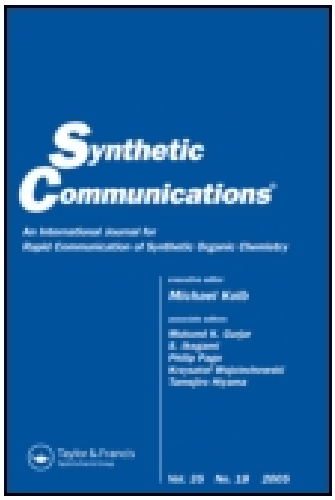

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An Efficient Synthesis of 5-Bromopyridine-2-carbonitrile

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ABSTRACT

5-Bromopyridine-2-carbonitrile was efficiently synthesized in two steps from 2,5-dibromopyridine with an overall yield of 75%.

Key Words: Acid catalyzed amide dehydration; Pd(0)-catalyzed cross coupling; Nucleophilic aromatic substitution.

As part of a discovery effort to identify novel anti-bacterial agents we required an efficient and reliable synthesis of 5-bromopyridine-2-carbonitrile (**1**). A literature survey revealed that although the synthesis of **1** had previously been reported,[1] it was only recovered as a minor

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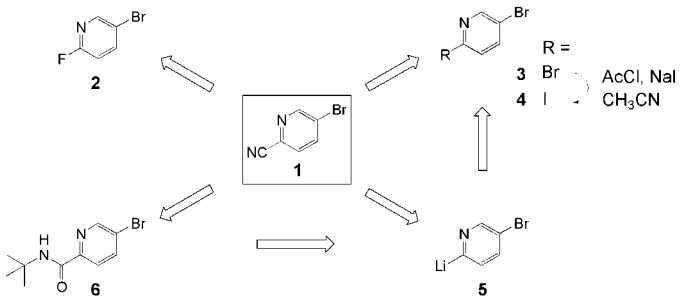


Scheme 1.

by-product during the cyanation of 3-substituted pyridine *N*-oxides with Me_3SiCN.

Our initial route to prepare **1** was relatively straightforward, involving the displacement of fluoride from 5-bromo-2-fluoropyridine (**2**) with NaCN or KCN in DMF at 150°C (Sch. 1). While this route afforded **1**, the yields were typically only 10–15%; starting material and by-products attributable to polymerization were also recovered. Attempts to optimize the procedure by changing the temperature, reaction time, or concentration of reagents afforded similarly poor results. Likewise, alternative solvents (DMF, DMSO, NMP, DME, toluene) gave no improvement.

We next evaluated a method involving Pd(0)-catalyzed cross-coupling of cyanide salts with halopyridines (Sch. 1). This was based on the recently-reported work of Maligres et al.[2] describing the syntheses of pyridinecarbonitriles via the treatment of bromopyridines with $Zn(CN)_2$ and Pd(0) with diphenylphosphine ferrocene (dppf) as a ligand. In a similar report, Song and Yee[3] reported the regioselective synthesis of 5-bromopyridine-2-carboxylic acid methyl ester from 2,5-dihalopyridines via palladium-catalyzed carbonylation in the presence of MeOH. Combining various aspects of these published methods, we attempted the synthesis of **1** from both 2,5-dibromopyridine (**3**) and 5-bromo-2-iodopyridine (**4**), prepared in one step from **3** following the procedure outlined in Ref.[3] In either case, the use of dppf did not furnish the expected product. Use of $Pd(PPh_3)_4$ in NMP did furnish the desired **1**; however, the numerous by-products generated during the course of this reaction, a problematic purification and irreproducible results placed serious constraints on the scale-up effort.

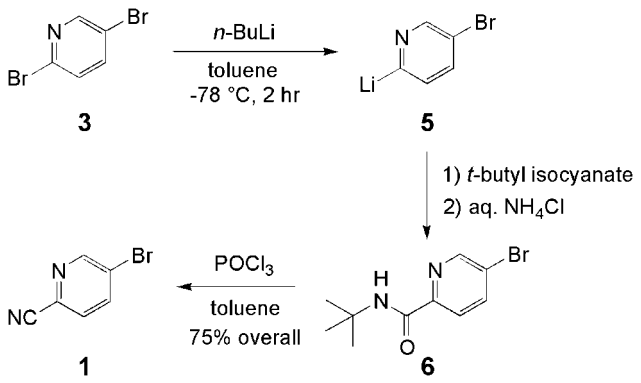
We next considered applying an approach developed by Wang et al.[4] that involved the regio-selective monolithiation of compound **3** (Sch. 1).

These authors had shown that treatment of 2,5-dibromopyridine with *n*-butyl lithium over 2 h afforded the thermodynamic product, 5-bromo-2-lithiopyridine (**5**). They further demonstrated that quenching **5** with various electrophiles afforded 2-substituted-5-bromopyridines. We hypothesized that quenching **5** with an electrophilic form of CN would, by analogy, furnish the desired **1**; however, our initial attempts to prepare **1** via the treatment of **5** with *p*-tosylcyanide or cyanogen bromide were not successful. In both cases, 3-bromopyridine was recovered upon workup.

Since using a suitable electrophilic cyano equivalent proved to be inadequate for direct introduction of the cyano group, we next explored an alternate approach that we postulated would lead, in one additional step, to **1** (Sch. 2). The key to this sequence would initially involve the synthesis of the *t*-butylamide **6** from **5** followed by the subsequent conversion to the desired **1**. Indeed, treatment of compound **5** with *t*-butyl isocyanate at −78°C in toluene cleanly and quantitatively furnished 5-bromopyridine-2-carboxylic acid *tert*-butylamide (**6**), which was converted smoothly to **1** following a modified literature procedure[5] that involved the dehydration of the amide in $POCl_3$ and toluene at 110°C. The structural identity of **1** was confirmed by comparing our analytical data with that reported previously for the compound.[1]

In summary, the title compound **1** was efficiently prepared from commercially available 2,5-dibromopyridine in a two-step yield of 75%. One attractive feature of the sequence is that it introduces the cyano functionality without the use of toxic metal cyanides.

5-Bromopyridine-2-carboxylic acid *tert*-butylamide (6). 2,5-Dibromopyridine (1.3 g, 5.5 mmol) was dissolved in toluene (65 mL), and the



Scheme 2.

mixture was purged with N_2 (g) and cooled to $-78^{\circ}C$. A solution of *n*-BuLi (6.5 mmol) in hexanes was added dropwise, and the mixture was stirred at this temperature for 2 h. A solution of *t*-butyl isocyanate (850 μL, 7.2 mmol) in 2.5 mL of toluene was added dropwise, and the reaction mixture was stirred for 1 h. The mixture was allowed to warm to $-10^{\circ}C$, and was quenched with aqueous NH_4Cl (130 mL) and stirred for 30 min. The layers were separated and the toluene layer was dried over Na_2SO_4, filtered, and concentrated to dryness to furnish 1.4 g (99%) of crude **6**, which was judged to be 90–95% pure by ^1H NMR: ^1H NMR (300 MHz, CD_3OD): δ 8.66 (d, 1H, $J = 1.2$), 8.12 (d, 1H, $J = 6.3$), 7.94 (d, 1H, $J = 6.3$), 1.44 (s, 9H).

5-Bromopyridine-2-carbonitrile (1). Crude **6** (1.4 g) was dissolved in a mixture of toluene (5 mL) and $POCl_3$ (5 mL). The resulting solution was stirred at $110^{\circ}C$ for 5 h. The reaction was cooled to room temperature and poured into a flask containing ice cold H_2O (80 mL). The pH of the resulting solution was adjusted to ≈12 by the slow addition of aqueous 2 N NaOH. The product was extracted from the aqueous layer using EtOAc (50 mL × 2). The organic layers were collected, dried over Na_2SO_4, and concentrated to dryness. Compound **1** (734 mg, 75% two step yield) was estimated to be 95% pure by ^1H NMR and was subsequently used in additional reactions without further purification. A small sample was recrystallized from hexanes to afford the analytical sample: $R_f = 0.50$ (hexanes:EtOAc = 4:1 v/v). ^1H NMR (300 MHz, $CDCl_3$): δ 8.79 (d, 1H, $J = 2.1$), 7.99 (d, 1H, $J = 2.1$, 8.4), 7.59 (d, 1H, $J = 8.4$). IR (NaCl, neat, cm^{-1}): 2232. LC-MS: $M + CH_3CN$ 224, retention time 2.22 min, purity 98.4% (method: Phenomenex Synergi 4 μ Hydro-RP column; 2 mL/min flow rate, 5−100% CH_3CN gradient in 0.1% formic acid). M.p.: 128–129°C (Lit. m.p. 100–110°C, 3 mmHg).

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