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Regioselective bromination: Synthesis of brominated methoxyquinolines

Osman Çakmak [a, *], Salih Ökten [b]

[a] Department of Nutrition and Dietetics, School of Health Sciences, İstanbul Gelişim University, 34315, Avcılar, İstanbul, Turkey
[b] Department of Maths and Science Education, Faculty of Education, Kırıkkale University, 71450, Yahşihan, Kırıkkale, Turkey

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ABSTRACT

Simple synthetic methods are described for the synthesis of valuable polyfunctional brominated methoxyquinolines **10**–**13**, **20**–**21**, and **24**–**25**. Three regioselective routes are described for convenient preparation of brominated methoxyquinolines at the C-2, C-3, and C-5 positions with consecutive reaction steps under mild reaction conditions using molecular bromine. While bromination of 6-bromo-8-methoxy-1,2,3,4-tetrahydroquinoline (**8**) selectively gave 3,6-dibromo-8-methoxyquinoline (**10**) and 3,5,6-tribromo-8-methoxyquinoline (**11**), the reaction of 6,8-dimethoxy-1,2,3,4-tetrahydroquinoline (**9**) resulted in the formation of 3-bromo-6,8-dimethoxyqinoline (**12**) and tribromide **13**. On the other hand, direct bromination of 6-methoxy- **17** and 6,8-dimethoxyquinoline (**19**) gave 5-bromo derivatives **20** and **21**. However, the reaction 3,6-dimethoxyquinoline (**8**) resulted in dibromination to form 2,5-dibromoquinoline (**24**). This process selectively led to functionalization of the quinoline ring at both the C-2 and C-5 positions.

1. Introduction

Developments in the synthesis of new quinoline derivatives are progressing and expanding hugely due to their pharmaceutical importance. Applications of quinoline derivatives have become widespread from anticancer drugs to almost every branch of medicinal chemistry.[1–3] A variety of heterocyclic ring systems for anticancer activity have been widely reported by a number of researchers to develop new approaches to a variety of heterocyclic ring systems, especially including 3-substituted quinoline derivatives.[3]

Several methods for the synthesis of haloquinolines have been reported, including direct halogenation, which always suffers from poor regioselectivity and overhalogenation,[4] but only a few methods for the regioselective synthesis of 3-haloquinolines are known.[5] The development of a new synthetic method for preparing halogen-containing quinolines would enable the synthesis of diverse quinoline frameworks because the halogen atom could enhance biological activity in many cases[6] and could also be used for further functionalization in preparing other molecules.[7,8]

There has been enormous interest in developing efficient methods for the synthesis of quinoline derivatives considering their significant applications in the field of bioorganic, industrial, and synthetic organic chemistry. The Skraup, Friedländer, Doebner–von Miller, and Combes syntheses[8,9] of quinoline derivatives are important classical synthetic approaches. Almost all synthetic strategies are based on metal catalyzed cyclizations or acid catalyzed cycloadditions.[9] However, quinoline synthesis has important disadvantages, such as harsh reaction conditions and highly acidic media,[10] that make it tedious to isolate the product from the crude mixture. For instance, the Skraup procedure includes reactions of *meta*- or 3,4-disubstituted anilines normally giving a mixture of regioisomers difficult to isolate. Most of these methods are not fully satisfactory with respect to yield,[11–13] reaction conditions,[11,13] generality,[13,14] and practical use.[11,13] These synthetic problems have encouraged researchers to develop a practical efficient procedure for the synthesis of these important heterocycles.[15]

It is interesting that despite the considerable synthetic and biological interest in quinoline derivatives, very few general synthetic routes are available starting from quinoline or tetrahydroquinoline cores themselves. Recently, we have found that the bromination reaction of substituted 1,2,3,4-tetrahydroquinolines is

* Corresponding author.
E-mail address: ocakmak@yildiz.edu.tr (O. Çakmak).

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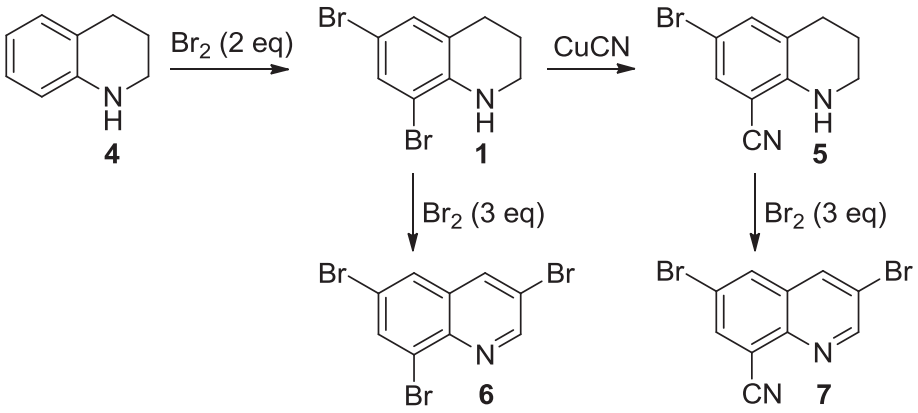


Scheme 1. Preparation of 3-bromo quinolines from tetrahydroquinolines.

a good starting point for functionalizing both rings. In our previous publications, brominated tetrahydroquinolines were transformed to their respective derivatives.[9,16] Bromination of 6-bromo-8-cyano-1,2,3,4-tetrahydroquinoline gave corresponding 3-brominated quinoline derivatives (Scheme 1).[16] This methodology uses neither metal catalyzed cyclizations nor acid catalyzed cycloadditions. The process constitutes a rapid and convenient method for obtaining selective brominated aromatic compounds as the sole products in high yields.

This work presented herein is a continuation of our ongoing research and focuses on the synthesis of polyfunctional quinolines, starting from methoxy 1,2,3,4-tetrahydroquinoline, which provides an efficient synthesis of brominated derivatives at C-3 and C-5 (Scheme 1). We are also interested in investigation of the biological activity and structure–activity relationship (SAR) results because the synthesized quinoline derivatives exhibited promising anticancer activities and interesting SARs (Scheme 2).[9,17–20]

2. Results and discussion

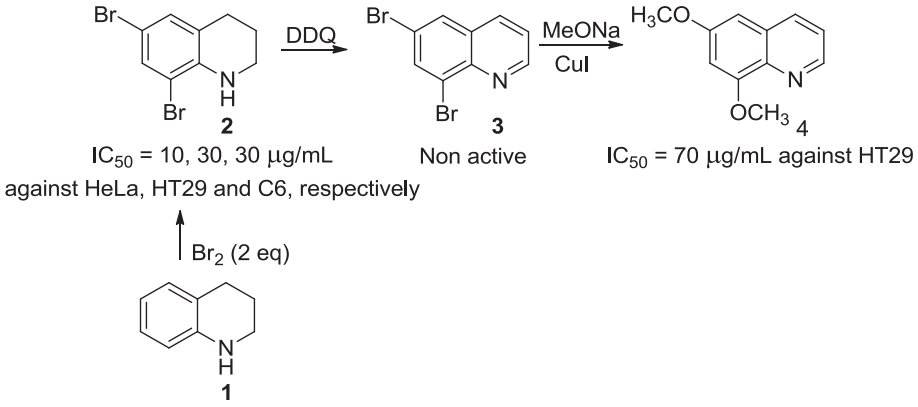
The starting compounds were synthesized according to our procedures reported previously starting from 1,2,3,4-tetrahydroquinoline (**1**) (Scheme 3).[9,21,22] First we studied bromination of methoxy quinolines **8** and **9** with different equivalents of bromine. The product ratios and conversions are compiled in Scheme 4. While bromination of **8** with three equivalents of bromine afforded compound **10**, bromination with four equivalents of bromine gave tribromide **11** (Scheme 4).

Dimethoxide **9** was brominated with 3 equivalents of bromine, and the dibromide **12** was obtained as the sole product in high yield (80%) in reaction conditions similar to those of compound **8**. On the other hand, bromination of **9** with four equivalents of bromine gave dibromide **13** in 78% yield. The dibromide **13** was also achieved by the bromination of compound **12** using one equivalents of bromine in 85% yield (Scheme 5).

The ^{1}H NMR spectra of compounds **10**, **11**, **12**, and **13** exhibit simple aromatic signals, which are established easily by their vicinal coupling patterns. The ^{1}H NMR spectra of **10** consisted of four characteristic aryl signals with *meta* couplings (^4J = 1.6 Hz), indicating the positions of the bromine groups. The observation of *meta* couplings and a singlet signal (δ 4.1) in the ^{1}H NMR spectrum of **10** is consistent with the methoxy group at C-8 and two bromines bound to the C-3 and C-5 positions (Table 1). In the ^{13}C NMR spectrum of **10**, methoxy (δ_C 55.6) and aryl signals also support the suggested structure.

Compound **11** was unambiguously assigned on the basis of its ^{1}H NMR spectrum due to the three CH signals, which are one singlet (7.31 ppm, H-7) and two doublets with *meta* coupling ($J_{2,4}$ = 2.0 Hz) at δ_H 8.92 and 8.75, belonging to H-2 and H-4, respectively. The presence of six quaternary and three CH carbon atoms in the ^{13}C NMR spectrum confirms two bromine atoms at the C-3 and C-5 positions in the structure (Table 1).

The NMR spectroscopy clearly identified that the expected products **12** and **13** are formed. The ^{1}H NMR spectrum of 3,6-dibromide **12** exhibits four *meta* coupled aryl signals (δ_H 8.65 and 8.51, $^4J_{5,7}$ = 1.8 Hz; δ_H 7.02 and 6.56, $^4J_{2,4}$ = 2.0 Hz) appearing downfield in comparison with starting material **9**.[9] However, the ^{1}H NMR of **13** consists of two *meta* coupled doublets of H-4 (δ_H 8.68,



Scheme 2. Structure-Activity Relationship for compounds **2**, **3** and **4**.