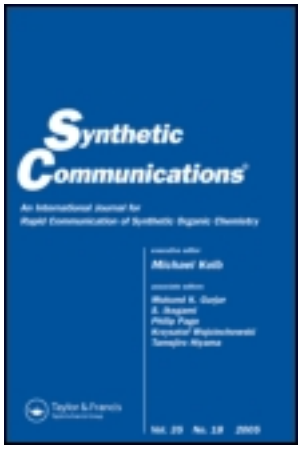

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ONE-POT NEW SYNTHETIC METHOD FOR 3-AMINO-2-QUINOXALINECARBONITRILE

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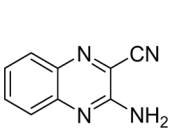
A new method for the preparation of 3-amino-2-quinoxalinecarbonitrile (1) was studied. A successful condensation reaction between bromomalononitrile and o-phenylenediamine in the presence of Lewis acid catalyst ($AlCl_3$) was achieved to produce compound 1.

Keywords: Aerobic oxidation; aminoquinoxalinecarbonitrile; bromomalononitrile; cyanation; Lewis acid catalyst; quinoxaline-1,4-dioxide

INTRODUCTION

3-Amino-2-quinoxalinecarbonitrile **1** and its 1,4-dioxide **2** were characterized as important precursors in the syntheses of biologically active fused quinoxaline ring systems[1,2] and complexes.[3–5] In the past few years, extensive studies showed that the compound **2** exhibited hypoxia-selective properties similar to those for tirapazamine.[6–8]



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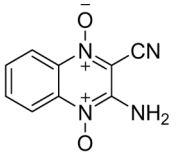

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Four steps for the synthesis of compound **1** starting from *o*-nitroaniline, with an overall yield about 23%, have been reported as a common method for its synthesis.[9,10] The last step in the previous procedure includes the reduction of quinoxaline-1,4-dioxide derivative **2** with sodium dithionite to form compound **1**.[10] However, three different products were obtained with equal ratios when we used the same methodology, which indeed will reduce the overall yield of compound **1** (12%). Two other syntheses for compound **1** have been reported by the

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condensation of *o*-phenylenediamine, either with diiminisuccinonitrile (31%)[11] or with 4-chloro-5-cyano-1,2,3-dithiazolium chloride (12%). Complexity and poor yields are the major drawbacks of these two methods.[12]

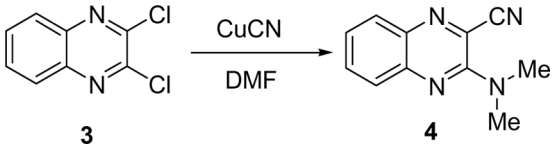
RESULTS AND DISCUSSION

As a part of our continuing efforts to synthesize **1** in good yield, several approaches have been elaborated. Direct cyanation of 3-amino-2-chloroquinoxaline with cuprous cyanide in dimethyl formamide through nucleaphilic aromatic substitution failed. However, the reaction of 2,3-dichloroquinoxaline (**3**) with cuprous cyanide in dimethyl formamide gave 3-(*N,N*-dimethylamino)-2-quinoxalinecarbonitrile (**4**) (Scheme 1).[13] The physical properties of **4** as well as the ^{1}H NMR spectra were identical with the reported data.[13] Cyanation of 2,3-dichloroquinoxaline using tetraethylammonium cyanide in dimethylsulfoxide (DMSO) gave quinoxaline-2,3-dicarbonitrile.[14]

Furthermore, direct condensation between *o*-phenylenediamine and bromomalononitrile (**5**), at different reaction conditions (solvents and temperatures), gave massive black material. Ferris and Orgel in 1965[15] reported that the reaction between bromomalononitrile and amines (morphiline, ammonia, or triethylamine) did not give the aminomalononitrile derivatives but instead the polycyanated products. This was attributed to the acidity of the proton for bromomalononitrile (dissociation constant $K = 10^{-5}$),[16] which favor, the formation of a stabilized carbanion rather than being attacked by the nucleophile in an S_N2 fashion as postulated by Ferris and Orgel.[15] The condensation of *o*-phenylenediamine with bromomalononitrile failed because the formation of **6**, which will attack another molecule of bromomalononitrile and displace the bromine atom to form the tetracyanoethylene **8** (Scheme 2).[15] Bromomalononitrile also reacts with alcohols when used as solvents[17] and with carbonyl compounds.[18]

After reports elaborated on the carbon acidity of bromomalononitrile,[16] no one elsewhere could replace the bromine atom by nucleophiles or bases and could not utilize this function in organic synthesis.

We adopted a solution to this problem by removing the bromide anion from bromomalononitrile (**5**) by reaction with an equivalent amount from Lewis acid catalyst (anhydrous $AlCl_3$) in acetonitrile as a solvent, forming the complex **9**. This was followed by condensation with *o*-phenylenediamine in the same reaction mixture to give compound **1** (Scheme 3). Compound **1** was detected by thin-layer chromatography (TLC) during the reaction progress and was increased by aerobic oxidation in the presence of oxygen gas (yield = 63%). The reaction mechanism may pass through formation of 1,4-dihydroquinoxaline derivative **10**, which is an inseparable



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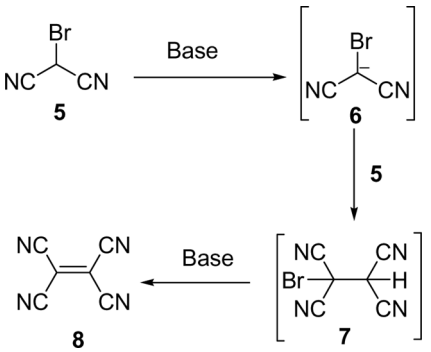
Scheme 1. Cyanation of 2,3-dichloroquinoxaline.

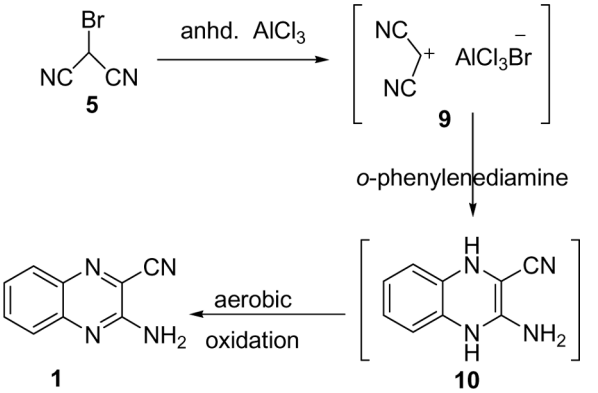


Scheme 2. Reaction of bromomalononitrile with bases.

and unstable intermediate and could oxidized to give compound **1** in the presence of oxygen (Scheme 3).

Acetonitrile is a good solvent for this reaction, but dichloromethane (DCM) gave poor yields (5%). Low temperature (−20°C) is essential during the addition of *o*-phenylenediamine to the reaction mixture. Silver nitrate ($AgNO_3$) as Lewis acid catalyst gave the same product **1**, but with fair yield (12%). It was found that with the use of titanium tetrachloride ($TiCl_4$) as Lewis acid catalyst, an inorganic complex was formed as a result of its reaction with o-phenylenediamine, and compound **1** was not detected.

Reported melting points of compound **1** in literature have a wide value range (210°C,[12] 196–200°C,[11] and 201–225°C[19]), but our melting point was fixed between 208 and 210°C. This difference in melting point encouraged us to correlate the spectral data of compound **1** with authentic material, prepared by the reduction of 1,4-dioxide derivative **2** with sodium dithionite.[10] The infrared (IR) data of compound **1** showed absorption characterizing the cyano group at 2233.16 cm^{-1}, and its mass spectrum reflected the presence of M^+ at 170 (100%). The ^1H NMR spectra of compound **1** in $CDCl_3$ as a solvent gave an exchangeable NH_2 proton at δ 5.38 ppm



Scheme 3. Synthesis of 3-amino-2-quinoxalinecarbonitrile.

with deviation from its reported value (δ 7.41 ppm).[12] This change in value from that previously published is because the author had used a different solvent (DMSO-d_6), which could form a hydrogen bond with NH_2 protons and shift them downfield. Repeating the ^{1}H NMR spectrum for compound **1** in DMSO-d_6 raised the chemical shift value for NH_2 protons to δ 7.39 ppm.

EXPERIMENTAL

Thin-layer (TLC) and column chromatography were performed using silica gel type 60, Merck 7731 and Merck 7734, respectively. Melting points were determined on a Gallenkamp melting-point apparatus. The IR spectra were recorded on a Jasco 4100 Fourier transform (FT)-IR spectrophotometer in KBr discs (ν max in cm^{-1}). The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker DRX NMR spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shift (δ) values are expressed in parts per million (ppm) and are referenced to the residual solvent signals of $CDCl_3$. The mass spectrum was recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analysis was recorded on a Perkin-Elmer 2400 C,H,N elemental analyzer.

3-Amino-2-quinoxalinecarbonitrile 1

Anhydrous aluminum chloride (1.33 g, 0.01 mol) was added to a solution of bromomalononitrile **5** (1.45 g, 0.01 mol) in acetonitrile (20 ml), at room temperature and refluxed for 2 h. The reaction mixture cooled to −20°C, and a solution of *o*-phenylenediamine (1.08 g, 0.01 mol) in acetonitrile (5 ml) was added dropwise during 20 min with stirring. After the addition was completed, the reaction mixture was kept at this temperature for a further 2 h. Then the reaction mixture was raised to room temperature, and oxygen gas was passed in through it for 2 h. The precipitate was filtered off and washed with acetonitrile (3 × 10 ml), and the filtrate was collected. After evaporation in vacuo, the residual mass was transferred to column chromatography using ethyl acetate–petroleum ether (10%). The separated solid was triturated with diethyl ether and recrystallized from cyclohexane to give a yellow powder **1** (1.07 g, 63%), mp 208–210°C. IR: 3417.24 and 3324.68 (NH_2), 2233.16 (CN). ^{1}H NMR ($CDCl_3$): 5.38 (2H, s, exch., NH_2), 7.52–757 (1H, m, ar), 7.71–7.76 (2H, m, ar), and 7.94–7.97 (1H, m, ar). ^{13}C NMR (DMSO): 136.52 (C-2), 134.78 (C-3), 132.73, 129.31, 128.77, 125.65, 125.51, 125.47, and 199.64 (CN). MS, *m/z* (%): 170 (100) [M^+], 144 (17.9), 143 (21.4), 118 (25) and 90 (46.4). Anal. calcd. for $C_9H_6N_4$ (170.17): C, 63.52; H, 3.55; N, 32.92. Found: C, 63.22; H, 3.39; N, 33.07.

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