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An efficient synthesis of 1,6- and 1,7-dibromo-3-aminoisoquinolines: versatile templates for the preparation of functionalized isoquinolines

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Abstract—An efficient synthetic route to 1,6- and 1,7-dibromo-3-aminoisoquinoline was devised. These intermediates served as ideal templates for the preparation of 3-aminoisoquinoline analogues functionalized at C(6) or C(7).
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Isoquinolines are widely known elements in natural products as well as in agents with potential therapeutic utility.[1] In the context of a medicinal chemistry program, we were interested in preparing a series of 1-oxo-3-amino- and 1,3-diaminoisoquinoline derivatives. For this, we required efficient access to large quantities of isoquinolines that could serve as scaffolds amenable to derivatization at multiple sites, particularly on the benzene ring. Since electrophilic substitution of isoquinolines at positions C(5)–C(8) has proven difficult,[2] relatively few 1-oxo-3-amino-, and 1,3-diaminoisoquinoline derivatives have been reported bearing carbon-based substituents at these positions.[3] Therefore, we focused on the construction of compounds carrying a single halide function on the benzene ring, anticipating that transition-metal catalyzed reactions would render easy access to these compounds. In particular, dibromoisoquinolines **1** and **2** (Fig. 1) were thought to be ideal intermediates since these would allow diversification at three separate sites through semi-orthogonal transformations: nucleophilic aromatic substitution (S_NAr) at C(1), electrophilic functionalization of the 3-amino group and transition-metal catalyzed reactions at either C(6) or C(7).

Substituted 1-bromo-3-aminoisoquinolines have been prepared from the corresponding dinitrile by treatment with HBr in acidic (AcOH) or nonpolar (Et_2O or benzene) solvents.[4] Therefore, our first objective was to develop a synthetic route to access bromo-substituted dinitriles **8** and **9** in multigram quantities (Scheme 1). We first attempted to apply a known route for the synthesis of similarly substituted compounds.[5] Unfortunately, it proved somewhat difficult to produce large quantities of these particular bromo-substituted dinitriles following this method. Benzylic bromination of 4-bromo-2-methylbenzonitrile (**3**) gave a mixture of bromide **4** and dibrominated material (LC/MS and TLC analysis). Because the dibromide side product was difficult to remove by recrystallization, we were forced to perform a tedious column chromatography for purification (48% isolated yield).

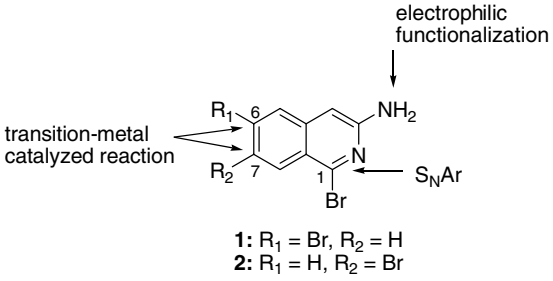

Figure 1. 1,6- and 1,7-Dibromo-3-aminoisoquinoline templates.

As this approach seemed impractical for our purposes, we next focused on installation of the benzylic nitrile through an S_NAr approach. Treatment of 4-bromo-2-fluorobenzonitrile **5** with the sodium anion of methyl cyanoacetate at 90 °C proceeded smoothly to give ester **7** in 74% yield.[6] Optimization of conditions that

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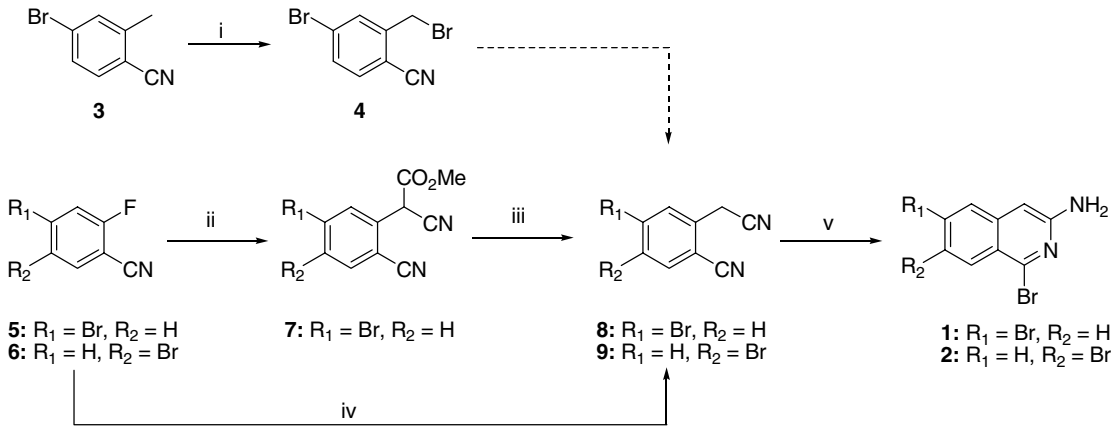


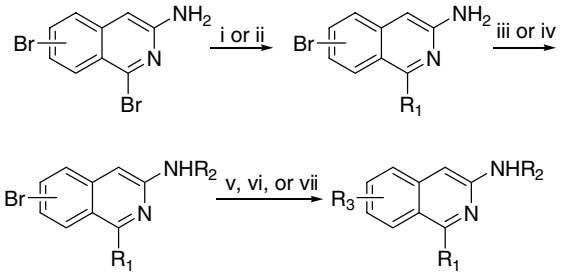
Scheme 1. Reagents and conditions: (i) *N*-bromosuccinimide, benzoyl peroxide, CCl_4, 48%; (ii) methyl cyanoacetate, NaH, DMSO, 90 °C, 74% for **7**; (iii) 2 equiv H_2O, DMSO, 115 °C, 93% for **8**; (iv) methyl cyanoacetate, NaH, DMSO, 90 °C; then H_2O, reflux (91% for **8**, 81% for **9**); (v) HBr (g), dichloroacetic acid, 0 °C to room temperature (59% for **1**, 73% for **2**).

promoted smooth decarboxylation of **7** to give dinitrile **8** proved elusive; for example, heating the ester in AcOH to 120 °C resulted in ester hydrolysis exclusively.[7] Basic conditions (NaOH, KOH, LiOH)[8] initiated nitrile hydrolysis competitively with decarboxylation. In addition, nucleophilic decarboxylation under Krapcho conditions (NaCN, LiCl, or NaCl in wet DMSO)[9] gave multiple products. Finally, it was found that simply heating the ester in wet DMSO (2 equiv H_2O) at 115 °C for 1 h in the absence of additional salt yielded decarboxylation to dinitrile **8** in 93% yield.[10]

Next, we attempted to combine the two steps into a one-pot procedure. Indeed, we found that upon completion of the S_NAr addition (followed by LC/MS), adding water as co-solvent and heating to reflux provided clean decarboxylation, enabling the isolation of **8** in 91% yield directly from **5**.[11] Analogous treatment of benzonitrile **6** gave **9** in slightly lower yield (81% yield for the two chemical steps).

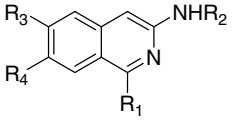
With an efficient synthesis of the dinitriles accomplished, our attention turned to isoquinoline formation. Treatment of dinitrile **8** with 30% HBr in AcOH as described by Johnson and Nasutavicus[4] for similar intermediates gave isoquinoline **1**. However, we found that the use of HBr in acetic acid produced inconsistent results. Most notably, various amounts of a 3-acetamide byproduct were observed.[12] Alternatively, addition of HBr (g) to a solution of **8** in benzene or Et_2O[4] was found to be impractical.[13]

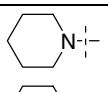
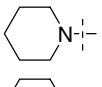
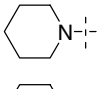
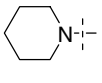
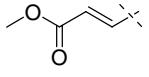
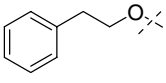
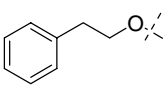
To solve this problem, we screened a variety of acidic solvents, which identified HBr (g) in dichloroacetic acid as a suitable condition to produce 1,6-dibromo-3-aminoisoquinoline free of acetylated byproduct.[14] These reaction conditions allowed the isolation of **1** (59%) and **2** (73%) on 10–20 g scale.[15] Access to such quantities of dibromoisoquinoline intermediates allowed efficient synthesis of multifunctional isoquinoline derivatives (Scheme 2, Table 1).[16]



Scheme 2. Reagents and conditions: (i) piperidine, 1,4-dioxane, 170 °C, microwave irradiation, 86–90%; (ii) phenethyl alcohol, NaH, DMF, 42%; (iii) acetic anhydride, NEt_3, 89–94%; (iv) methanesulfonyl chloride, pyridine/CH_2Cl_2 (1:1), 81%; (v) cat. $Pd(PPh_3)_4$, cat. CuI, TMS–acetylene, NEt_3, 80 °C, 94% for both reactions; (vi) cat. $Pd_2(dba)_3$, cat. P(*t*-Bu)$_3$, KF, boronic acid, 65 °C, 1,4-dioxane, 70–87%; (vii) cat. $Pd_2(dba)_3$, cat. P(*t*-Bu)$_3$, *N*,*N*-dicyclohexylmethylamine, methyl acrylate, 1,4-dioxane, 80 °C, 87%.

Table 1. Isoquinoline analogues prepared via dibromo- intermediates **1** and **2**



Entry	R_1	R_2	R_3	R_4
1		Ac	Ph	H
2		Ac	TMS—≡—	H
3		Ac	H	Ph
4		Ms	H	
5		Ac	TMS—≡—	H
6		Ac		H

As expected, the C(1) bromide could be selectively displaced via S_NAr displacement by an amine (microwave irradiation, entries 1–4)[17] or an alkoxide anion (ambient temperature, entries 5 and 6).[18] Next, the 3-amino group was converted to an acetamide (Ac, entries 1–3, 5 and 6) or a methyl sulfonamide (Ms, entry 4).[5a,b] Finally, the C(6) and C(7) bromides participated in Sonogashira (entries 2 and 5),[19] Heck (entry 4),[20] and Suzuki couplings (entries 1, 3 and 6)[21] to give good yields of substituted isoquinolines.

In conclusion, an efficient synthetic route for the preparation of 1,6- and 1,7-dibromo-3-aminoisoquinolines in multigram quantity is presented. As demonstrated in Scheme 2 and Table 1, these compounds serve as versatile intermediates for the synthesis of multisubstituted 1-oxo-3-amino- and 1,3-diaminoisoquinoline derivatives with various substituents at C(6) and C(7). This general strategy should be applicable for the preparation of other multisubstituted 3-aminosoquinolines.

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11. *Procedure for the preparation of 4-bromo-2-(cyanomethyl)benzonitrile* (**8**). Methyl cyanoacetate (22.1 mL, 250 mmol) was slowly added to a suspension of sodium hydride (10.0 g, 250 mmol, 60% dispersion in mineral oil) in DMSO (75 mL) at 0 °C. The mixture was stirred for 30 min at room temperature before 4-bromo-2-fluorobenzonitrile (25.0 g, 125 mmol) was added as a solution in DMSO (125 mL) via cannula. The yellow solution was heated to 90 °C for 2 h, H_2O (450 mL) was added, and the reaction was heated to reflux for 8 h. The mixture was cooled to 5 °C and 0.1 N HCl (250 mL) was added. After stirring at 5 °C for 30 min, the resulting precipitate was filtered, washed with water and dried to afford 4-bromo-2-(cyanomethyl)benzonitrile (25.17 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (1H, s), 7.65 (1H, d, $J = 8.4$ Hz), 7.57 (1H, d, $J = 8.2$ Hz), 3.99 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 135.21, 134.14, 132.39, 132.34, 128.88, 115.84, 115.25, 110.98, 22.35.
12. In one case, small amounts of nitrile hydrolysis were also observed (10–15% by LC/MS analysis).
13. Preliminary experiments showed that continuous addition of HBr (g) was required for the reaction to proceed.
14. Minor amounts of nitrile hydrolysis was also observed.
15. *Procedure for the preparation of 1,6-dibromoisoquinolin-3-amine* (**1**). HBr (g) was bubbled through dichloroacetic acid (100 mL) at 0 °C for 10 min. 4-Bromo-2-(cyanomethyl)benzonitrile (25.0 g, 113 mmol) was added and the mixture was stirred at 0 °C for 15 min, warmed to room temperature and stirred for 1 h. The yellow suspension was cooled back to 0 °C and Et_2O (100 mL) was added slowly. After stirring at 0 °C for 30 min, the precipitate was filtered, washed with Et_2O (200 mL) and dried. The solid was taken up in H_2O (100 mL) and 1 N NaOH was added until the pH reached 12. The resulting suspension was stirred for 15 min, the solid was filtered and then dried. This solid was suspended in $CHCl_3$ (2 L) and the resulting white precipitate was filtered off. The filtrate was concentrated under vacuum to give 1,6-dibromoisoquinoline-3-amine as a yellow solid (20.0 g, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (1H, d, $J = 1.8$ Hz), 7.78 (1H, d, $J = 9.0$ Hz), 7.34 (1H, dd, $J = 9.0, 2.0$ Hz), 6.58 (1H, s), 6.49 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.23, 142.71, 141.40, 130.03, 126.62, 126.15, 125.16, 119.73, 96.63.
16. All compounds in Table 1 were characterized by ^{1}H NMR, ^{13}C NMR and high resolution mass spectrometry (to within 4.0 ppm). All were >95% pure as analyzed by LC/MS (Phenomenex, MAX RP, 4 μm, 50 × 2.0 mm, 1 mL/min, (A) 0.1% TFA in H_2O, (B) 0.1% TFA in MeCN, 10–100% B in 10 min).
17. Smith Synthesizer® microwave reactor (Personal Chemistry, Upssala, Sweden). See Ref. 5b.
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