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Proceeding Paper

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

Victor V. Dotsenko [1,2,3,*], Karina V. Khalatyan [1], Alena A. Russkih [1] and Aminat M. Semenova [1,4]

[1] Department of organic chemistry and technologies, Kuban State University, 149 Stavropolskaya Str, 350040 Krasnodar, Russia; halatyan.karina@yandex.ru (K.V.K.); alena.russkih.19988@gmail.com (A.A.R.); aminat-7@yandex.ru (A.M.S.)
[2] ChemEx Lab, Vladimir Dal' Lugansk National University, 20A/7 Molodezhny, 91034 Lugansk, Russia
[3] Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., 355009 Stavropol, Russia
[4] North-Caucasus State Humanitarian Technological Academy, 36 Stavropolskaya St., Cherkessk 369000, Russia
* Correspondence: victor_dotsenko@bigmir.net
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Abstract: Benzofuroxane reacts under Beirut reaction conditions with active methylene nitriles to give new 2-aminoquinoxaline-1,4-dioxides. The treatment of known 2-amino-3-cyanoquinoxaline-1,4-dioxide with chloroacetyl chloride afforded corresponding chloroacetamide which is useful for the preparation of various heterocycles bearing a quinoxaline-1,4-dioxide core system.

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

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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 their biological activity (for reviews see [1–6]). Thus, 2-aminoquinoxaline-1,4-dioxides are known to possess leishmanicidal and antiplasmodial activities [7,8], anti-tumor activity [9], and antitubercular effects [10,11]. On the other hand, Tirapazamine (3-amino-1,2,4-benzotriazine-1,4-dioxide) (Figure 1), which has been known for a long time as an anticancer drug, has a very closely related 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 the development of new antiprotozoal and anticancer agents.

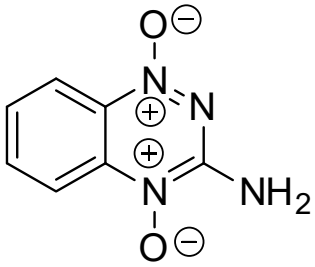
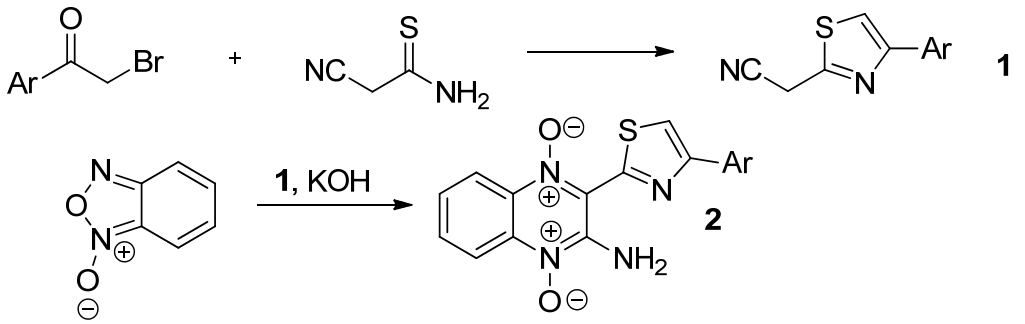


Figure 1. The structure of Tirapazamine (3-amino-1,2,4-benzotriazine-1,4-dioxide) closely related to 2-aminoquinoxaline-1,4-dioxides.

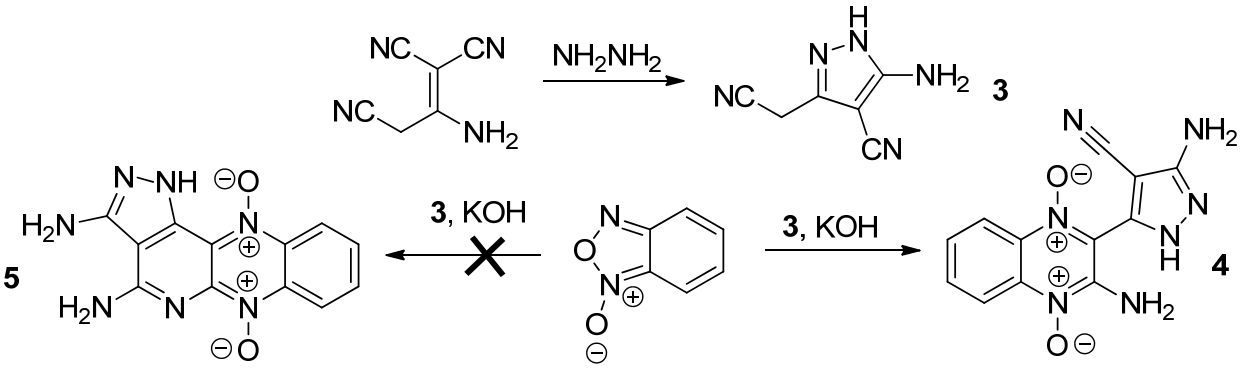
2. Results and Discussion

First, we reacted benzofuroxane with 2-cyanomethylthiazoles [12], easily available by the 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.



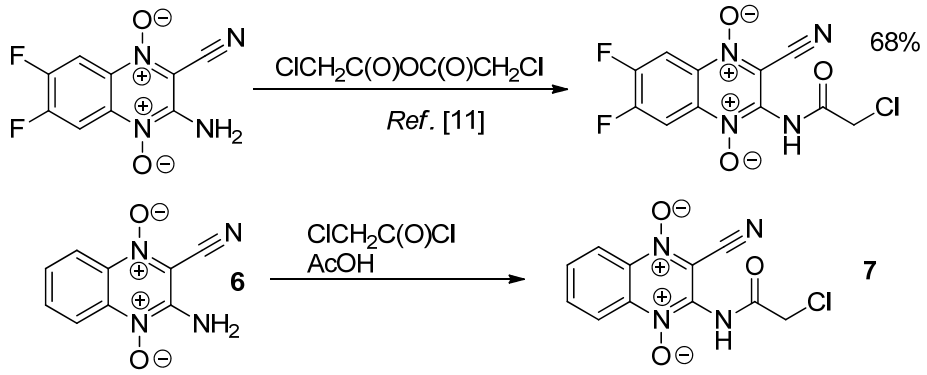
Scheme 1. The synthetic pathway to 2-aminoquinoxaline-1,4-dioxides **2**.

Then, cyanomethylpyrazole **3**, prepared by the 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 its NMR data cannot be interpreted unambiguously. Thus, the IR spectrum revealed the presence of an amino group and conjugated CN group, while the band corresponding to the non-conjugated CN group was 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], which 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 a 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

3.1. Preparation of Compound **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 produce 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, the red color of 6 disappeared and the reaction mass turned bright yellow and then brick orange. The mixture was heated under vigorous stirring until the starting of 6 was fully consumed (TLC (thin-layer chromatography) control). The brick-orange precipitate was filtered off and washed with EtOH to produce pure chloroacetamide 7 at a yield of 90%. The compound is soluble in hot DMF and DMSO, but sparingly soluble in AcOH, EtOH.

The representative spectra are given below (Figures 2–6):

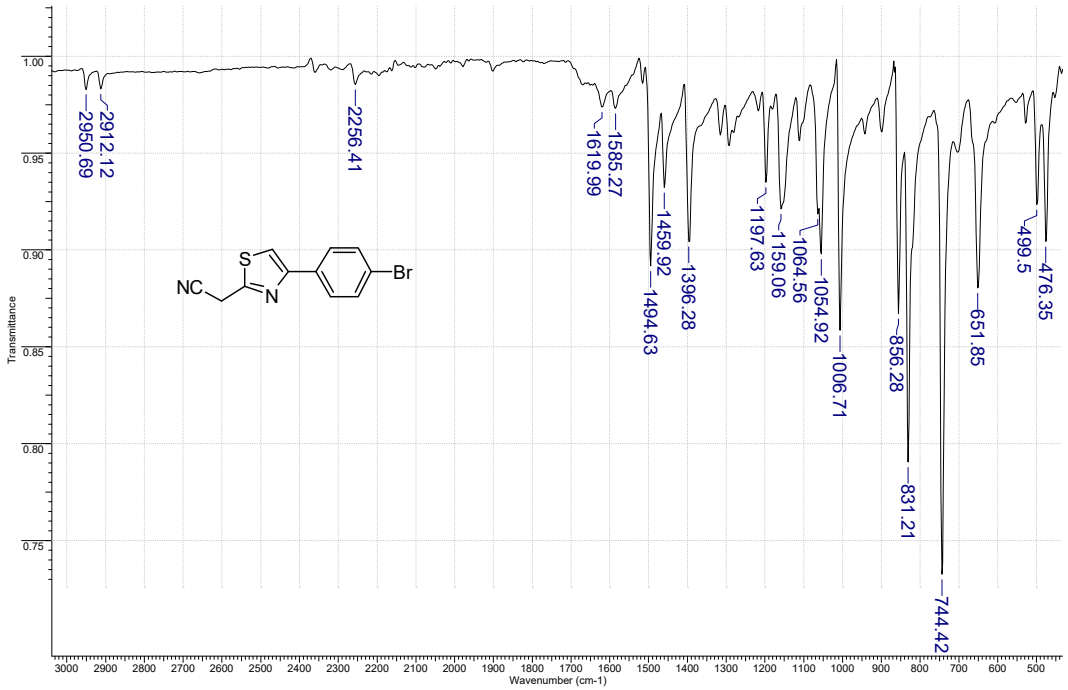


Figure 2. The FT–IR (ATR—Attenuated total reflectance mode) spectrum of 4-(4-bromophenyl)-2-cyanomethylthiazole **1a**.

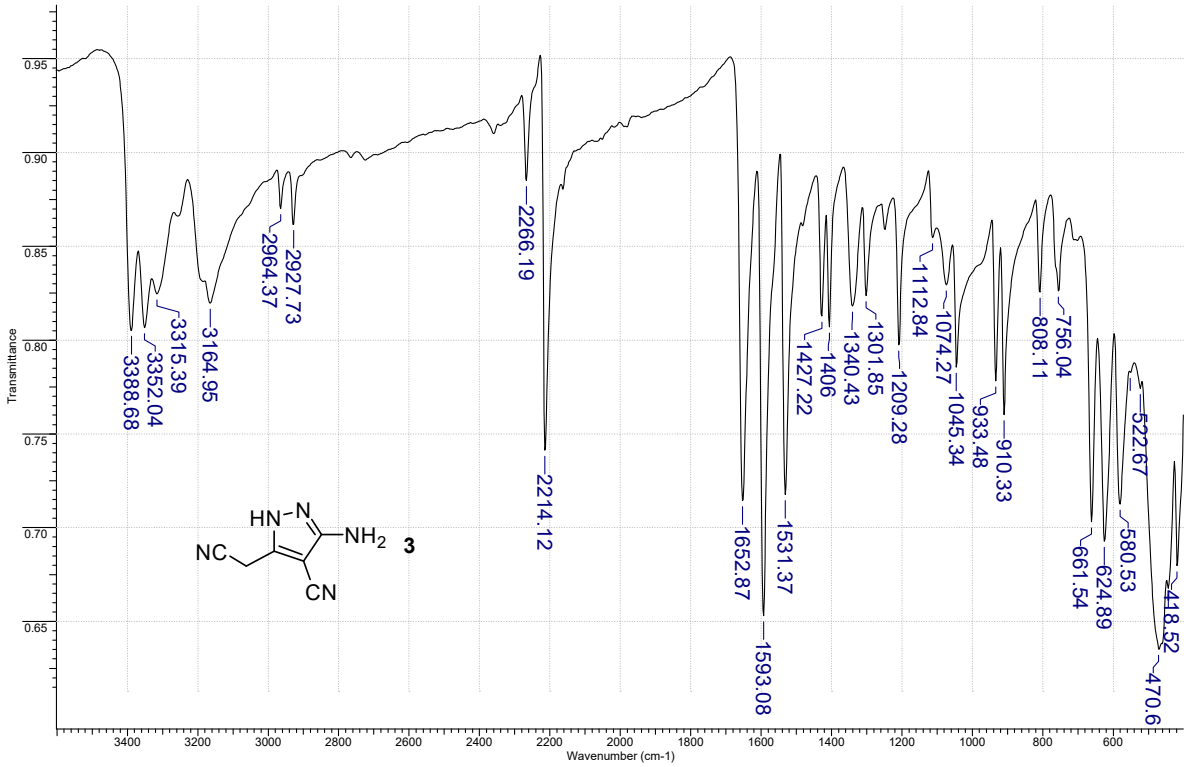


Figure 3. The FT–IR (ATR mode) spectrum of 3-amino-5-(cyanomethyl)-1H-pyrazole-4-carbonitrile **3**.

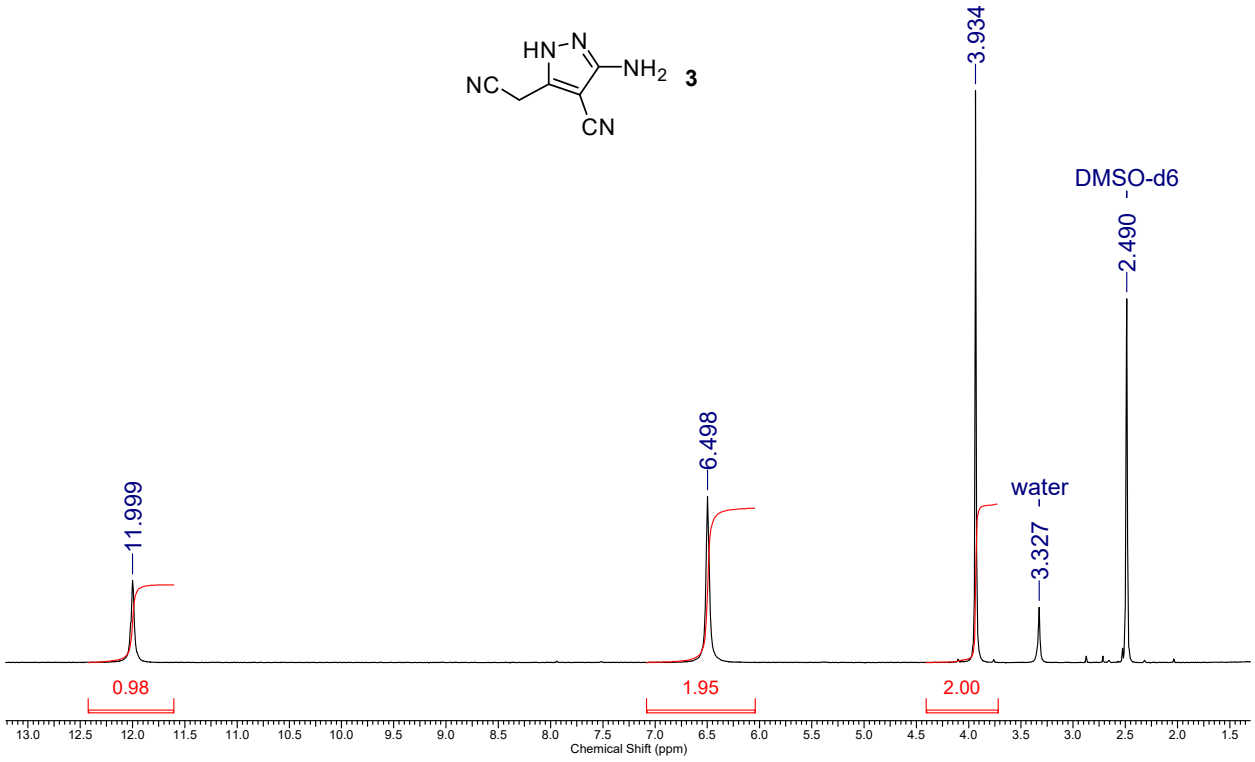


Figure 4. ^{1}H NMR spectrum (400 MHz, DMSO-d$_6$) of 3-amino-5-(cyanomethyl)-1H-pyrazole-4-carbonitrile **3**.

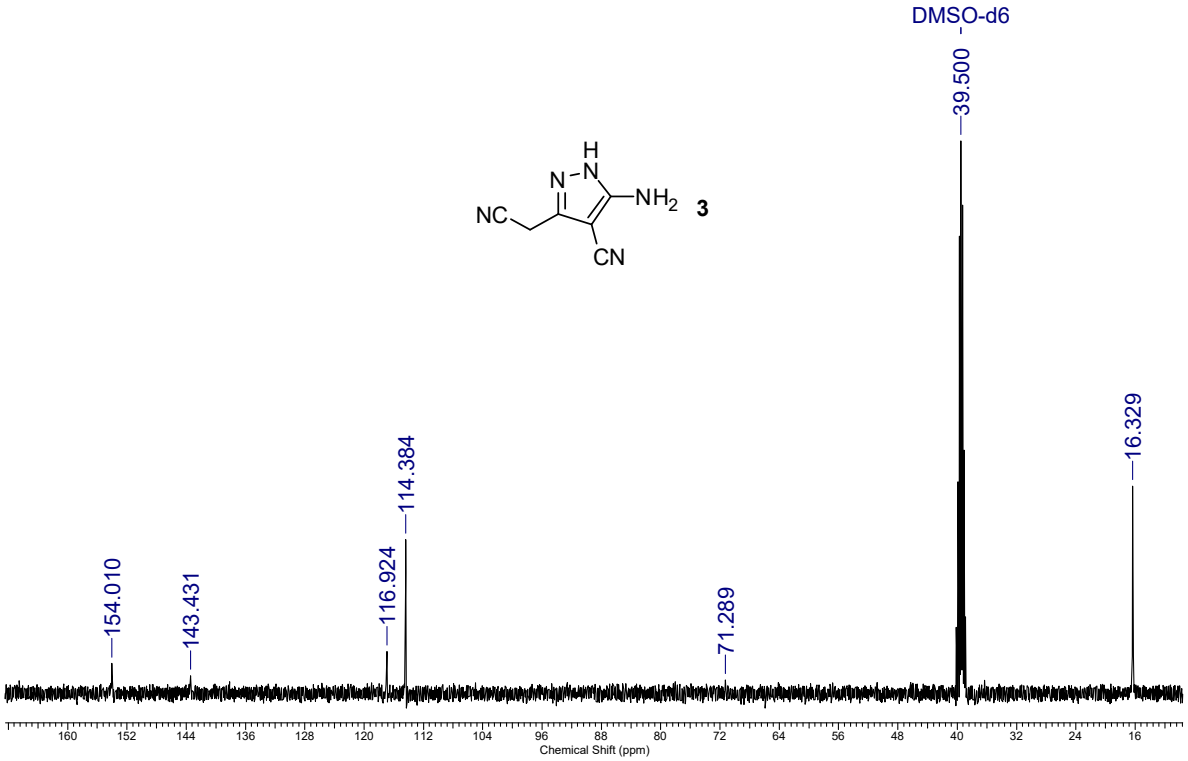


Figure 5. ^{13}C NMR spectrum (101 MHz, DMSO-d$_6$) of 3-amino-5-(cyanomethyl)-1H-pyrazole-4-carbonitrile **3**.

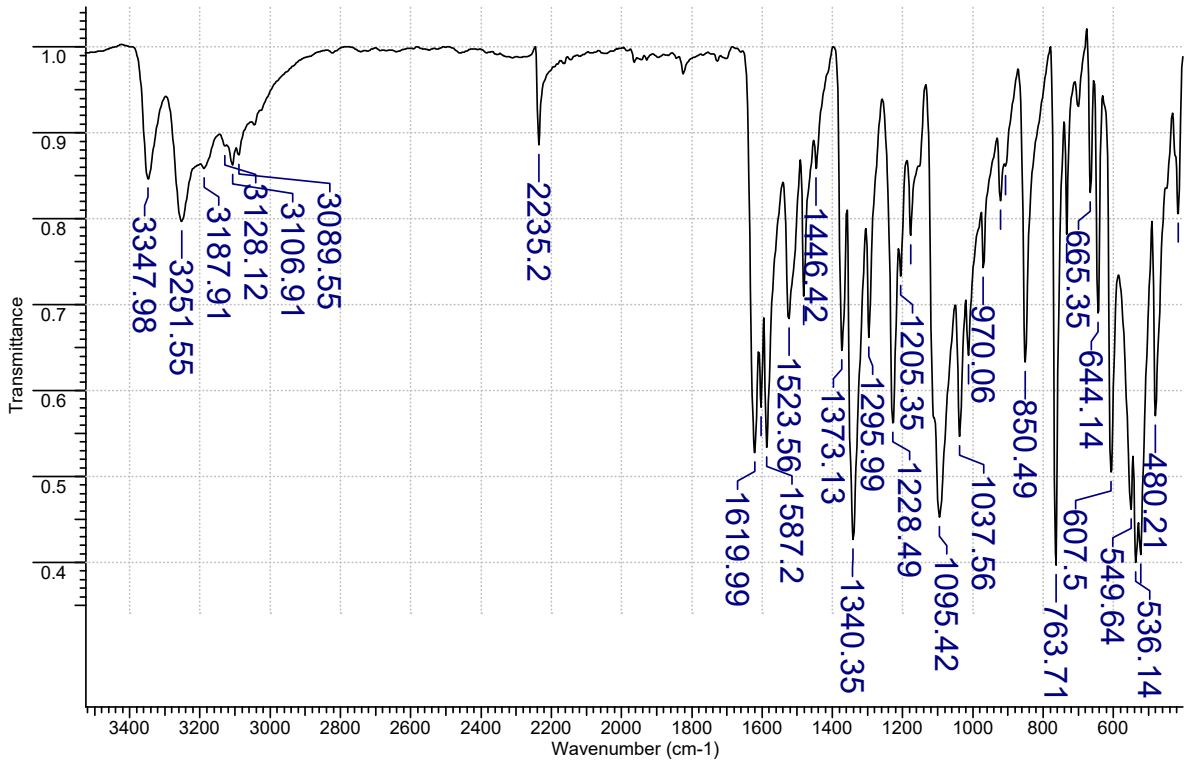


Figure 6. The FT-IR (ATR mode) spectrum of 2-amino-3-cyanoquinoxaline 1,4-dioxide **6**.

Author Contributions: Conceptualization, V.V.D.; methodology, V.V.D.; formal analysis, K.V.K., A.A.R., A.M.S.; investigation, K.V.K., A.A.R., A.M.S.; writing—original draft preparation, V.V.D.; writing—review and editing, V.V.D.; supervision, V.V.D.; funding acquisition, V.V.D. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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