Preparation of 2,7-Diamino-1,8-naphthyridine: A Useful Building Block for Supramolecular Chemistry

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Abstract: A two-step conversion of 2-chloro-7-amido-1,8-naphthyridine to 2,7-diamino-1,8-naphthyridine is described. The process, which involves a nucleophilic aromatic substitution reaction with 4-methoxybenzylamine and subsequent deprotection, can be carried out on a large scale.

Keywords: heterocycles, nucleophilic aromatic substitution, supramolecular systems, hydrogen bond, amine protecting group

2,7-Diamino-1,8-naphthyridine (1) and its analogs have been shown to be very useful intermediates for the synthesis of molecular building blocks that self-assemble into a variety of super-structures using their donor-acceptor-donor (DAAD) array of hydrogen-bonding sites.1–4 These compounds are also reported to possess a variety of pharmacological effects such as antimycobacterial, antitumor, antiallergic and benzodiazepine receptor activity.5 Further interest in this class of compounds has involved the study of their coordination complexes which show strong luminescence6 and catalytic activity in oxidation reactions.7

The logical precursor to 1 is 2,7-dichloro-1,8-naphthyridine (2) whose synthesis was reported by Newkome in 1981.6 Indeed, Collin and Youinou9 and later Reedijk7 treated 2 continuously with ammonia gas in phenol at 170 °C for 20 hours affording a variable yield of 1 (Scheme 1). We found that treatment of 2 with ammonium hydroxide in a sealed tube afforded 1 in 70% yield. Although the inconvenient and costly use of gaseous ammonia was avoided, the scale of the reaction was limited and since the original report1d we observed three separate sealed tube explosions. The palladium-mediated coupling of aromatic and heteroaromatic chlorides with lithium amides has proven to be a very useful method.10 It was examined with 2 but the yields were variable, the product was difficult to separate from by-products, and it was difficult to perform on a large scale.

An alternative starting material is 2-chloro-7-acetamido-1,8-naphthyridine (3), which can be prepared by acetylation of amine 4,1d and subsequent reaction with phosphorous oxychloride (Scheme 2). The synthesis of 4 from 2,6-diaminopyridine and DL-malic acid was reported by Newkome as a precursor to 2.5 The conversion of 3 to 1 occurred in a steel bomb in 74% yield but the scale was limited.

We report here a simple alternative method to accomplish the 3 → 1 conversion that avoids the high pressure conditions and can be carried out on a large scale. As outlined in Scheme 3, 4-methoxybenzylamine serves as a high boiling ammonia surrogate, by virtue of ready loss of the 4-methoxybenzyl protecting group upon treatment with acid. A second equivalent of amine removes the acetamide group.

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separation to give crude 5, which in turn could be deprotected with acid giving ca. 95–98% pure 1 obtained by precipitation.

The main limitation in the method of preparation of 1 described herein is the cost of the 4-methoxybenzylamine, which must be used in excess. Nonetheless, it represents a safer alternative to our previously published procedure\(^1\) and one that allows 1 to be prepared readily on multigram scale. As such, the utility of this already useful building block in supramolecular chemistry should be increased.

**Typical Experimental Procedures**

**Gram Scale Preparation of N-(4-Methoxybenzyl)-2,7-diamino-1,8-naphthyridine (5)**

To a mixture of 3 (4.0 g, 18 mmol) and commercially available 4-methoxybenzylamine (7.1 mL, 54 mmol) was added pyridine (70 mL) under N\(_2\). The mixture was heated to reflux for 48 h and then cooled to r.t. The majority pyridine was removed in vacuo giving a brown mud. The crude material was purified by column chromatography (SiO\(_2\), gradient from EtOAc to 70:30 EtOAc–MeOH), followed by recrystallization from CHCl\(_3\)-MeOH to give 4.2 g (83%) of 5 as a pale yellow solid: mp 141–143 °C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 7.98 (2 \text{ H}, t, J = 8.6 \text{ Hz}, \text{ ArH}), 7.83 (4 \text{ H}, s, \text{ NH}_2), 7.59 (2 \text{ H}, d, J = 8.6 \text{ Hz}, \text{ ArH}), 6.83 (2 \text{ H}, d, J = 8.6 \text{ Hz}, \text{ ArH}), 6.56 (2 \text{ H}, d, J = 8.6 \text{ Hz}, \text{ ArH})\). 13C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 158.65, 153.18, 140.37, 137.40, 132.24, 129.57, 114.32, 109.36, 106.83, 55.70, 44.01\). MS (ESI): \(m/z\) 281.1402; found: 281.1398 [M+H]+.

**Multigram Scale Preparation of 2,7-Diamino-1,8-naphthyridine (1)**

A mixture of 2-(4.2 g, 15 mmol) and concd HCl (30 mL) was heated to reflux for 2 h. The solution was allowed to cool to r.t. giving precipitate of 1. The precipitate was collected by vacuum filtration, washed with CH\(_2\)Cl\(_2\)-H\(_2\)O, and dried in vacuo to yield 2.3 g (95%) of 1, which in turn could be deprotected with acid giving ca. 95–98% pure 1 by \(^1\)H NMR of 3 as a brown solid.

To 186 g of the crude mixture obtained above was added pyridine (500 mL) and 4-methoxybenzylamine (283 mL, 2.19 mol) under N\(_2\). The mixture was heated to reflux for 72 h and then cooled to r.t. The majority of the pyridine was removed in vacuo giving a brown sludge. EtOAc was added to form a slurry that was collected by filtration. The filtered solid and concd HCl (2.5 L) was heated to 90 °C (solution temperature) for 2 h. The mixture was allowed to cool to r.t. giving partial crystallization of the mixture with sludge. The mixture was neutralized with aq NaOH and then aq NaOH at 0 °C. CH\(_3\)Cl\(_2\) (1 L) was added to the neutralized solution and the mixture was stirred for 30 min, giving a precipitate that was collected with vacuum filtration, washed with CH\(_3\)Cl\(_2\)-H\(_2\)O, and dried in vacuo to yield 142 g (86%) of 1 estimated to be ca. 95–98% pure by \(^1\)H NMR. Spectral properties were identical to that prepared above.

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**References**