastava, S. K.. *Curr. Med. Chem.* **2001**, *8*, 1535; (b) Mihaly, G. W.; Ward, S. A.; Edwards, G. *Br. J. Clin. Pharmacol.* **1985**, *19*, 745; (c) Sadeque, A. J.; Wandel, C.; He, H.; Shah, S.; Wood, A. J. *Clin. Pharmacol. Ther.* **2000**, *68*, 231; (d) Sweeney, T. R. *Med. Res. Rev.* **1981**, *1*, 281.
2. (a) Kirsch, R.; Kleim, J.; Riess, G.; Rosenstock, B.; Rösner, M.; Winkler, I. PCT Int. Appl. WO1997037977, 1997.; (b) Azuma, R.; Saeki, M.; Yamamoto, Y.; Hagiwara, Y.; Grochow, L. B.; Donehower, R. C. *Xenobiotica* **2002**, 63; (c) Baker, W. R.; Ryckman, D. M.; Cai, S.; Dimitroff, M.; Shang, X. PCT Int. Appl. WO2002018345, 2002.; (d) Jaroch, S.; Lehmann, M.; Schmees, N.; Berger, M.; Rehwinkel, H.; Krolikiewicz, K.; Skuballa, W.; Schäcke, H.; Schottelius, A. PCT Int. Appl. WO2003082827, 2003.
3. (a) Combes, A. *Bull. Soc. Chim. Fr.* **1888**, *49*, 89; (b) Yamashkin, S. A.; Yudin, L. G.; Kost, A. N. *Chem. Heterocycl. Compd.* **1993**, 845; (c) Sanna, P.; Carta, A.; Paglietti, G. *Heterocycles* **1999**, *51*, 2171.
4. (a) Conrad, M.; Limpach, L. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 944; (b) Jaroszewski, J. W. *J. Heterocycl. Chem.* **1990**, *27*, 1227; (c) Wang, H.-K.; Bastow, K. F.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1996**, *39*, 1975; (d) Raban, M.; Martin, V. A.; Craine, L. *J. Org. Chem.* **1990**, *55*, 4311.
5. (a) Friedlander, P. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2572; (b) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37; (c) Thummel, R. P. *Synlett* **1992**, 1; (d) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257; (e) Arcadi, A.; Chiarini, M.; Giuseppe, S. D.; Marinelli, F. *Synlett* **2003**, 203; (f) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K. *Synlett* **2004**, 963.
6. (a) Gould, R. G.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890; (b) Dave, C. G.; Shah, R. D. *Heterocycles* **1999**, *51*, 1819; (c) Zhang, M. Q.; Haemers, A.; Berghe, V. D.; Pattyn, S. R.; Bollaert, W.; Levshin, I. *J. Heterocycl. Chem.* **1991**, *28*, 673.
7. (a) Meth-Cohn, O. *Heterocycles* **1993**, *35*, 539; (b) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110; (c) Hayes, R.; Meth-Cohn, O. *Tetrahedron Lett.* **1982**, *23*, 1613.
8. (a) Bergstrom, F. W. *Chem. Rev.* **1944**, *35*, 77; (b) Deady, L. W.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 2040.
9. (a) Skraup, Z. H. *Ber.* **1880**, *13*, 2086; (b) O'Neill, P. M.; Tingle, M. D.; Mahmud, R.; Storr, R. C.; Ward, S. A.; Park, B. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2309; (c) Fujiwara, H.; Kitagawa, K. *Heterocycles* **2000**, *53*, 409; (d) Boger, D. L.; Boyce, C. W. *J. Org. Chem.* **2000**, *65*, 4088.
10. (a) Li, J. *Named Reactions in Heterocyclic Chemistry*; John Wiley & Sons: Hoboken, 2005. p. 488; (b) Eva, R. R. U.S. Patent 6103904, 2000.
11. Leir, C. M. *J. Org. Chem.* **1977**, *42*, 911.
12. (a) Johnson, C. N.; Rami, H. K.; Stemp, G.; Thewlis, K.; Thompson, M.; Vong, A.K.K. PCT Int. Appl. WO 2002034754, 2002.; (b) Ward, S. E. PCT Int. Appl. WO 2003068771, 2003.
13. Fukata, G.; Kubota, Y.; Mataka, S.; Thiemann, T.; Tashiro, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 592.
14. Choi, H. Y.; Chi, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 9202.
15. Guest, H.R.; Stansbury, H.A., Jr. U.S. Patent 2815385, 1957.
16. (a) Sauer, E.; Polz, K.; Schopf, G.; Bendig, J. *J. Prakt. Chem.* **1991**, *333*, 467; (b) Seeboth, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 307; (c) Gilbert, E. E. *Sulfonation and Related Reactions*; John Wiley & Sons: New York, 1965. p 166.