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Bromination of quinoxaline and derivatives: Effective synthesis of some new brominated quinoxalines

Sefa Uçar [a], Selçuk Eşsiz [a, b], Arif Daştan [a, *]

[a] Atatürk University, Science Faculty, Department of Chemistry, TR-25240, Erzurum, Turkey
[b] Hakkari University, Engineering Faculty, Department of Chemical Engineering, TR-30000, Hakkari, Turkey

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ABSTRACT

The synthesis of brominated quinoxaline derivatives starting from several kinds of quinoxaline by different bromination strategies was studied. First the synthesis of some brominated quinoxalines was accomplished along with the development of an alternative and effective synthesis of some known compounds. A new, clean, and effective synthetic method for selective reduction of quinoxaline to 1,2,3,4-tetrahydroquinoxaline was also developed. The products obtained were characterized by means of NMR spectroscopy, elemental analyses, and mass spectrometry.

1. Introduction

The chemistry of benzenoid hydrocarbons such as naphthalene goes back to the 19th century.[1] Although many investigations have been performed on this kind of molecule, benzenoid hydrocarbons are still valuable due to their importance in both material sciences and medicinal chemistry. Two nitrogen-containing heteroaromatic naphthalene derivatives, called diazanaphthalene and naphthyridines or diazines, are important structures found in many natural and synthetic compounds.[2]

Among them, 1,4-diazanaphthalene, that is to say quinoxaline (**1**), is a crucial core structure of various macrocyclic antibiotics such as echinomycin,[3] levomycin,[4] and actinoleutin[5] that are known to inhibit growth of Gram-positive bacteria, and are active against various transplantable tumors. Even small analogues such as varenicline (**2**)[6] and brimonidine (**3**)[7] have valuable pharmaceutical effects. (Fig. 1). In addition to biological and pharmaceutical effects, molecules consisting of a quinoxaline unit, have many important applications in material sciences. For example, quinoxaline derivatives are useful as electroluminescent materials,[8] organic semiconductors,[9] dyes,[10] and electrical/photochemical materials.[11] Their ability to harvest both singlet and triplet energy for emission improves device efficiency. For example, a few compounds with quinoxaline unit are used for dye-sensitized solar cells.[10b,12]

Consequently, significant efforts have been made to develop efficient methods for the synthesis of quinoxalines and their derivatives. The traditional method relies on condensation of 1,2-diamines with 1,2-dicarbonyl compounds,[13] while oxidative cyclization of α-hydroxy ketones or α-halide ketones with 1,2-diamines has also been widely used.[14] Although these methods work well for a few derivatives at routine positions, quinoxalines substituted in more specific positions suffer when the substituted 1,2-diamines and 1,2-dicarbonyl compounds are used as starting materials.

Furthermore, brominated compounds are versatile key compounds and starting materials for many organic transformations. Halogens may be reductively or permutationally replaced by lithium or magnesium, and the organometallic intermediate converted into a functionalized derivative by reaction with an appropriate electrophile. In addition, the C–Br bond formed in arenes can be easily transformed into a C–C bond and C–hetero atom bond via Ullmann, Heck, Stille, Suzuki etc. reactions.[15] For this reason, the synthesis of halogenated arenes is extremely important in organic chemistry and material science.

In our previous works, we examined the bromination of naphthalene and its derivatives and we obtained many new naphthalene derivatives.[16] Cakmak and co-workers also studied the bromination

* Corresponding author.
E-mail address: adastan@atauni.edu.tr (A. Daştan).

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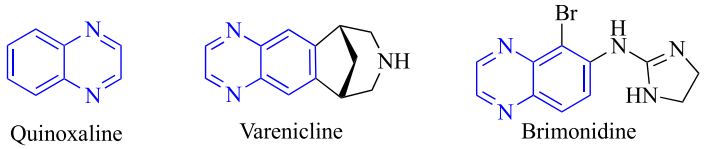


1 2 3

Fig. 1. Quinoxaline and its derivatives.

and functionalization of benzenoid aromatic compounds such as naphthalene, anthracene, and quinoline.[17] Due to our sustained interest in the bromination of aromatic compounds and derivatives, we aimed to study quinoxalines to find a regioselective bromination method for the parent compounds. Although bromination of naphthalene has been investigated in detail by many groups,[16–18] direct bromination of diazanaphthalenes is not common, owing to the lower activity of these compounds in electrophilic reactions. Diazanaphthalenes are electron-deficient in nature, and N-bromo complexes form easily during the bromination reaction. For this reason, direct bromination of quinoxaline has not been reported in the literature to achieve brominated products as key compounds for other kinds of functionalization. Brominated quinoxalines **9**,[19] **10**,[20] **11**,[21] and **12**[22] have been obtained by condensation of benzene-1,2-diamines **4**–**7** with glyoxal (**8**) (Scheme 1). Although the last step works well, synthesis of halogenated benzene-1,2-diamines in specific positions is not easy and consequently there are no practical and general methods for the synthesis of many halogenated derivatives. In addition, most of this conversion was patented.[20,21] Continuing our work on the bromine functionalization of hydrocarbons, herein we describe the halogenation of quinoxaline and derivatives under different conditions.

2. Results and discussion

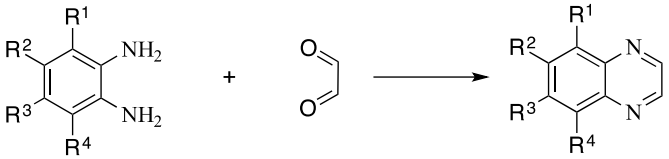
Our work in this study is based on three main strategies: i) bromination of quinoxaline (**1**) with different reagents, solvents, and temperatures, ii) reduction of one ring of quinoxaline (**1**), and bromination of the tetrahydroquinoxalines with different reagents, solvents, and temperatures to access brominated quinoxalines, iii) synthesis of N-oxides of quinoxalines and bromination of them to obtain quinoxalines with bromine atoms in specific positions.

2.1. Bromination of quinoxaline (1) under different conditions

We first investigated the bromination of quinoxaline (**1**) under various conditions described in Table 1 and Scheme 2, and from this reaction the formation of different kinds of brominated product **9**–**14** was observed. Under the conditions in entries 5, 8, and 9, monobromide **10** was obtained exclusively in 51–65% yield. The reaction of **1** at 82 °C with 8 equiv. bromine in acetonitrile resulted in formation of only dibromide **12** in considerably high yield (entry 3). The photobromination reaction of **1** with molecular bromine (entry 7) gave us monobromide **9** in 70% yield as well as the dibromides **12** (10%) and **11** (3%). Synthesis of **9** starting from **1** using NBS in the presence of H_2SO_4 was first studied by Brown and Gouliaev[23] and they obtained **9** in only 12% yield. In the present work, thus, we have developed a good method for monobromide **9**. As is well known,[16,20] in the bromination reaction of hydrocarbons at high temperature, especially supported by photochemical conditions, the process proceeds via a radical intermediate. In some cases there is competition between the radical and the ionic reactions. In view of these points, we assumed that the reaction took place via addition of a bromine radical to a double bond, and elimination of the formed tetrabromide.[16,17,24] In other reaction conditions (entries 1, 2, 4, 6, 10, and 11) the formation of different product mixtures was observed. The reaction mixtures in that case were easily separated by column chromatography using SiO_2 with *n*-hexane/AcOEt. From this reaction, the dibromide **13** was synthesized in low yield. A better synthetic method was developed for dibromide **14**,[25] by photochemical bromination of **1** (entry 6) and bromination of **1** with molecular bromine in the presence of barium carbonate (entry 4) (Scheme 2).

2.2. Reduction of quinoxaline (1) and bromination of tetrahydroquinoxalines (15 and 19) under different conditions

In our previous work we showed that bromination of saturated naphthalene, i.e. decalin, gave us a new kind of brominated naphthalene derivative in high yield.[16a] Similarly Cakmak and coworkers successfully brominated 1,2,3,4-tetrahydronaphthalene, tetralin.[17] Those methods encouraged us to study the bromination of reduced quinoxalines **15** and **19** under different reaction conditions. The compound **19** is commercially available, but isomeric **15** is expensive. Therefore, we first aimed to synthesize **15** starting from **1**. Many effective methods for reduction of quinoxaline **1** to **15** exist in the literature and few of them are patented.[26] In addition, although Birch reduction is one of the best methods for controlled reduction of aromatic rings, to the best of our knowledge, Birch reduction of **1** has not been reported in the literature. Reduction of **1** with metallic sodium in liquid ammonia gave the target compound **15** as the sole product in moderate yield (65%). Alternatively



4 (R^1=Br, R^2=R^3=R^4=H)
5 (R^2=Br, R^1=R^3=R^4=H)
6 (R^1=R^3=Br, R^2=R^4=H)
7 (R^1=R^4=Br, R^2=R^3=H)

8

9 (R^1=Br, R^2=R^3=R^4=H)
10 (R^2=Br, R^1=R^3=R^4=H)
11 (R^1=R^3=Br, R^2=R^4=H)
12 (R^1=R^4=Br, R^2=R^3=H

Scheme 1. Synthesis of some bromoquinoxalines