Practical synthesis of 7-bromo-4-chloro-1H-indazol-3-amine: an important intermediate to Lenacapavir

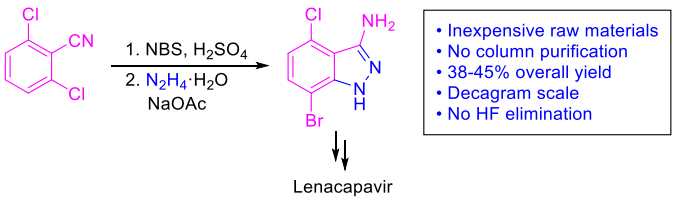
*Naeem Asad,‡ Michael Lyons,‡ Shirley Muniz Machado Rodrigues, Justina M. Burns, Thomas D. Roper, G. Michael Laidlaw, Saeed Ahmad, B. Frank Gupton, Douglas Klumpp, Limei Jin**

Medicines for All Institute, Virginia Commonwealth University, Richmond, VA, 23284-3068.

‡These authors contributed equally

Email: jinl3@vcu.edu

TOC (Abstract figure)



KEYWORDS: Lenacapavir, indazol-3-amine, hydrazine, regioselective cyclization, process development.

ABSTRACT

7-Bromo-4-chloro-1H-indazol-3-amine is a heterocyclic fragment used in the synthesis of Lenacapavir, a potent capsid inhibitor for the treatment of HIV-1 infections. In this manuscript,

we describe a new approach to synthesizing 7-bromo-4-chloro-1H-indazol-3-amine from inexpensive 2,6-dichlorobenzonitrile. This synthetic method utilizes a two-step sequence including a regioselective bromination and heterocycle formation with hydrazine to give the desired product in an overall isolated yield of 38-45%. The new protocol has been successfully demonstrated on hundred-gram scales without the need of column chromatography purifications. This new synthesis provides a potential economical route to large scale production of this heterocyclic fragment of Lenacapavir.

INTRODUCTION

3-Aminoindazoles are a privileged class of heterocyclic structures common to many biologically active compounds. For example, this structure is found in the glycogen synthase 3β inhibitor **1**, a substance having potential for the treatment of Alzheimer's disease (Figure 1).[1] The 3-aminoindazole (**2**) was developed as a possible treatment of iron deficiency,[2] while linifanib (**3**)

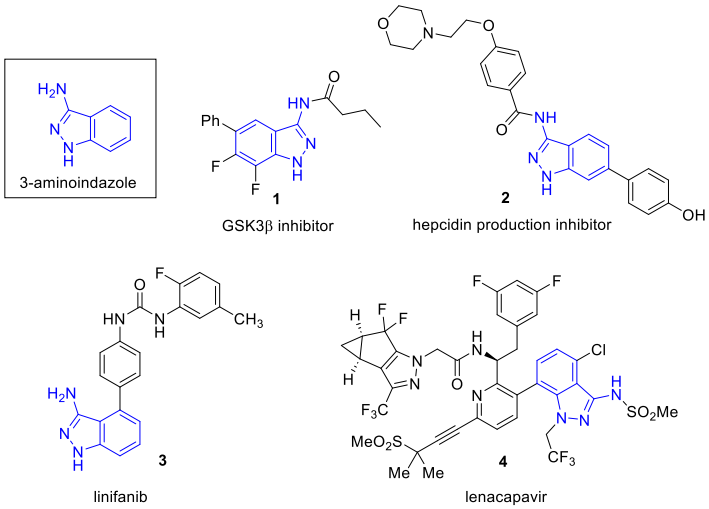
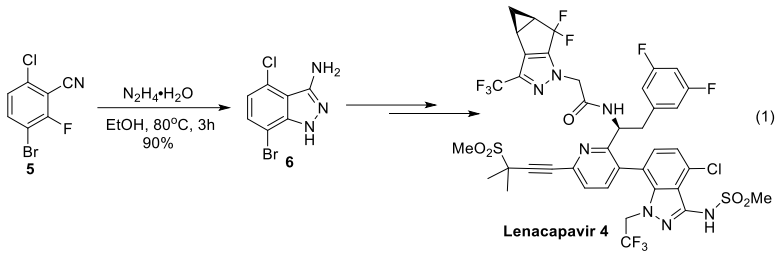


Figure 1. Biologically active 3-aminoindazoles.

is a potent tyrosine kinase receptor inhibitor used to suppress tumor growth.[3] Recently, Gilead developed Lenacapavir (**4**) which exhibits high-potency in the treatment of human immunodeficiency virus (HIV).[4,5] Among the synthetic routes used to prepare 3-aminoindazoles,

S_NAr chemistry has often been utilized. For example, in the synthesis of Lenacapavir, 3-bromo-6-chloro-2-fluorobenzonitrile (**5**) reacts with hydrazine to provide the 3-aminoindazole (**6**) in 90% yield (eq 1).[4]



(1)

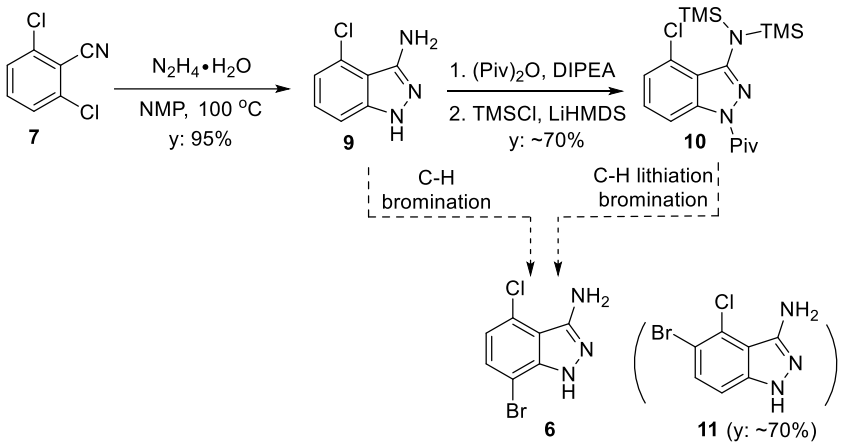
A similar transformation is done with 2,6-dichlorobenzonitrile (**7**) and hydrazine to form the 3-aminoindazole leading to linifanib (**3**).[6] While 2-chloro and 2-fluorobenzonitriles are commonly used in this method, 2-bromobenzonitriles have provided 3-aminoindazoles through transition metal-catalyzed reactions.[7] The 3-aminoindazole scaffold has also been prepared from S_NAr chemistry with hydrazine and a 2-nitrobenzonitrile.[8] Besides these approaches, synthetic routes to 3-aminoindazoles have utilized 2-fluorocarboxylic acids (via thioamides), ortho-haloaryl hydrazines in Pd-catalyzed cyclizations, C-N coupling of halogenated indazoles, intramolecular N-N coupling reactions, and others.[9–11]

With the promising results from the clinical trials of Lenacapavir, it is vitally important that this substance can be prepared economically on a large scale.[12] While the 3-aminoindazole fragment of Lenacapavir has been prepared on pilot plant scale (eq 1), the synthetic route utilizes a costly 3-bromo-6-chloro-2-fluorobenzonitrile (**5**)[13] and the heterocycle synthesis leads to the elimination of HF.[6] We envisioned that 3-bromo-2,6-dichlorobenzonitrile (**8**) might be used as precursor to synthesize 3-aminoindazole (**6**) using a similar S_NAr cyclization with hydrazine, perhaps allowing for the use of the less expensive 2,6-dichlorobenzonitrile as the starting material. In the following manuscript, we describe our work in the preparation of the 3-aminoindazole

fragment of Lenacapavir. The new chemistry leverages a highly regioselective bromination and selective cyclization step to provide efficient route to the functionalized heterocycle.

RESULTS AND DISCUSSION

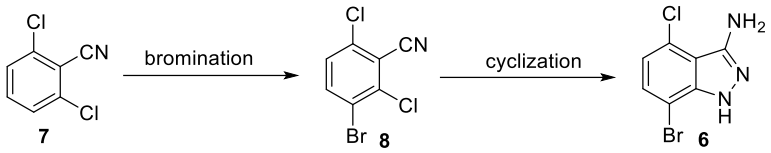
Our initial efforts to make 7-bromo-4-chloro-1H-indazol-3-amine **(6)** involved forming the 3-aminoindazole ring first and then brominating the heterocyclic product. In accord with the literature, the 3-aminoindazole (**9**) was prepared from condensation of **7** with hydrazine hydrate in 95% of yield (Scheme 1).[6] Direct bromination of compound **9** was not successful. Treatment of **9** with NBS afforded the undesired regioisomer **11** as the major product (based on ^{1}HNMR, GCMS).



Scheme 1. Initial attempt to synthesis of **6**.

As another approach to functionalize the 7-position, we sought to carryout regioselective functionalization of protected 3-aminoindazole derivative **10**. Treating **10** with different organolithium reagents, such as n-butyllithium (BuLi), lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LiHMDS) followed by treatment with bromine resulted in a complex mixture of products. Functionalization of the 7-position was also attempted with borylation of the lithiation products of **10**, using $B(OMe)_3$ and $B(OiPr)_3$ after reaction with the organolithium base.

This approach also failed to yield any desired product with functionalization at the 7-position, but rather resulted in recovering the starting material 3-aminoindazole.



Scheme 2. Synthesis of indazole **6** through regioselective cyclization of **8**.

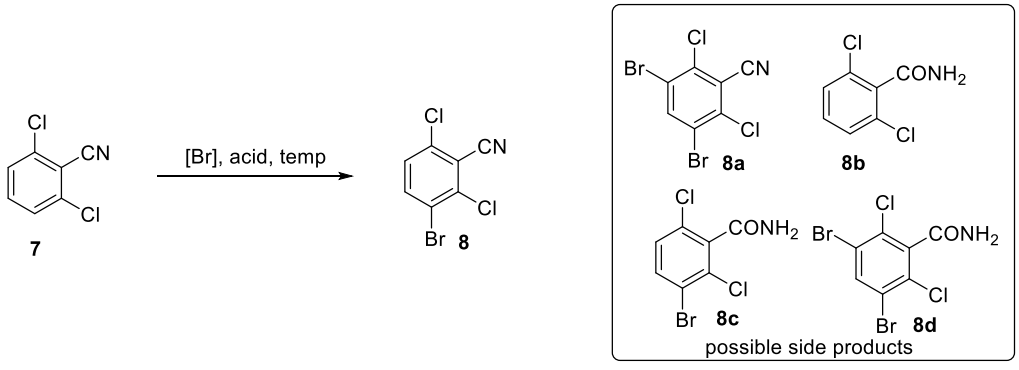
1. Synthesis of 3-bromo-2,6-dichlorobenzonitrile

As alternative approach, it was hypothesized that bromination of 2,6-dichlorobenzonitrile could provide compound **8** and this derivative could afford the desired 3-aminoindazole **6** (Scheme 2). 3-Bromo-2,6-dichlorobenzonitrile **8** was initially prepared according to a reported method as follows. Treatment of **7** with potassium bromate and sulfuric acid to afford **8** in ~60% yield after column purification.[14] Unfortunately, this bromination method possessed potential safety issues as it is an extremely exothermic reaction. The conversion was also accompanied by side reactions, such as over-bromination and hydrolysis of the cyano group. Decreasing the reaction temperature to 0 °C and -10 °C resulted in lower conversion with a similar low product purity.

To identify a more practical and safer bromination condition to prepare 3-aminoindazole **8**, alternate brominating reagents and conditions were explored (Table 1). Two commonly used brominating reagents Br_2 and NBS were investigated. Reactions with bromine resulted in hydration of the cyano group to an amide. More hydrolyzed side-products were observed under elevated temperatures (Table 1, entries 1-3). N-Bromosuccinimide (NBS) was identified as the optimal brominating reagent for this transformation. Initial reaction of **7** with 1.2 equivalents of NBS at 25 °C afforded product **8** in a 75 A%, along with 12 A% of **7** and 12 A% of dibrominated

product **8a** detected by GC-MS total ion chromatography (TIC) (Table 1, entry 4). With an increase in reaction temperature, hydration of the nitrile group and over-bromination was dominated (Table 1, entries 5-6). By decreasing the equivalents of NBS to 1.07 (25 °C), the reaction furnished **8** in >93 A% without hydration of the nitrile group or over-bromination (Table 1, entry 7). Investigation of equivalents and concentration of H_2SO_4 identified that 10-11 equivalents of 96% H_2SO_4 was optimal for the bromination (Table 1, entries 8-12). Comparing to the reaction with 10 equivalents of 96% H_2SO_4 the experiment with 11 equivalents of 96% H_2SO_4 was superior only by 1%, thus 10 equivalents of 96% H_2SO_4 was used for scale-up. Notably, swapping H_2SO_4 to other acids such as TFA or acetic acid resulted in no reaction (Table 1, entries 13-14). As a result, the optimal bromination condition was identified for scale-up (NBS (1.07 eq), 96% H_2SO_4 (10 eq), 25 °C, 18h). The optimized condition was demonstrated on hundred-gram scale (25-300 g) reactions. After completion of reaction, the product mixture was poured into 15 volumes of ice-cold water and the resulting precipitate was collected by filtration. The filter cake was washed with 3 volumes of ethyl acetate to obtain the desired 3-aminoindazole **8** in 75-80% isolated yield with 95-96% of purity (qNMR) (Table 1, entries 15-18).

Table 1. Bromination of 2,6-dichlorobenzonitrile **7**



Entry[a]	[Br] (eq.)	Acid		GC-MS analysis (TIC A%)[c]

		(eq.)	Temp (°C)	7	8	8a	8b	8c	8d
1[b]	Br_2 (2)	96% H_2SO_4 (10)	25	72	-	-	28	-	-
2[b]	Br_2 (2)	96% H_2SO_4 (10)	60	4	-	-	96	-	-
3[b]	Br_2 (2)	96% H_2SO_4 (10)	100	3	-	-	97	-	-
4[b]	NBS (1.2)	96% H_2SO_4 (10)	25	12	75	12	-	-	-
5[b]	NBS (1.2)	96% H_2SO_4 (10)	60	0.5	0.5	5	-	66	28
6[b]	NBS (1.2)	96% H_2SO_4 (10)	100	-	-	4	-	61	32
7	NBS (1.07)	96% H_2SO_4 (10)	25	3	93	4	-	-	-
8	NBS (1.07)	96% H_2SO_4 (5)	25	21	70	9	-	-	-
9	NBS (1.07)	96% H_2SO_4 (9)	25	7	92	-	-	-	-
10	NBS (1.07)	96% H_2SO_4 (11)	25	2	94	4	-	-	-
11	NBS (1.07)	60% H_2SO_4 (10)	25	>95	-	-	-	-	-
12	NBS (1.07)	80% H_2SO_4 (10)	25	14	66	20	-	-	-
13	NBS (1.07)	TFA (10)	60	>95	-	-	-	-	-
14	NBS (1.07)	Acetic acid (10)	60	>95	-	-	-	-	-
15[d]	NBS (1.07)	96% H_2SO_4 (10)	25	4	93	3	-	-	-
16[e]	NBS (1.07)	96% H_2SO_4 (10)	25	5	91	4	-	-	-
17[f]	NBS (1.07)	96% H_2SO_4 (10)	25	5	91	4	-	-	-

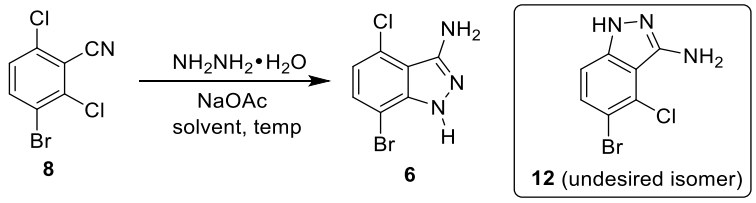
[a]All reactions were performed with 2,6-dichlorobenzonitrile (2 g) under the conditions shown in the table for 18h unless otherwise stated. [b] 0.1g of 2,6-dichlorobenzonitrile. [c]All these data were IPC of crude reaction mixtures obtained by GC-MS total ion chromatogram (TIC) and reported as A% unless otherwise stated. [d]25g of 2,6-dichlorobenzonitrile; isolated yield: 76%, 96% purity by qNMR. [e]125g of 2,6-dichlorobenzonitrile; isolated yield: 81%, 96% purity by qNMR. [f]290g of 2,6-dichlorobenzonitrile, isolated yield: 80%, 95% purity by qNMR.

2. Synthesis of 7-bromo-4-chloro-1H-indazol-3-amine

With 3-bromo-2,6-dichlorobenzonitrile (**8**) in hand, the cyclization with hydrazine hydrate was investigated (Table 2). As shown in Table 2, a variety of solvents such as aprotic polar solvents, protic solvents, basic solvents, and other organic solvents were screened in the cyclization chemistry. The cyclization in aprotic polar solvents such as NMP and DMSO performed smoothly under a mild condition (60 °C, 2 eq. of hydrazine hydrate and 1.2 eq of NaOAc).[15] Unfortunately,

both chloro groups of **8** reacted with hydrazine without preference, resulting in ~50:50 ratio of **6** and **12** (Table 2, entries 1-2). The ratio of **6**:**12** improved to 65:35 when switching the solvent to ethanol and further improved to 70:30 with IPA as a solvent (Table 2, entries 3-4). In order to achieve >95% conversion of **8**, an elevated reaction temperature (95 °C) and excess hydrazine was needed. However, these promising results inspired our further solvent screening for a better regioselectivity. Among all other solvents screening, DIPEA and 2-MeTHF were identified to afford a higher ratio of the desired regioisomer (Table 2, entries 5-9). Considered a "green" type of solvent, 2-MeTHF was selected for further optimization. Equivalents of hydrazine were investigated to obtain an optimal condition for this transformation. It was found that 4 equivalents of hydrazine hydrate afforded >98% conversion of compound **8**. (Table 2, entries 10-11). In addition, solvent volume screen showed that 5 V of 2-MeTHF afforded >99% conversion with 70:30 ratio of **6**/**12** (Table 2, entry 12). As a result, the optimized condition of the cyclization was identified for scale up (hydrazine hydrate (4 eq), NaOAc (1.2 eq), 2-MeTHF (5 V), 95 °C).

Table 2. Optimization of cyclization of **8**[a]



Entry	Solvent	Temp (°C)	Eq. of $NH_2NH_2 \cdot H_2O$	Conversion (%)[b]	Ratio[b] **6:12**
1[b]	NMP	60	2	100	~50:50
2[b]	DMSO	60	2	100	~50:50
3	EtOH	95	10	100	65:35
4	IPA	95	10	100	70:30

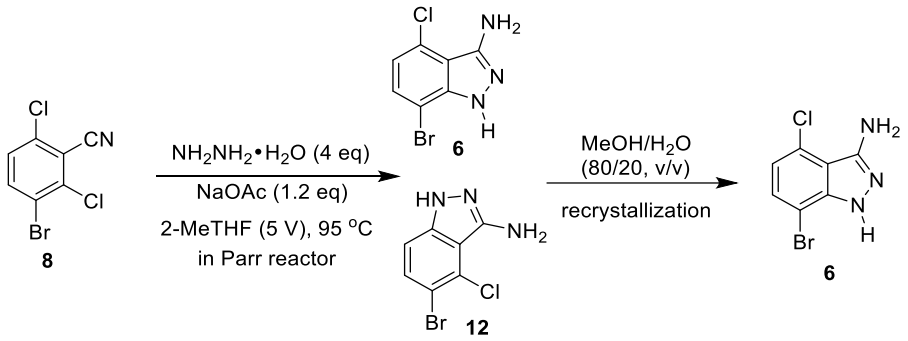
5	DIPEA	95	10	100	75:25
6	Pyridine	95	10	100	68:32
7	THF	95	10	100	70:30
8	Diglyme	95	10	100	70:30
9	2-MeTHF	95	10	100	73:27
10	2-MeTHF	95	8	100	70:30
11	2-MeTHF	95	4	98	70:30
12[c]	2-MeTHF	95	4	99	70:30

[a]All reactions were performed in heavy wall pressure vessels with **8** (0.5 g) in the presence of NaOAc (1.2eq) under the conditions shown in the table for 18h, unless otherwise stated, 10 solvent volumes were used (V) = mL/g of **8**. [b]The ratio of the crude reaction mixture was monitored by ^{1}HNMR. [c]5 V of 2-MeTHF was used.

Parenthetically, the transformation in 2-MeTHF needs an internal temperature of > 90 °C to obtain a full conversion thus a pressure reactor was utilized for scaling up. A mixture of **8** (20 g), NaOAc (1.2 eq) and 4 eq. of hydrazine hydrate in 2-MeTHF (5 V) was stirred in a Parr reactor at 95°C (internal temperature) affording >95% conversion after 18h. It is worth mentioning that as Kruger and coworkers found that the addition of sodium acetate is needed to mitigate the safety concerns regarding the utilization of hydrazine hydrate in scale.[15] The sodium acetate may quench the resulting HCl during the cyclization, which suppressed the possible formation of high energic hydrazine HCl conjugates. Although the two isomers could be separated by column chromatography, a more scalable purification method by recrystallization to afford the desired isomer was identified. After screening a variety of solvents, a binary solvent of MeOH/H_2O (80/20, v/v) was found as optimal for the recrystallization. For instance, a mixture of regioisomers (molar ratio of **6**/**12**: 70/30) was dissolved in MeOH/H_2O (80/20, v/v) at 80°C, after cooling to room temperature the desired isomer **6** was obtained as a solid in ~80% of recovery yield with ~97% of purity (qNMR). The protocol was successfully demonstrated with three batches on 20-80 g scale reactions. As shown in Table 3, in a Parr reactor, with 2-MeTHF as a solvent, the

reaction of **8** and hydrazine hydrate at 95°C afforded the crude of regioisomers (molar ratio of **6**/**12**: 70/30) in a quantitative yield. After treating the regioisomers with MeOH/H_2O (80/20, v/v) the desired isomer **6** was obtained in 50-56% isolated yield with 96-98% of purity (qNMR) (Table 3, entries 1-3).

Table 3. Synthesis and purification of 7-bromo-4-chloro-1H-indazol-3-amine

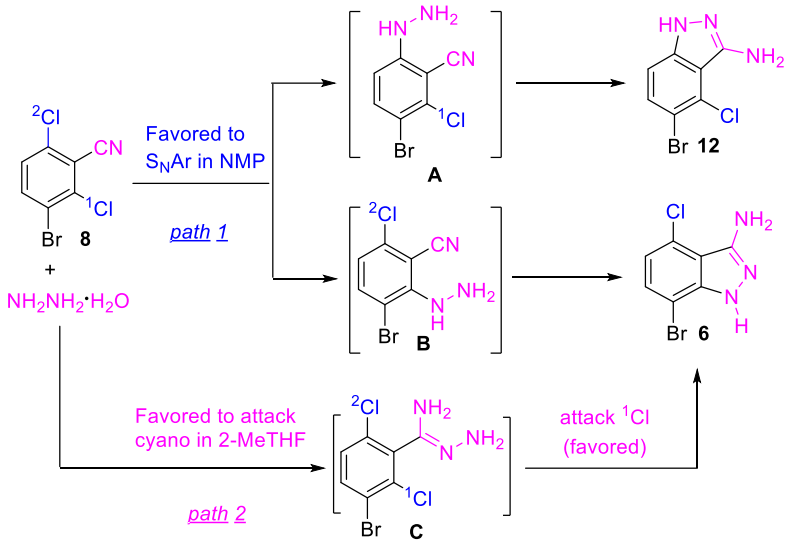


Entry[a]	Reaction scale	A% (GCMS (TIC)) of crude[b]			**6** after crystallization[c]	
		8	**12**	**6**	Purity by GCMS (TIC A%)	Isolated yield
1	20g	2	28	70	97%[d]	50%
2	40g	<1	29	70	98%[e]	56%
3	80g	<1	29	70	96%[f]	53%

[a]All reactions were performed in a Parr reactor with **8** (20-80 g), hydrazine hydrate (4 eq), NaOAc (1.2 eq), 2-MeTHF (5 V), 95 °C (internal temperature), 18h. [b]All these crude mixtures were monitored by GC-MS (TIC) and reported as A%. [c]The crude was dissolved in MeOH/H_2O (80/20, v/v) at 80°C, then cooled to rt, collected by filtration, washed by MTBE. The purity was measured by GCMS-TIC A%). [d]Containing ~2% of **12** and ~1% unknown impurity. [e]Containing ~2% of unknown impurity. [f]Containing ~2% of **12** and ~2% unknown impurity.

The subtle steric and electronic distinction of the two chlorine atoms might play an important role in regioselective cyclization of **8** with hydrazine hydrate. However, the detailed mechanistic basis of the regioselectivity is unclear. It is known that the condensation reaction between 2,6-dichlorobenzonitrile and hydrazine hydrate can proceed with two possible pathways: 1) S_NAr

occurred first followed by an intramolecular cyano attack; or 2) cyano attack occurred first followed by an intramolecular S_NAr reaction.[6,15] The reaction of **8** and hydrazine might proceed with a similar pathway. As shown in Scheme 3, the indazole **6** could be formed through either hydrazine attacking chloro first (S_NAr reaction) followed by an intramolecular cyclization (path 1) or the hydrazine attacking cyano group first followed by an intramolecular S_NAr cyclization (path 2). Both pathways afforded the indazole **6**. It is believed that pathway 1 might need less energy in transformation of the intermediates to the indazole **6** (fast reaction rate, less hydrazine and low reaction temperature) while pathway 2 might need a higher energy to convert the intermediates to the indazole compound (long reaction time, more hydrazine, higher reaction temperature). Our experimental results indicated that the regioselective cyclization was highly solvent dependent. We assume that in the aprotic polar solvent, such as NMP, the pathway 1 was dominant and the fast reaction rate resulted in no selectivity. On the other hand, the pathway 2 was dominant in 2-MeTHF. Presumably, the resulting intermediate **C** favors the intramolecular S_NAr reaction on ^1Cl to afford the compound **6**, in which the induction effect of ortho bromine atom might play the role.



Scheme 3. A plausible pathway for the formation of indazole.

CONCLUSIONS

A practical synthesis of the heterocyclic compound 7-bromo-4-chloro-1H-indazol-3-amine has been developed from the readily available and inexpensive raw material 2,6-dichlorobenzonitrile. The two-step synthetic sequence utilizes a highly regioselective bromination and cyclization to give an overall yield from 38-45% for the functionalized 3-aminoindazole (**6**). A mild bromination condition (NBS/H_2SO_4) was identified, affording bromide **8** in 76-81% yield from 2,6-dichlorobenzonitrile. The subsequent regioselective cyclization in 2-MeTHF afforded the desired 3-aminoindazole regioisomer in 50-56% of isolated yield with purity up to 98% (qNMR). The two-step protocol was demonstrated on hundred-gram scales and eliminates the need for column chromatography purification. This new chemistry provides a practical synthetic route to 7-bromo-4-chloro-1H-indazol-3-amine (**6**), a heterocyclic fragment used in the synthesis of the potent anti-HIV therapeutic, Lenacapavir.

SUPPORTING INFORMATION

The Supporting Information is available free of charge at https://pubs.acs.org/doi/SOMEJOURNALLINK These data include additional experimental details and analytical methods.

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