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Krishna Kumar Gnanasekaran
Oklahoma State University - Stillwater

Mario Rivera
University of Kansas, Lawrence

Richard A. Bunce
Oklahoma State University - Stillwater

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4,7-Diaminoisoindoline-1,3-dione

Krishna Kumar Gnanasekaran[1], **Mario Rivera**[2], and **Richard A. Bunce**[1]

[1]Department of Chemistry, Oklahoma State University, Stillwater, OK 74078-3071, USA

[2]Department of Chemistry, R. N. Adams Institute for Bioanalytical Chemistry, University of Kansas, Lawrence, KS 66047-1620, USA

A recent synthesis in our drug discovery program required access to 4,7-diaminoisoindoline-1,3-dione (**1**, also 3,6-diaminophthalimide) in 250–500 mg quantities. This compound has been previously reported from the known 4,7-dichloroisobenzofuran-1,3-dione (also 3,6-dichlorophthalic anhydride).[1] The preparation of this anhydride involved zinc promoted hydrodechlorination of 3,4,5,6-tetrachlorophthalic anhydride under basic conditions to initially give 3,4,6-trichlorophthalic acid.[2–4] Further dechlorination with zinc generated 3,6-dichlorophthalic acid,[2–4] and boiling in toluene with azeotropic removal of water gave 3,6-dichlorophthalic anhydride.[3,4] We repeated this sequence on a small scale to get all of these compounds with physical and spectral properties identical to those reported.[2–4] Subsequent reaction of 3,6-dichlorophthalic anhydride with excess aq NH_3 and CuI (sealed tube, 120–130°C, 8 h) according to the literature procedure,[1] however, gave a product that melted at 273–275°C, which did not match the reported value. Spectral analysis of this material suggested that it was 4-amino-7-chloroisoindoline-1,3-dione rather than the diamino compound. The ^{1}H NMR spectrum displayed a singlet at δ 11.1 (1H) for the imide proton, two doublets at δ 7.38 and δ 7.02 (1H each) for the coupled protons at C6 and C7, and a broad singlet at δ 6.53 (2H) for the amino protons. Additionally, the ^{13}C NMR showed eight carbons rather than four carbons expected for the symmetrically substituted phthalimide, and the mass spectrum gave parent ion peaks at 196 and 198 in an approximate 3:1 ratio.[5] Though the original work apparently did yield the correct product from 3,6-dichlorophthalimide, problems were documented when 3,6-dichlorophthalic anhydride was used as the starting material. Since the 4-amino-7-chloro derivative did not meet our needs and the procedure was rather labor intensive, this approach was not repeated, but instead, we opted to develop our own route to the 4,7-diamino compound. Our findings are reported below.

The successful synthesis required two steps and was more straightforward than the earlier procedure. Commercially available 4-aminoisoindoline-1,3-dione (**2**, also 3-aminophthalimide) was brominated with *N*-bromosuccinimide in methanol to give 7-bromo-4-aminoisoindoline-1,3-dione (**3**) as the exclusive product in 75% yield. Since this compound precipitated directly from the reaction mixture, an extensive work-up procedure was not necessary.

Address correspondence to Richard A. Bunce, Department of Chemistry, Oklahoma State University, 107 Physical Sciences, Stillwater, OK 74078-3071. rab@okstate.edu.

The bromide was simply filtered and dried prior to use in the next reaction. Treatment of **3** under conditions modified from those reported by Ma and co-workers[6] (excess aq NH_3, 10 mol% of CuI, 20 mol% of L-proline, sealed tube, 110°C, 3 h) afforded 4,7-diaminoisoindoline-1,3-dione (**1**) in 42% yield. Again, upon cooling, the product crystallized directly from the reaction mixture and required only filtration and drying before use.

In conclusion, we have developed a short, efficient synthesis of 4,7-diamino-isoindoline-1,3-dione. Though the starting 4-aminoisoindoline-1,3-dione is more expensive than the tetrachlorophthalic anhydride used in the earlier approach, the current procedure is much faster and reliably affords a 32% overall yield of the final product.

Experimental Section

All commercial reagents were used as received. 4-Aminoisoindoline-1,3-dione (**2**) was purchased from Oxchem Corporation (Wood Dale, IL). Unless otherwise specified, all reactions were run under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel GF plates (Analtech, No 21521). Melting points were uncorrected. ^{1}H- and ^{13}C-NMR spectra were measured at 400 MHz (^{1}H) and 101 MHz (^{13}C). Chemical shifts (δ) are referenced to internal $(CH_3)_4Si$ and coupling constants (J) are given in Hz. Low-resolution mass spectra (EI/DP) were obtained at 30 eV. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

4-Amino-7-bromo-1,3-dione (3)

4-Aminoisoindoline-1,3-dione (**2**, 2.00 g, 12.3 mmol) was dissolved in MeOH (200 mL), and the solution was treated with *N*-bromosuccinimide (2.19 g, 12.3 mmol). The reaction was stirred at room temperature for 50 min. The solid that precipitated was collected by filtration and washed with MeOH to give bromide **3** (2.21 g, 9.21 mmol, 75%) as a yellow powder, mp 287–289°C. ^{1}H NMR (DMSO-d_6): δ 11.1 (s, 1H), 7.51 (d, J = 8.9 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 6.53 (br s, 2H); ^{13}C NMR (DMSO-d_6): δ 170.0, 167.7, 146.5, 139.6, 130.2, 123.6, 112.4, 101.6; MS: *m/z* 240, 242 ($C_8H_5BrN_2O_2$, $M^{+\cdot}$, *ca.* 1:1).

Anal—Calcd for $C_8H_5BrN_2O_2$: C, 42.51; H, 1.78; N, 6.20. Found: C, 42.63; H, 1.86; N, 6.14.

4,7-Diaminoisoindoline-1,3-dione (1)

A clean, dried 100-mL Chemglass screw cap pressure vessel® (CG-1880-R-02) with a perfluoro O-ring (CG-309-210) was charged with bromide **3** (1.00 g, 4.17 mmol), copper (I) iodide (80 mg, 10 mol%), L-proline (100 mg, 20 mol%) and aq NH_3 (15 mL of 15 M, *ca* 225 mmol). The screw cap was replaced and the reaction was heated to 110°C for 3 h. The reaction was cooled to 23°C and red needles of the product separated. These crystals were filtered, washed with water and dried under vacuum to provide diamine **1** (310 mg, 1.75 mmol, 42%) as a red solid, mp 294–296°C [lit[4] mp 298°C (dec)]. ^{1}H NMR (DMSO-d_6): δ

10.5 (s, 1H), 6.82 (s, 2H), 5.75 (s, 4H); ^{13}C NMR (DMSO-d_6): δ 170.8, 138.5, 125.6, 108.8; MS: *m/z* 177 ($C_8H_7N_3O_2$, $M^{+\cdot}$).

Anal—Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.35; H, 4.04; N, 23.61.

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