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New Quinoxaline-1,4-dioxides Derived from Beirut Reaction of Benzofuroxane with Active Methylene Nitriles †

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Abstract: Benzofuroxane reacts under Beirut reaction conditions with active methylene nitriles to give new 2-aminoquinoxaline-1,4-dioxides. Treatment of known 2-amino-3-cyanoquinoxaline-1,4-dioxide with chloroacetyl chloride afforded corresponding chloroacetamide useful for preparation of various heterocycles bearing quinoxaline-1,4-dioxide core system

Keywords: Beirut reaction; benzofuroxane; 2-aminoquinoxaline-1,4-dioxides; hetarylacetonitriles; malononitrile

1. Introduction

Quinoxaline-1,4-dioxides, mostly prepared through the Beirut reaction described for the first time by M. Haddadin and C. Issidorides at the American University of Beirut, Lebanon in 1965, have been recognized as compounds of practical interest, primarily due to the wide spectrum of biological activity (for reviews see [1–6]). Thus, 2-aminoquinoxaline-1,4-dioxides are known to possess leishmanicidal and antiplasmodial activities [7,8], antitumor activity [9], antitubercular effects [10,11]. On the other hand, long time known anticancer drug Tirapazamine (3-amino-1,2,4-benzotriazine-1,4-dioxide) (Figure 1) has a very close structure. The above reasons prompted us to study the reactions of benzofuroxane with some active methylene nitriles in order to prepare new compounds with 2-aminoquinoxaline-1,4-dioxide core. Such compounds may be useful for development of new antiprotozoal and anticancer agents.

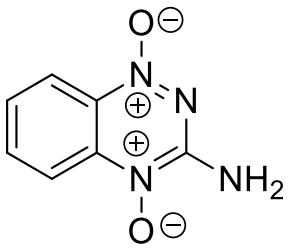
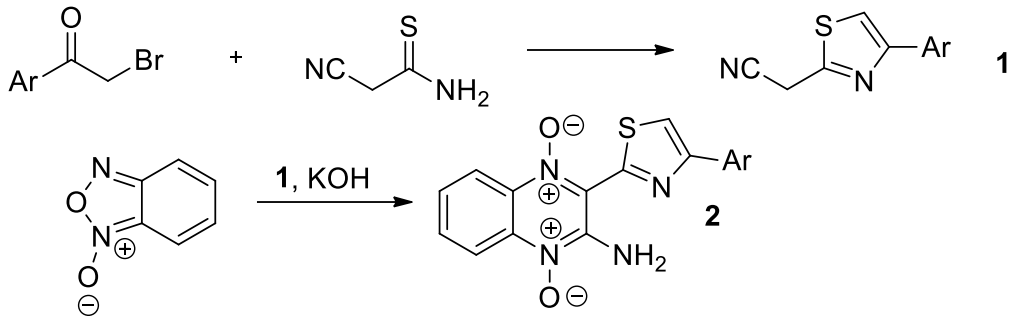


Figure 1. The structure of Tirapazamine (3-amino-1,2,4-benzotriazine-1,4-dioxide) closely related to 2-aminoquinoxaline-1,4-dioxides.

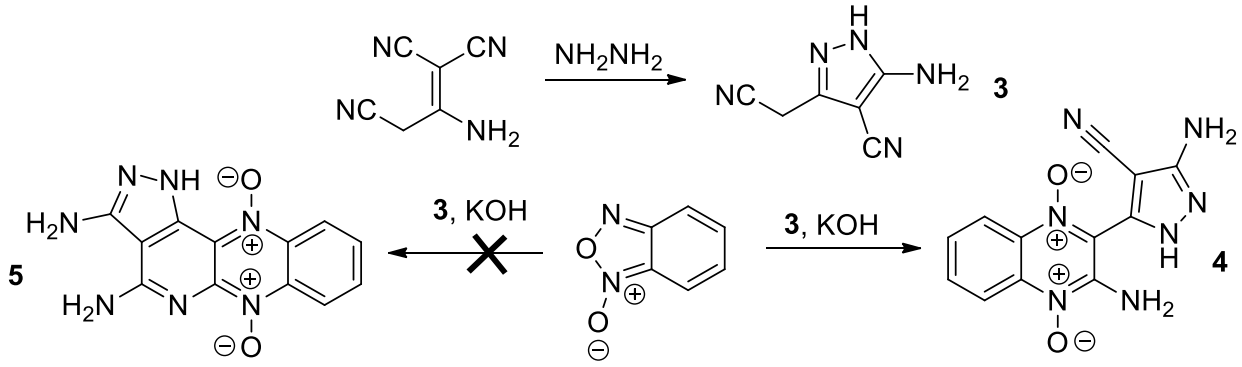
2. Results and Discussion

First, we reacted benzofuroxane with 2-cyanomethylthiazoles [12], easily available by Hantzsch reaction of cyanothioacetamide [13,14] with phenacyl bromides (Scheme 1). Hybrid polyheterocycles **2**, bearing both thiazole and quinoxaline fragments, were recognized as the reaction products.



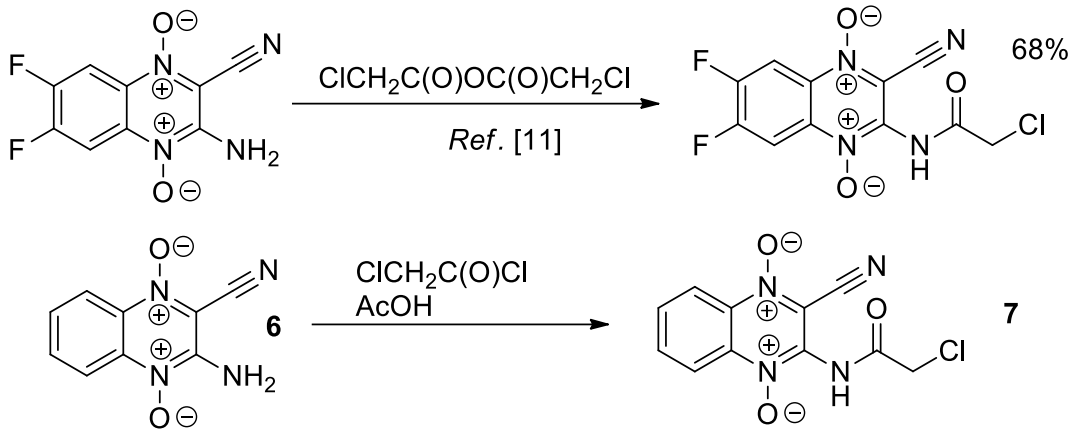
Scheme 1. The synthetic pathway to 2-aminoquinoxaline-1,4-dioxides **2**.

Next, cyanomethylpyrazole **3** prepared by reaction of malononitrile dimer with hydrazine [15,16], reacted with benzofuroxane to give a product with the suggested structure **4** (Scheme 2). The evidence for the structure of compound **4** rests chiefly on its FT-IR spectrum, while NMR data cannot be interpreted unambiguously. Thus, the IR spectrum revealed the presence of amino group and conjugated CN group, while the band corresponding to non-conjugated CN group is absent. This fact allows one to exclude the possible structure **5** (Scheme 2). The studies on the structure and reactions of compound 4 are in progress.



Scheme 2. The synthetic pathway to 2-aminoquinoxaline-1,4-dioxide **4**.

Finally, we prepared 2-amino-3-cyanoquinoxaline-1,4-dioxide **6** by known method [17], was reacted with chloroacetyl chloride. After short-term heating in AcOH, a bright yellow precipitate of chloroacetamide **7** formed (Scheme 3). It should be noted that the only reported method for the chloroacetylation of 2-aminoquinoxaline-1,4-dioxides was based on the reaction of 6,7-difluoro-2-quinoxalinecarbonitrile 1,4-di-N-oxide with hardly available chloroacetic anhydride [11]. The compound **7** is expected to be promising reagent for the synthesis of polyheterocyclic ensembles with quinoxaline core fragment.



Scheme 3. Chloroacetylation of 2-amino-3-cyanoquinoxaline-1,4-dioxides.

3. Experimental

Preparation of Compounds **2**. *General Procedure*

Equimolar amounts of thiazol-2-ylacetonitrile **1** and benzofuroxane were dissolved in DMF and treated with the 1.5 eq. of base (KOH or Et_3N). The dark colored reaction mixture was left to stand in a freezer for 24-72 h, then diluted with cold alcohol. The precipitated solid was filtered off and recrystallized to give analytically pure samples of quinoxalines **2**.

Chloroacetylation of Compound **6**

2-Amino-3-cyanoquinoxaline 1,4-dioxide 6 (0.01 mol) was suspended in glacial AcOH (15 mL) and treated with chloroacetyl chloride (0.011 mol). When the reaction mixture was gently heated to 50 °C, red color of 6 disappeared and the reaction mass turned bright yellow. The mixture was heated under vigorous stirring until the starting 6 was fully consumed (TLC control). The yellow precipitate was filtered off and washed with EtOH to give pure chloroacetamide 7. Yield 90%. The compound is soluble in DMF and DMSO, but sparingly soluble in AcOH, EtOH.

The representative spectra are given below (Figures 1–5):

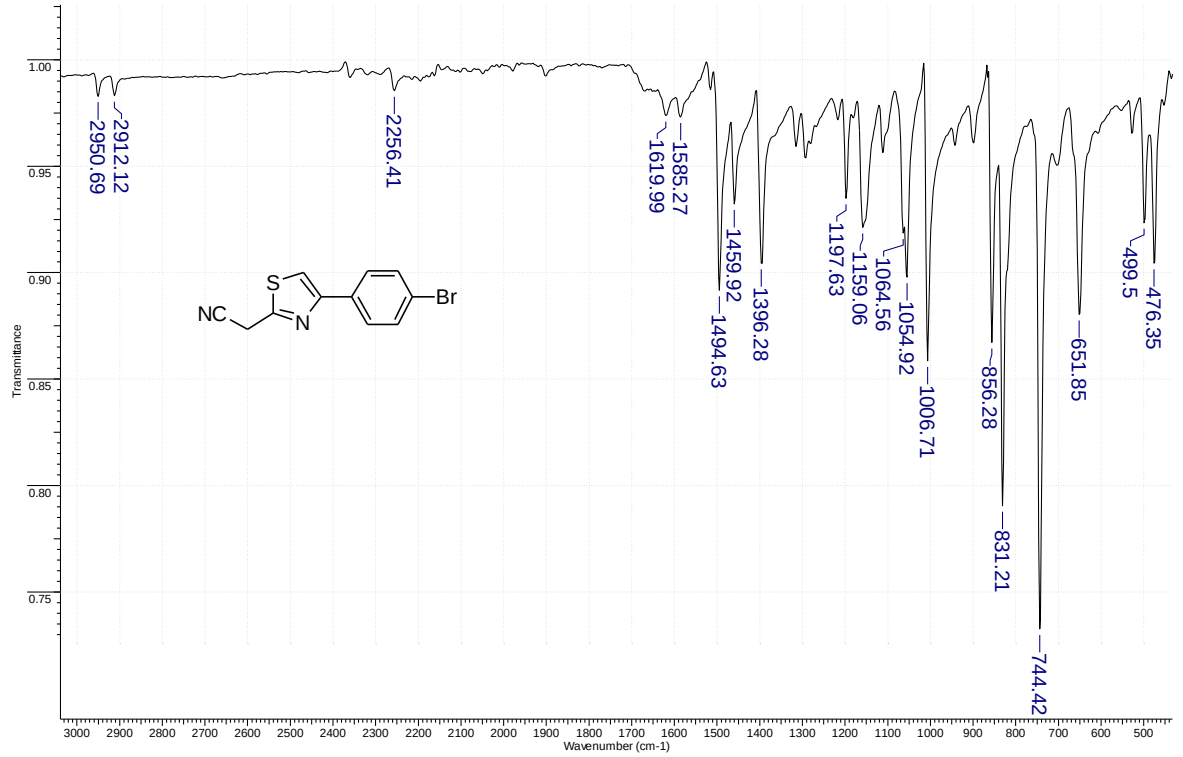


Figure 1. The FT-IR (ATR mode) spectrum of 4-(4-bromophenyl)-2-cyanomethylthiazole **1a**.

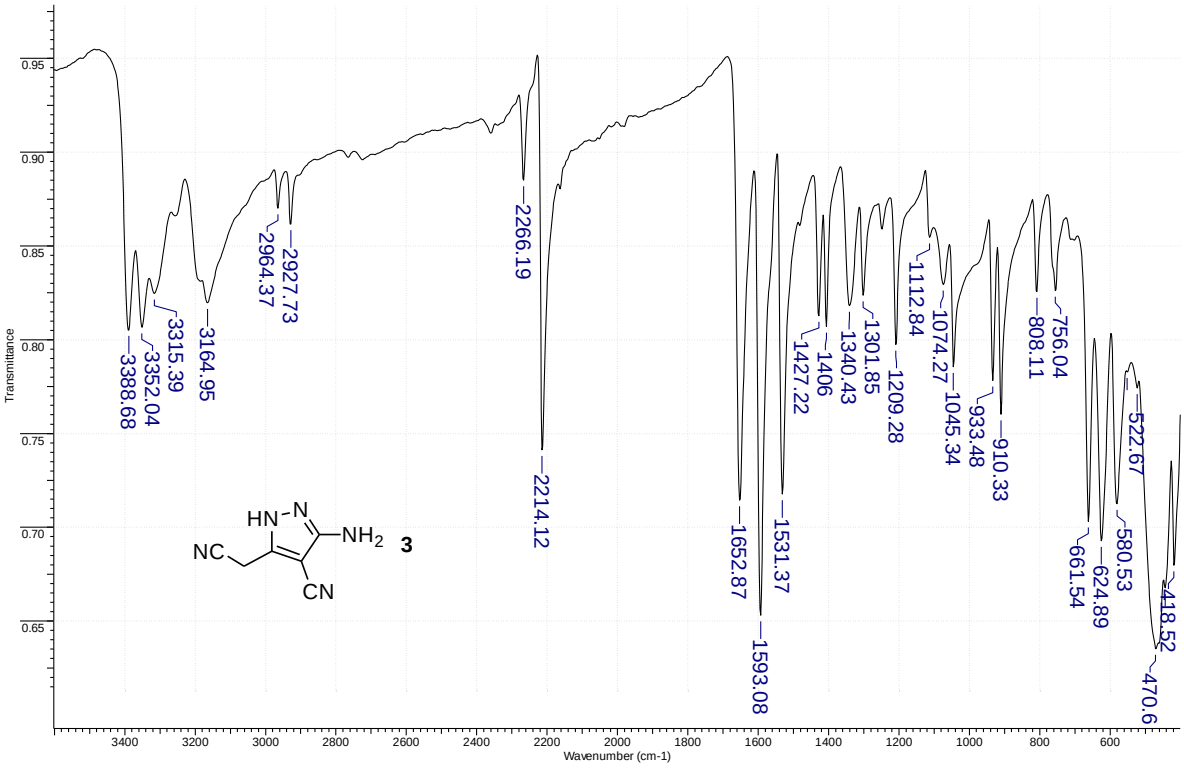


Figure 2. The FT-IR (ATR mode) spectrum of 3-amino-5-(cyanomethyl)-1H-pyrazole-4-carbonitrile **3.**

Figure 3. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of 3-amino-5-(cyanomethyl)-1H-pyrazole-4-carbonitrile **3.**

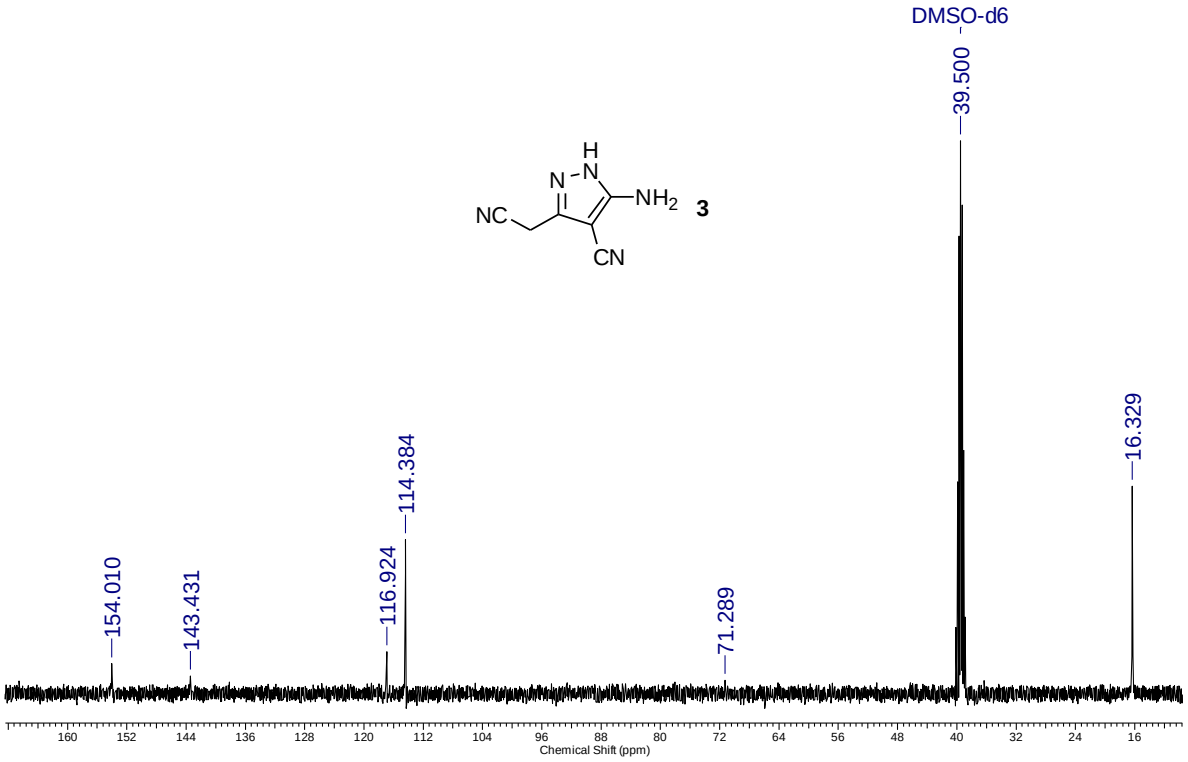


Figure 4. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of 3-amino-5-(cyanomethyl)-1H-pyrazole-4-carbonitrile **3.**

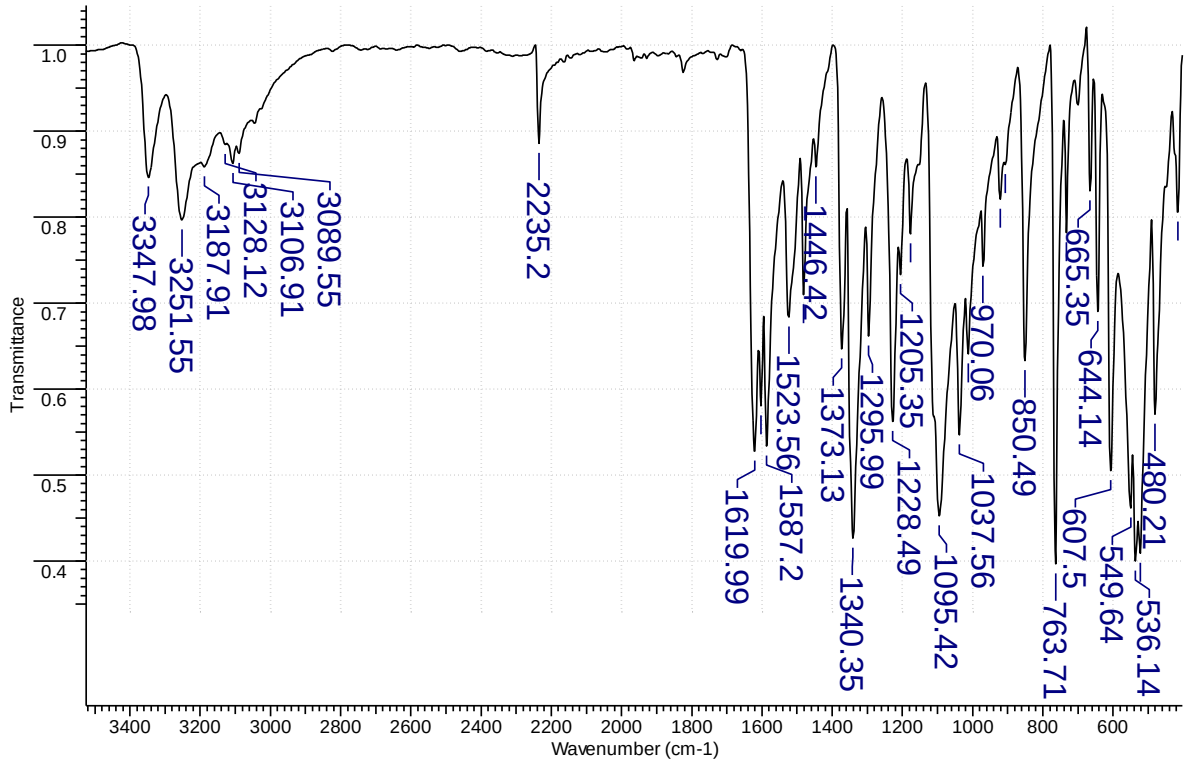


Figure 5. The FT-IR (ATR mode) spectrum of 2-amino-3-cyanoquinoxaline 1,4-dioxide **6**.

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