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Synthesis of 3-Cyano-1*H*-indoles and Their 2′-Deoxyribonucleoside Derivatives through One-Pot Cascade Reactions

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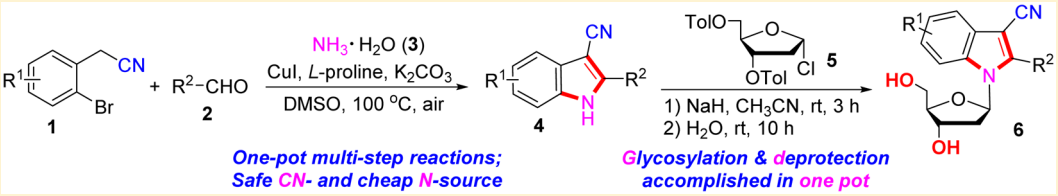
Supporting Information



ABSTRACT: An efficient and economical synthetic approach toward 3-cyano-1*H*-indoles through the reactions of 2-(2-bromophenyl)acetonitriles with aldehydes and aqueous ammonia is presented. Mechanically, this novel protocol involves a one-pot cascade procedure consisting of an aldol-type condensation, a copper-catalyzed amination by using aqueous ammonia as a cheap and safe nitrogen source, and an intramolecular Michael addition followed by a dehydrogenative aromatization. Interestingly, the indole products thus obtained were found to be ready substrates for the preparation of indole 2′-deoxyribonucleosides through an unprecedented and highly practical glycosylation procedure in which the required C−N bond formation and toluoyl protecting group removal were accomplished efficiently in one pot.

INTRODUCTION

Indole derivatives have attracted much attention due to their diverse medicinal activities, ubiquitous occurrence in nature, and multiple uses in organic synthesis.[1,2] In particular, 3-cyano-substituted indoles are key building units embedded in lead compounds currently being developed as estrogen receptor ligands, hepatitis C virus inhibitors, or therapeutic agents for cardiovascular diseases.[3,4] Moreover, 3-cyanoindoles are also indispensable intermediates for the preparation of a broad range of fine chemicals.[5] Because of their importance, a number of synthetic methods leading to 3-cyanoindoles have been developed. Based on the structural characteristics of the substrates used therein, the existing synthetic methods might be roughly classified into the following three categories: (1) functional group transformation or structural manipulation of 3-carbonyl-, oximido-, hydroxymethyl-, or halide-substituted indoles;[5a,6] (2) direct C(sp^2)−H cyanation on the 3-position of indoles without prefunctionalization;[5b,7,8] and (3) cyclization of nonindole substrates such as functionalized benzenes.[9] While these literature synthetic strategies are generally efficient and reliable, the first and the third methods usually necessitate multiple synthetic steps if commercial reagents are used as the starting materials. Meanwhile, the C−H cyanation protocol often employs noble metal catalysts and/or toxic cyano sources which many cases are only suitable for *N*-protected indoles. As a result, new synthetic approaches toward 3-cyanoindoles with a free −NH unit through simple procedures by directly using commercially available, inexpensive, and safe reagents are still urgently needed.

Cascade reactions in which two or more transformations are well accomplished in one pot to afford complex products from simple starting materials are rapidly gaining popularity. In comparison with step-by-step operations, cascade reactions have the advantages of obviated isolation and purification of intermediates and minimized generation of waste chemicals. In addition, copper-catalyzed C−N bond formation is a powerful and economical tool for the construction of *N*-heterocycles.[2c,10] In this regard, our recent study has focused on the synthesis of fused *N*-heterocycles through copper-catalyzed amination by using aqueous ammonia as a cheap and safe nitrogen source.[11] As a continuation of our interest in this aspect, we have studied the one-pot, three-component cascade reaction of the commercially available 2-(2-bromophenyl)acetonitriles with aldehydes and aqueous ammonia. From this reaction, a series of diversely substituted *N*-unprotected 3-cyanoindoles were obtained in good to excellent yields through an easy-to-perform one-pot procedure. Herein, we report our results in this regard.

RESULTS AND DISCUSSION

Initially, a mixture of 2-(2-bromophenyl)acetonitrile (**1a**), benzaldehyde (**2a**), and aqueous ammonia (**3**) was treated with CuI and K_2CO_3 in DMF at 100 °C under air for 20 h. From this reaction, the desired 2-phenyl-1*H*-indole-3-carbonitrile (**4a**) was obtained in a yield of 32% (Table 1, entry 1). To improve the efficiency, different copper salts such as CuCl,

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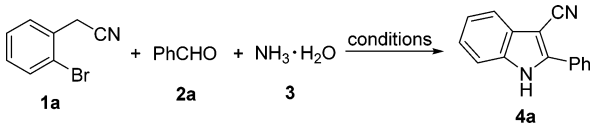
Table 1. Optimization Study on the Formation of 4a[a]



1a 2a 3 4a

entry	catalyst	base	ligand[c]	solvent	yield[b] (%)
1	CuI	K_2CO_3		DMF	32
2	CuCl	K_2CO_3		DMF	16
3	CuBr	K_2CO_3		DMF	18
4	$CuCl_2$	K_2CO_3		DMF	15
5	$Cu(OAc)_2$	K_2CO_3		DMF	22
6	$Cu(OTf)_2$	K_2CO_3		DMF	trace
7	CuI	K_2CO_3	L-proline	DMF	75
8	CuI	K_2CO_3	DMEDA	DMF	45
9	CuI	K_2CO_3	TMEDA	DMF	51
10	CuI	K_2CO_3	1,10-Phen	DMF	60
11	**CuI**	**K_2CO_3**	**L-proline**	**DMSO**	**88**
12	CuI	K_2CO_3	L-proline	NMP	21
13	CuI	K_2CO_3	L-proline	^{i}PrOH	20
14	CuI	K_2CO_3	L-proline	PEG-400	64
15	CuI	Na_2CO_3	L-proline	DMSO	65
16	CuI	Cs_2CO_3	L-proline	DMSO	67
17	CuI	K_3PO_4	L-proline	DMSO	62
18	CuI	^{t}BuOK	L-proline	DMSO	68
19	CuI		L-proline	DMSO	57
20		K_2CO_3	L-proline	DMSO	

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), **3** (26%, 0.5 mL), catalyst (0.05 mmol), ligand (0.1 mmol), base (0.5 mmol), solvent (2 mL), 100 °C, sealed tube, air, 20 h. [b]Isolated yield. [c]DMEDA for *N*,*N*′-dimethylethylenediamine, TMEDA for *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, 1,10-Phen for 1,10-phenanthroline.

CuBr, $CuCl_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$ were tried as possible catalysts. However, they were found to be less effective than CuI in promoting this reaction (entries 2−6). On the other hand, the yield of **4a** increased significantly in the presence of ligand, especially L-proline (entries 7−10). Next, DMSO, 1-methyl-2-pyrrolidinone (NMP), ^{i}PrOH, or PEG-400 was used as the reaction medium (entries 11−14). Among them, DMSO turned out to be the most efficient, affording **4a** in a yield of 88% (entry 11). Subsequent studies on the effect of different bases showed that Na_2CO_3, Cs_2CO_3, K_3PO_4, and ^{t}BuOK were less efficient than K_2CO_3 in promoting this cascade reaction (entries 15−18 vs 11). Next, control experiments showed that the yield of **4a** decreased in the absence of a base (entry 19), and the formation of **4a** was not observed without a copper catalyst (entry 20).

With the optimized reaction conditions in hand, we then examined a series of substrates to determine the influence of steric and electronic parameters on the efficiency of this cascade procedure. First, with **1a** and **3** as model substrates, the scope of aldehyde (**2**) was explored. The results listed in Table 2 showed that phenyl aldehydes with either electron-donating alkyl and alkoxyl groups or electron-withdrawing cyano and trifluoromethyl groups attached on the phenyl ring underwent this cascade process smoothly to give the corresponding products **4a**−**k** in good to excellent yields. Notably, various functional groups were well tolerated under the reaction conditions without showing obvious electronic and steric effects. Halogenated aromatic moieties survived the reaction conditions well, allowing for subsequent structural elaboration of the products. Next, with 1-naphthaldehyde, thiophene-2-carbaldehyde, or isonicotinaldehyde, the corresponding reactions took place smoothly to give **4l**, **4m**, or **4n** in 87%, 66%, or 57% yield, respectively. Promisingly, in addition to aromatic aldehydes, alkyl aldehydes were also found to be suitable for this reaction to provide products **4o**−**r** in generally good yields.

Next, the scope of the 2-(2-bromophenyl)acetonitrile substrate (**1**) was studied. The results listed in Table 3 showed that **1** bearing either a strong electron-withdrawing trifluoromethyl group or two electron-donating methoxy groups reacted smoothly with various aldehydes (**2**) and aqueous ammonia (**3**) to give diversely substituted 3-cyanoindoles (**4s**−**z**) in yields ranging from 63% to 89%.

On the basis of the above results and previous studies, a plausible pathway for the formation of 2-phenyl-1*H*-indole-3-carbonitrile (**4a**) is proposed in Scheme 1. Initially, an aldol-type condensation between **1a** and **2a** affords an *α*,*β*-unsaturated nitrile as intermediate **A**.[12] Next, a Cu(I)-catalyzed and ligand-assisted aryl amination of **A** with aqueous ammonia (**3**) as the nitrogen source affords intermediate **D**, most likely via intermediates **B** and **C**. Then, **D** undergoes an intramolecular Michael addition to give intermediate **E**. Finally, a dehydrogenative aromatization occurs with **E** to afford **4a**. It is worth noting that under the catalysis of copper compound[13] air could act as an efficient and sustainable terminal oxidant for the aromatization of the in situ formed indoline to give the corresponding indole product.

To verify the proposed reaction mechanism, some control experiments were carried out. First, **1a** was treated with **2a** under standard reaction conditions for 2 h, from which 2-(2-bromophenyl)-3-phenylacrylonitrile, the proposed intermediate **A** as described in Scheme 1, was obtained in a yield of 90% (Scheme 2, eq 1). Second, a mixture of **1a**, **2a**, and **3** in DMSO was treated with CuI, L-proline and K_2CO_3 at 100 °C under a nitrogen atmosphere for 18 h. From this reaction, 2-phenylindoline-3-carbonitrile, the proposed intermediate **E**, was obtained in a yield of 83% (eq 2). Third, **A** was treated with **3** under standard reaction conditions for 15 h, from which **4a** was obtained in a yield of 91% (eq 3). Fourth, when **E** was subjected to standard reaction conditions for 1 h, **4a** could be obtained in a yield of 97% (eq 4). Fifth, **E** was stirred in DMSO under air but in the absence of all other reagents at 100 °C for 4 h. Under this circumstance, the formation of **4a** was not observed (eq 5). This result suggested that air alone could not promote the transformation of indoline (**E**) toward indole (**4a**). Taking all of the related results (Scheme 2, eqs 2, 4 and 5) into account and based on previous reports,[13] it is reasonable to suggest that in the oxidative transformation of **E** toward **4a**, air is most likely acting as a terminal oxidant while the copper compound should have acted as a catalyst to promote this oxidation process.

Meanwhile, it is well-known that many indole nucleoside analogues possess significant biological activities.[14] In particular, Townsend et al. reported that 3-substituted indole 2′-deoxyribonucleosides (IDNs) are highly effective against human cytomegalovirus (HCMV).[15] Moreover, IDNs have also been used in the extension of the genetic alphabet since the indole unit represents an important artificial DNA base owing to its structural similarity to guanine and adenine. For example, a substituted IDN has been designed and used as a nonpolar isostere of *syn*-8-oxoguanine to act as a probe for the recognition and repair of oxidative DNA damage and to study the *syn*−*anti* conformational effect.[16] In view of the importance of IDNs and as a continuation of our ongoing

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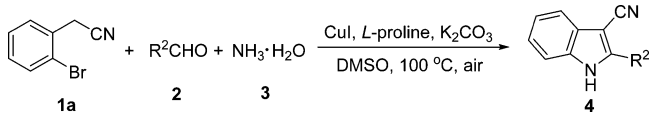
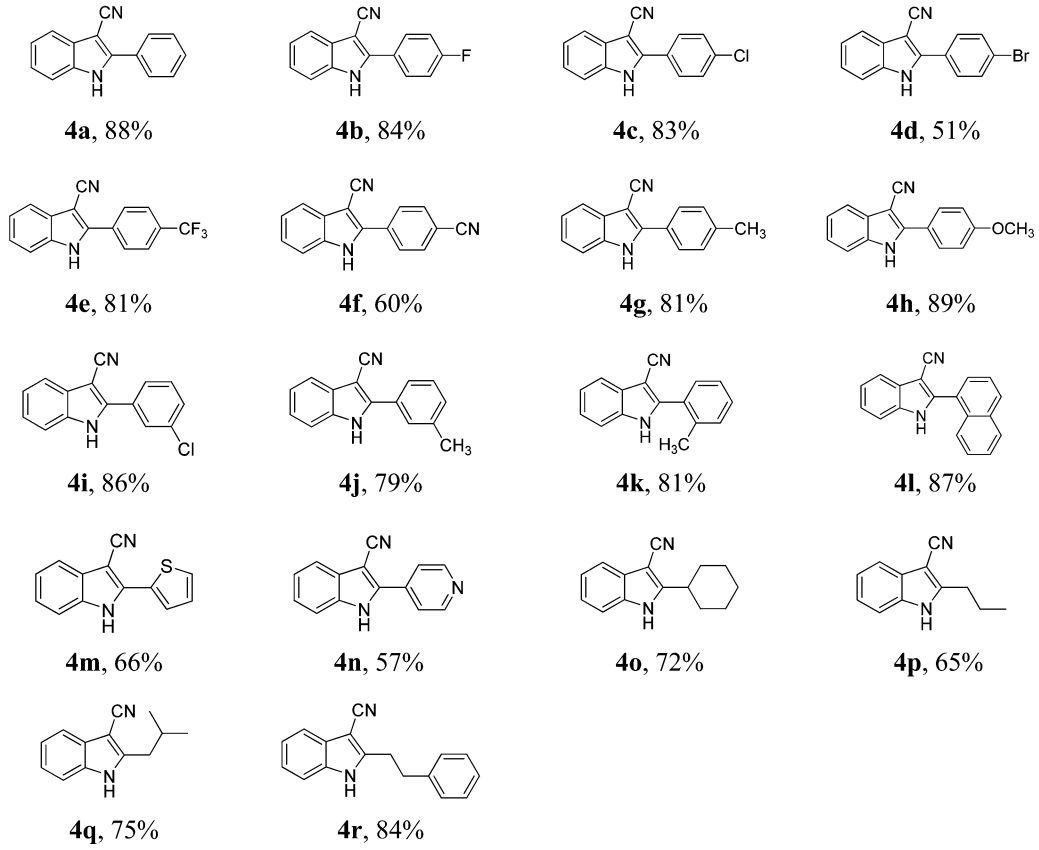
Table 2. Substrate Scope for the Synthesis of 3-Cyanoindole Derivatives I[a,b]

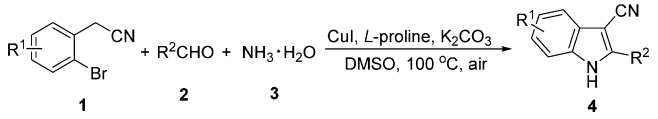


1a 2 3 4

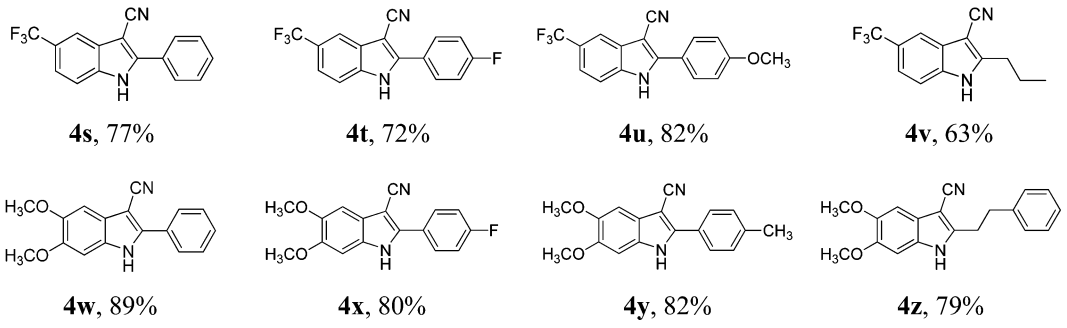


[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), **3** (26%, 0.5 mL), CuI (0.05 mmol), L-proline (0.1 mmol), K_2CO_3 (0.5 mmol), DMSO (2 mL), 100 °C, sealed tube, air, 20 h. [b]Isolated yield.

Table 3. Substrate Scope for the Synthesis of 3-Cyanoindoles II[a,b]



1 2 3 4



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), **3** (26%, 0.5 mL), CuI (0.05 mmol), L-proline (0.1 mmol), K_2CO_3 (0.5 mmol), DMSO (2 mL), 100 °C, sealed tube, air, 20 h. [b]Isolated yield.

interest in the synthesis and biological activity of nucleoside analogues,[17] we set out to synthesize some novel IDNs by using the indole derivatives obtained above as the nucleobases. We noticed that in previous studies IDNs were obtained through two separate synthetic steps:[15,16] (1) glycosylation of the -NH free indoles with Hoffer's chlorosugar (1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose) in dry acetonitrile under the promotion of sodium hydride affording toluoyl-

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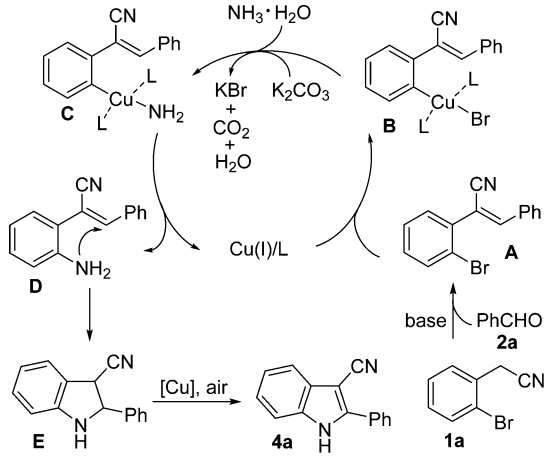
Scheme 1. Proposed Reaction Mechanism for the Formation of 4a



protected IDNs; (2) treatment of the toluoyl-protected IDNs with a solution of sodium methoxide in methanol to remove the toluoyl protecting groups giving the target IDNs with free hydroxyl units. Bearing in mind the advantages of one-pot cascade reactions, we were interested in developing a one-pot cascade procedure for the preparation of IDNs directly from indoles and Hoffer's chlorosugar. For this purpose, different bases as the reaction promoter and various solvents as the reaction medium were screened by using **4a** and Hoffer's chlorosugar (**5**) as model substrates. After much trial and error, we were pleased to find that by first treating **4a** with Hoffer's chlorosugar (**5**) in the presence of 5 equiv of sodium hydride in anhydrous acetonitrile at room temperature for 3 h followed by adding 5 equiv of water and stirring the resulting mixture at room temperature for 10 h, the required C−N bond formation and toluoyl protecting group removal could be efficiently accomplished in one pot to give the desired IDN **6a** with free hydroxyl groups in a total yield of 70% (Scheme 3).

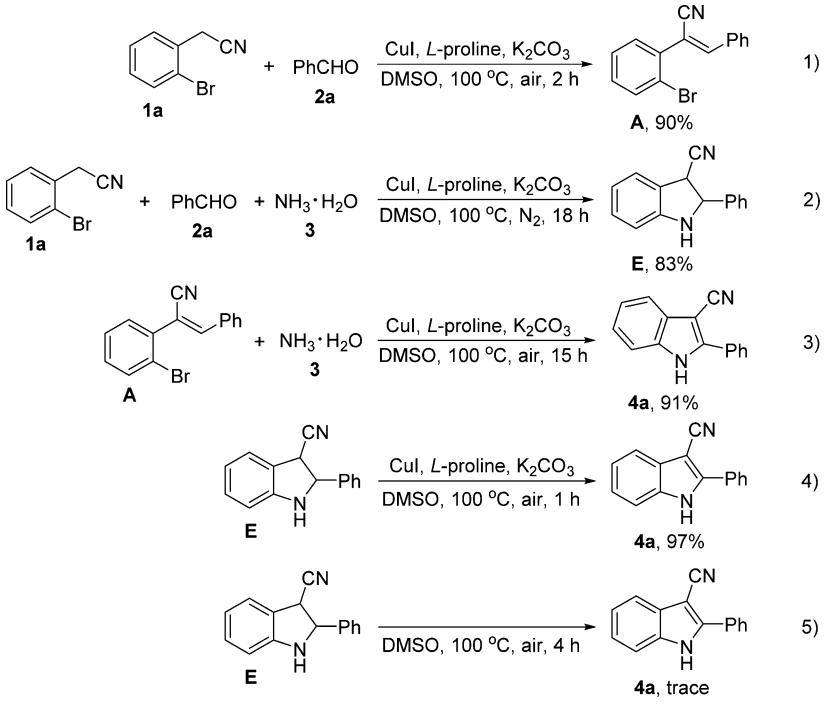
In addition, our following studies showed that this novel nucleoside formation protocol was well suitable for indole substrates with either electron-donating or electron-withdrawing groups attached on the indole scaffold or the 2-phenyl unit to give a series of diversely substituted IDNs (**6a−g**) in reasonably good yields (Table 4).

In summary, we have developed an efficient and sustainable synthetic approach toward 3-cyano-1*H*-indoles via copper-catalyzed one-pot cascade reaction of the commercially available 2-(2-bromophenyl)acetonitriles, aldehydes, and aqueous ammonia. Substrate generality studies showed that this novel process provided a facile access toward diversely substituted −NH-free 3-cyanoindoles with good efficiency. Control experiments indicated that air actually acted as an oxidant for this cascade procedure. As a further aspect, the indole products thus obtained were found to be ready substrates for the preparation of indole 2′-deoxyribonucleosides via an unprecedented glycosylation procedure, in which the required C−N bond formation and the toluoyl protecting group removal were efficiently accomplished in one pot. Compared with literature procedures, the synthetic protocols developed herein showed advantages such as commercially available and nontoxic starting materials, broad substrate scope with a wide range of functional group tolerance, and obviation of tedious step by step operations. With these notable features, they are expected to find applications in synthetic and medicinal chemistry.

EXPERIMENTAL SECTION

1. General Methods. Reagents and solvents were purchased from commercial suppliers and used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded at 400 or 600 MHz and 100 or 150 MHz, respectively. Chemical shifts were referenced to tetramethylsilane in $CDCl_3$ or DMSO-d_6. Multiplicity was indicated

Scheme 2. Control Experiments in Supporting the Proposed Reaction Mechanism



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Scheme 3. One-Pot Cascade Reaction Leading to IDN 6a

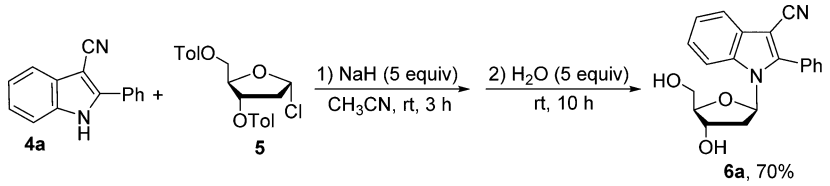
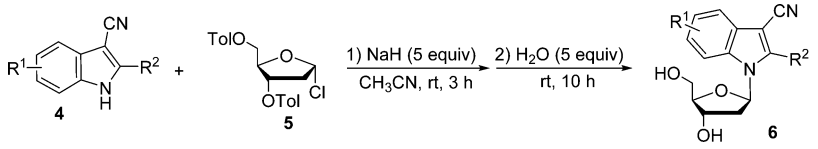
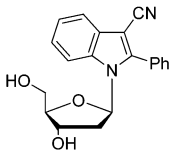
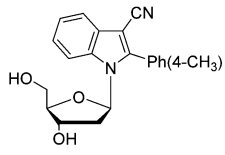


Table 4. One-Pot Synthesis of Indole 2′-Deoxyribonucleosides[a,b]

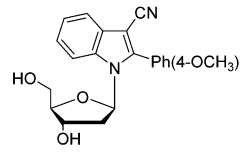




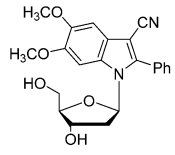
6a, 70%



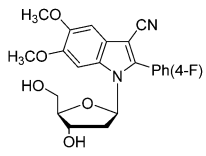
6b, 68%



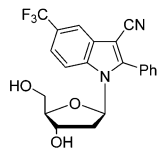
6c, 71%



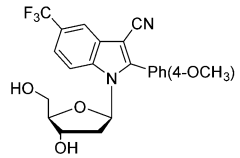
6d, 67%



6e, 69%



6f, 68%



6g, 67%

[a]Reaction conditions: **4** (0.3 mmol), **5** (0.33 mmol), NaH (1.5 mmol), CH_3CN (3 mL), rt, 3 h; then, H_2O (27 μL), rt, 10 h. [b]Isolated yield.

as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets); td (triplet of doublets); br s (broad singlet), etc. Coupling constants are given in hertz. High-resolution mass spectra (HRMS) were obtained via ESI mode by using a MicrOTOF mass spectrometer. The conversion of starting materials was monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm).

2. Typical Procedure for the Preparation of 2-Phenyl-1*H*-indole-3-carbonitrile (4a). To a tube containing a solution of 2-(2-bromophenyl)acetonitrile (**1a**, 98 mg, 0.5 mmol) in DMSO (2 mL) were added CuI (9.5 mg, 0.05 mmol), L-proline (11.5 mg, 0.1 mmol), K_2CO_3 (69 mg, 0.5 mmol), benzaldehyde (**2a**, 80 mg, 0.75 mmol), and aqueous ammonia (**3**, 26%, 0.5 mL). The tube was then sealed, and the mixture was stirred at 100 °C under an air atmosphere for 20 h. After being cooled to room temperature, the mixture was quenched with water and extracted with ethyl acetate (10 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether−ethyl acetate (5:1) as the eluent to give **4a** (96 mg, 88%). Other 3-cyanoindole derivatives (**4b−z**) were obtained in a similar manner.

*2-Phenyl-1H-indole-3-carbonitrile (**4a**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (96 mg, 88%). Mp: 230−231 °C (lit.[11d] mp 233−234 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.24−7.34 (m, 2H), 7.52−7.58 (m, 2H), 7.60−7.66 (m, 3H), 7.99 (d, J = 7.6 Hz, 2H), 12.62 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 81.3, 112.6, 117.0, 118.4, 122.0, 123.9, 127.0, 128.3, 129.30, 129.33, 129.9, 135.5, 144.7. MS: m/z 219 $[M + H]^+$.

*2-(4-Fluorophenyl)-1H-indole-3-carbonitrile (**4b**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (99 mg, 84%). Mp: 240−241 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.26 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 8.8 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 8.02 (dd, J_1 = 8.4 Hz, J_2 = 5.2 Hz, 2H), 12.62 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 81.4, 112.6, 116.4 (d, $^2J_{C-F}$ = 22.5 Hz), 116.9, 118.3, 122.1, 123.9, 125.9 (d, $^4J_{C-F}$ = 2.8 Hz), 128.2, 129.3 (d, $^3J_{C-F}$ = 8.7 Hz), 135.5, 143.8, 162.8 (d, $^1J_{C-F}$ = 246.4 Hz). HRMS calcd for $C_{15}H_{10}FN_2$: 237.0823 $[M + H]^+$, found 237.0828.

*2-(4-Chlorophenyl)-1H-indole-3-carbonitrile (**4c**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (105 mg, 83%). Mp: 291−292 °C (lit.[11d] 287−289 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.26 (t, J = 7.2 Hz, 1H), 7.30−7.34 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 12.67 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 82.2, 113.2, 117.2, 118.9, 122.6, 124.6, 128.66, 128.69, 129.1, 129.9, 135.1, 136.0, 143.8. MS: m/z 253 $[M + H]^+$.

*2-(4-Bromophenyl)-1H-indole-3-carbonitrile (**4d**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (75 mg, 51%). Mp: 299−301 °C (lit.[11d] mp 301−302 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 7.29 (d, J = 7.2 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 12.68 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 82.3, 113.2, 117.3, 118.9, 122.7, 123.8, 124.6, 128.7, 129.0, 129.3, 132.8, 136.1, 143.9. MS: m/z 297 $[M + H]^+$.

*2-(4-(Trifluoromethyl)phenyl)-1H-indole-3-carbonitrile (**4e**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (116 mg, 81%). Mp: 267−268 °C (lit.[11d] mp 260−262 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.30 (t, J = 7.2 Hz, 1H), 7.36−7.39 (m, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 8.20 (d, J = 8.0 Hz, 2H), 12.82 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 83.2, 113.4, 117.0, 119.1, 122.8, 124.4 (q, $^1J_{C-F}$ = 271.05 Hz), 125.0, 126.8 (q, $^3J_{C-F}$ = 3.45 Hz), 128.2, 128.7, 130.2 (q, $^2J_{C-F}$ = 31.35 Hz), 133.7, 136.3, 143.1. MS: m/z 287 $[M + H]^+$.

*2-(4-Cyanophenyl)-1H-indole-3-carbonitrile (**4f**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (73 mg, 60%). Mp: >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.30 (t, J = 8.0 Hz, 1H), 7.36−

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J. Org. Chem. 2016, 81, 9530−9538

7.40 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H), 12.83 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 83.0, 112.0, 112.9, 116.5, 118.4, 118.7, 122.4, 124.7, 127.5, 128.2, 133.2, 133.5, 135.8, 142.2. HRMS calcd for $C_{16}H_{10}N_3$: 244.0869 $[M + H]^+$, found 244.0868.

*2-(p-Tolyl)-1H-indole-3-carbonitrile (**4g**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (94 mg, 81%). Mp: 289−290 °C (lit.[11d] mp 287−288 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.39 (s, 3H), 7.22−7.28 (m, 1H), 7.31 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 12.54 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.9, 80.9, 112.5, 117.1, 118.2, 121.9, 123.7, 126.6, 126.8, 128.3, 129.8, 135.4, 139.8, 144.9. MS: m/z 233 $[M + H]^+$.

*2-(4-Methoxyphenyl)-1H-indole-3-carbonitrile (**4h**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (110 mg, 89%). Mp: 283−284 °C (lit.[11d] mp 280−282 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.85 (s, 3H), 7.19 (d, J = 8.8 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.26−7.30 (m, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 9.2 Hz, 2H), 12.47 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.4, 80.2, 112.4, 114.8, 117.3, 118.1, 121.7, 121.8, 123.5, 128.3, 128.4, 135.4, 144.9, 160.5. MS: m/z 249 $[M + H]^+$.

*2-(3-Chlorophenyl)-1H-indole-3-carbonitrile (**4i**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (109 mg, 86%). Mp: 267−268 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.25- 7.31 (m, 1H), 7.32−7.35 (m, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.63−7.67 (m, 2H), 7.96 (d, J = 7.6 Hz, 1H), 8.02 (s, 1H), 12.71 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 82.1, 112.8, 116.7, 118.5, 122.2, 124.3, 125.5, 126.5, 128.1, 129.6, 131.2, 131.3, 134.0, 135.5, 142.7. HRMS calcd for $C_{15}H_{10}ClN_2$: 253.0527 $[M + H]^+$, found 253.0526.

*2-(m-Tolyl)-1H-indole-3-carbonitrile (**4j**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (92 mg, 79%). Mp: 245−246 °C (lit.[11d] mp 248−250 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.42 (s, 3H), 7.25 (t, J = 7.2 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.33−7.36 (m, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.78−7.80 (m, 2H), 12.58 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0, 81.2, 112.6, 117.0, 118.3, 122.0, 123.8, 124.1, 127.4, 128.3, 129.2, 129.3, 130.6, 135.5, 138.6, 144.8. MS: m/z 233 $[M + H]^+$.

*2-(o-Tolyl)-1H-indole-3-carbonitrile (**4k**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (94 mg, 81%). Mp: 182−183 °C (lit.[11d] mp 181−183 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.37 (s, 3H), 7.28 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.45−7.50 (m, 2H), 7.52 (d, J = 7.2 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.2, 86.8, 111.7, 116.3, 119.5, 122.4, 124.2, 126.3, 128.0, 129.2, 130.2, 131.1, 134.8, 137.0, 145.9. MS: m/z 233 $[M + H]^+$.

*2-(Naphthalen-1-yl)-1H-indole-3-carbonitrile (**4l**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (117 mg, 87%). Mp: 266−268 °C (lit.[11d] mp 266−268 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.29−7.38 (m, 2H), 7.58−7.64 (m, 3H), 7.69−7.73 (m, 2H), 7.79−7.81 (m, 1H), 7.86- 7.89 (m, 1H), 8.08−8.10 (m, 1H), 8.16 (d, J = 8.4 Hz, 1H), 12.71 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 85.6, 113.2, 116.8, 118.9, 122.5, 124.2, 125.5, 125.9, 127.1, 127.8, 127.9, 128.1, 129.1, 129.4, 130.8, 131.2, 133.8, 136.0, 145.4. MS: m/z 269 $[M + H]^+$.

*2-(Thiophene-2-yl)-1H-indole-3-carbonitrile (**4m**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (74 mg, 66%). Mp: 207−209 °C (lit.[11d] 206−208 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.25 (t, J = 7.2 Hz, 1H), 7.27−7.34 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.85−7.86 (m, 2H), 12.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 80.7, 112.4, 116.5, 118.2, 122.1, 124.1, 127.7, 127.9, 128.3, 129.0, 131.1, 135.4, 139.2. MS: m/z 225 $[M + H]^+$.

*2-(Pyridin-4-yl)-1H-indole-3-carbonitrile (**4n**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (62 mg, 57%). Mp: 274−275 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.32 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.97 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 8.84 (d, J = 6.4 Hz, 2H), 12.96 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 83.3, 113.0, 116.3, 118.7, 120.5, 122.4, 124.8, 128.1, 135.8, 136.2, 141.0, 150.7. HRMS calcd for $C_{14}H_{10}N_3$: 220.0869 $[M + H]^+$, found 220.0875.

*2-Cyclohexyl-1H-indole-3-carbonitrile (**4o**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (81 mg, 72%). Mp: 166−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25−1.35 (m, 1H), 1.39−1.50 (m, 2H), 1.56−1.66 (m, 2H), 1.78−1.82 (m, 1H), 1.87−1.92 (m, 2H), 2.06−2.10 (m, 2H), 3.01−3.09 (m, 1H), 7.22−7.26 (m, 2H), 7.27−7.40 (m, 1H), 7.66−7.68 (m, 1H), 8.64 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7, 26.2, 32.4, 37.6, 83.2, 111.4, 116.6, 119.0, 122.0, 123.4, 127.8, 134.2, 153.6. HRMS calcd for $C_{15}H_{16}N_2Na$: 247.1206 $[M + Na]^+$, found 247.1176.

*2-Propyl-1H-indole-3-carbonitrile (**4p**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (60 mg, 65%). Mp: 116−117 °C (lit.[11d] mp 115−117 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 0.94 (t, J = 7.2 Hz, 3H), 1.74−1.80 (m, 2H), 2.87 (t, J = 7.2 Hz, 2H), 7.17−7.23 (m, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 12.07 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 13.7, 22.5, 29.5, 84.8, 111.5, 116.7, 118.9, 122.0, 123.4, 127.7, 134.7, 149.3. MS: m/z 185 $[M + H]^+$.

*2-Isobutyl-1H-indole-3-carbonitrile (**4q**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (74 mg, 75%). Mp: 116−117 °C (lit.[11d] mp 116−117 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.00 (s, 3H), 1.02 (s, 3H), 2.09−2.20 (m, 1H), 2.82 (d, J = 7.2 Hz, 2H), 7.22−7.28 (m, 2H), 7.39−7.42 (m, 1H), 7.65−7.68 (m, 1H), 8.83 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.4, 29.3, 36.6, 85.5, 111.5, 116.7, 119.0, 122.0, 123.4, 127.6, 134.6, 148.5. MS: m/z 199 $[M + H]^+$.

*2-Phenethyl-1H-indole-3-carbonitrile (**4r**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (103 mg, 84%). Mp: 128−129 °C (lit.[11d] mp 125−126 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 3.09 (t, J = 7.8 Hz, 2H), 3.21 (t, J = 7.8 Hz, 2H), 7.17−7.23 (m, 5H), 7.28 (t, J = 7.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 12.17 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 29.2, 34.7, 83.2, 112.7, 116.8, 118.3, 121.9, 123.3, 126.7, 127.6, 128.6, 128.9, 135.3, 140.6, 149.4. MS: m/z 247 $[M + H]^+$.

*2-Phenyl-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**4s**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (110 mg, 77%). Mp: > 310 °C (lit.[11d] 321−323 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.58−7.69 (m, 4H), 7.76 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 8.01 (d, J = 7.2 Hz, 2H), 13.03 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 82.9, 114.2, 116.3 (q, $^3J_{C-F}$ = 4.5 Hz), 116.5, 120.8 (q, $^3J_{C-F}$ = 3.75 Hz), 123.3 (q, $^2J_{C-F}$ = 31.65 Hz), 125.3 (q, $^1J_{C-F}$ = 270.3 Hz), 127.7, 128.1, 129.2, 129.9, 131.0, 137.7, 147.5. MS: m/z 287 $[M + H]^+$.

*2-(4-Fluorophenyl)-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**4t**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (109 mg, 72%). Mp: 278−279 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.51 (t, J = 8.8 Hz, 2H), 7.60 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 8.02−8.06 (m, 2H), 13.00 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 82.4, 113.5, 115.7 (q, $^3J_{C-F}$ = 4.3 Hz), 115.9, 116.4 (d, $^2J_{C-F}$ = 21.4 Hz), 120.3 (q, $^3J_{C-F}$ = 2.6 Hz), 122.8 (q, $^2J_{C-F}$ = 31.7 Hz), 124.8 (q, $^1J_{C-F}$ = 269.7 Hz), 125.2 (d, $^4J_{C-F}$ = 4.0 Hz), 127.5, 129.5 (d, $^3J_{C-F}$ = 8.7 Hz), 137.1, 145.9, 163.1 (d, $^1J_{C-F}$ = 247.7 Hz). HRMS calcd for $C_{16}H_9F_4N_2$: 305.0697 $[M + H]^+$, found 305.0689.

*2-(4-Methoxyphenyl)-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**4u**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (130 mg, 82%). Mp: 231−233 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.88 (s, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.91 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 12.89 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.4, 81.2, 113.3, 114.8, 115.4 (q, $^3J_{C-F}$ = 4.6 Hz), 116.4, 120.0 (q, $^3J_{C-F}$ = 3.1 Hz), 121.0, 122.6 (q, $^2J_{C-F}$ = 31.4 Hz), 124.9 (q, $^1J_{C-F}$ = 269.7 Hz), 127.8, 128.7, 137.1, 147.1, 160.9. HRMS calcd for $C_{17}H_{12}F_3N_2O$: 317.0896 $[M + H]^+$, found 317.0888.

*2-Propyl-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**4v**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (79 mg, 63%). Mp: 168−169 °C (lit.[11d] mp 171−173 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 0.96 (t, J = 7.2 Hz, 3H), 1.77−1.83 (m, 2H), 2.92 (t, J = 7.2 Hz, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 12.54 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6, 22.4, 29.5, 85.7, 112.0, 115.7, 116.6 (q, $^3J_{C-F}$ = 4.7 Hz), 120.3 (q, $^3J_{C-F}$ = 4.2

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J. Org. Chem. 2016, 81, 9530−9538

Hz), 124.6 (q, $^2J_{C-F}$ = 32.2 Hz), 124.7 (q, $^1J_{C-F}$ = 271 Hz), 127.1, 136.2. 151.2. MS: *m/z* 253 $[M + H]^+$.

*5,6-Dimethoxy-2-phenyl-1H-indole-3-carbonitrile (**4w**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (124 mg, 89%). Mp: 266−267 °C (lit.[9a] mp 263−264 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.84 (s, 3H), 3.85 (s, 3H), 7.02 (s, 1H), 7.08 (s, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 7.2 Hz, 2H), 12.31 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.66, 55.72, 81.2, 95.4, 99.8, 117.4, 121.2, 126.3, 129.2, 129.7, 129.8, 142.5, 146.6, 148.1. MS: *m/z* 279 $[M + H]^+$.

*2-(4-Fluorophenyl)-5,6-dimethoxy-1H-indole-3-carbonitrile (**4x**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (119 mg, 80%). Mp: 237−238 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.84 (s, 3H), 3.85 (s, 3H), 7.00 (s, 1H), 7.08 (s, 1H), 7.45−7.49 (m, 2H), 7.94−7.98 (m, 2H), 12.33 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.67, 55.71, 81.2, 95.4, 99.8, 116.3 (d, $^2J_{C-F}$ = 21.8 Hz), 117.3, 121.1, 126.4 (d, $^4J_{C-F}$ = 3.1 Hz), 128.6 (d, $^3J_{C-F}$ = 9.2 Hz), 129.8, 141.5, 146.7, 148.1, 162.4 (d, $^1J_{C-F}$ = 246.0 Hz). HRMS calcd for $C_{17}H_{14}FN_2O_2$: 297.1034 $[M + H]^+$, found 297.1031.

*5,6-Dimethoxy-2-(p-tolyl)-1H-indole-3-carbonitrile (**4y**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (120 mg, 82%). Mp: 225−226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.39 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 7.00 (s, 1H), 7.07 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 12.24 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.9, 55.67, 55.72, 80.7, 95.4, 99.8, 117.5, 121.2, 126.2, 127.0, 129.7, 129.8, 139.0, 142.7, 146.6, 147.9. HRMS calcd for $C_{18}H_{17}N_2O_2$: 293.1285 $[M + H]^+$, found 293.1283.

*5,6-Dimethoxy-2-phenethyl-1H-indole-3-carbonitrile (**4z**).* Eluent: petroleum ether−ethyl acetate (5:1). White solid (121 mg, 79%). Mp: 188−189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.05 (t, *J* = 7.2 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 3.80 (s, 6H), 6.97 (s, 1H), 6.98 (s, 1H), 7.18−7.22 (m, 3H), 7.28 (t, *J* = 7.2 Hz, 2H), 11.85 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 28.7, 34.4, 55.7, 82.4, 95.7, 100.0, 116.7, 119.8, 126.2, 128.1, 128.4, 128.8, 140.0, 146.1, 146.6, 147.1. HRMS calcd for $C_{19}H_{19}N_2O_2$: 307.1441 $[M + H]^+$, found 307.1438.

3. Typical Procedure for the Preparation of 1-((2*R*,4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-phenyl-1*H*-indole-3-carbonitrile (6a). To a flask containing **4a** (65 mg, 0.3 mmol) were added acetonitrile (3 mL) and sodium hydride (60% w/w dispersion in mineral oil, 60 mg, 1.5 mmol). After the mixture was stirred at room temperature for 5 min, Hoffer's chlorosugar (130 mg, 0.33 mmol) was added, and the stirring was continued at room temperature for 3 h. Then, water (27 μL, 1.5 mmol) was added, and the resulting mixture was stirred at room temperature for 10 h. Upon completion, the mixture was neutralized with diluted hydrochloric acid, and extracted with ethyl acetate (10 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using dichloromethane-methanol (10:1) as the eluent to give **6a** (70 mg, 70%). Other indole 2′-deoxyribonucleosides (**6b**−**g**) were obtained in a similar manner.

*1-((2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-phenyl-1H-indole-3-carbonitrile (**6a**).* Eluent: dichloromethane−methanol (10:1). White solid (70 mg, 70%). Mp: 210−212 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.09−2.14 (m, 1H), 2.71−2.78 (m, 1H), 3.71−7.78 (m, 3H), 4.40−4.42 (m, 1H), 5.23 (br s, 2H), 6.07−6.11 (m, 1H), 7.34−7.38 (m, 2H), 7.63−7.72 (m, 6H), 8.12−8.14 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 61.0, 70.0, 85.7, 86.1, 87.1, 114.8, 115.8, 118.7, 122.8, 123.9, 127.3, 128.4, 129.1, 129.7, 130.3, 133.8, 147.8. HRMS calcd for $C_{20}H_{18}N_2O_3Na$: 357.1210 $[M + Na]^+$, found 357.1218. $[\alpha]_D^{20}$ = +4.7 (*c* = 0.30, MeOH).

*1-((2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-(p-tolyl)-1H-indole-3-carbonitrile (**6b**).* Eluent: dichloromethane−methanol (10:1). White solid (71 mg, 68%). Mp: 211−212 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.05−2.10 (m, 1H), 2.45 (s, 3H), 2.68−2.76 (m, 1H), 3.68−3.77 (m, 3H), 4.39 (d, *J* = 3.6 Hz, 1H), 5.12 (t, *J* = 5.2 Hz, 1H), 5.29 (d, *J* = 4.8 Hz, 1H), 6.05−6.08 (m, 1H), 7.32−7.36 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.68 (dd, J_1 = 6.4 Hz, J_2 = 3.2 Hz, 1H), 8.10 (dd, J_1 = 6.4 Hz, J_2 = 3.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0, 38.6, 61.0, 70.0, 85.7, 85.8, 87.1, 114.8, 115.8, 118.6, 122.7, 123.8, 125.4, 127.3, 129.6, 129.7, 133.8, 140.2, 148.0. HRMS calcd for $C_{21}H_{20}N_2O_3Na$: 371.1366 $[M + Na]^+$, found 371.1368. $[\alpha]_D^{20}$ = +7.8 (*c* = 0.36, MeOH).

*1-((2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-(4-methoxyphenyl)-1H-indole-3-carbonitrile (**6c**).* Eluent: dichloromethane−methanol (10:1). White solid (78 mg, 71%). Mp: 147−148 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.11−2.15 (m, 1H), 2.26 (br s, 2H), 2.88−2.93 (m, 1H), 3.83−3.97 (m, 6H), 4.67 (t, *J* = 3.6 Hz, 1H), 6.18 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 7.29−7.30 (m, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.65−7.66 (m, 1H), 7.72−7.73 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 38.7, 55.5, 61.9, 70.8, 85.2, 85.4, 87.3, 113.1, 114.7, 116.3, 119.9, 120.7, 122.8, 124.0, 128.4, 131.2, 133.9, 148.4, 161.1. HRMS calcd for $C_{21}H_{20}N_2O_4Na$: 387.1315 $[M + Na]^+$, found 387.1316. $[\alpha]_D^{20}$ = +2.5 (*c* = 0.40, MeOH).

*1-((2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5,6-dimethoxy-2-phenyl-1H-indole-3-carbonitrile (**6d**).* Eluent: dichloromethane−methanol (10:1). White solid (79 mg, 67%). Mp: 175−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.01−2.13 (m, 1H), 2.35 (br s, 1H), 2.60 (br s, 1H), 2.78−2.85 (m, 1H), 3.81−4.01 (m, 9H), 4.71 (t, *J* = 4.0 Hz, 1H), 6.14 (t, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 7.31 (s, 1H), 7.46−7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.0, 56.2, 56.4, 61.4, 70.5, 85.3, 85.5, 87.0, 96.8, 100.7, 116.6, 121.5, 128.3, 128.8, 129.1, 129.7, 129.9, 146.2, 147.2, 148.0. HRMS calcd for $C_{22}H_{22}N_2O_5Na$: 417.1421 $[M + Na]^+$, found 417.1409. $[\alpha]_D^{20}$ = +15.7 (*c* = 0.49, MeOH).

*2-(4-Fluorophenyl)-1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-5,6-dimethoxy-1H-indole-3-carbonitrile (**6e**).* Eluent: dichloromethane−methanol (10:1). White solid (85 mg, 69%). Mp: 202−203 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.04 (br s, 2H), 2.11−2.15 (m, 1H), 2.86−2.91 (m, 1H), 3.88−4.06 (m, 9H), 4.76 (t, *J* = 3.6 Hz, 1H), 6.11 (t, *J* = 7.2 Hz, 1H), 7.14 (s, 1H), 7.23−7.26 (m, 2H), 7.30 (s, 1H), 7.52−7.54 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.0, 56.3, 56.4, 61.5, 70.7, 85.3, 85.4, 87.6, 96.7, 100.8, 116.4 (d, $^2J_{C-F}$ = 22.95 Hz), 121.4, 124.9 (d, $^4J_{C-F}$ = 2.85 Hz), 128.3, 131.8 (d, $^3J_{C-F}$ = 8.1 Hz), 145.0, 147.3, 148.1, 163.6 (d, $^1J_{C-F}$ = 250.5 Hz). HRMS calcd for $C_{22}H_{21}FN_2O_5Na$: 435.1327 $[M + Na]^+$, found 435.1326. $[\alpha]_D^{20}$ = +5.8 (*c* = 0.38, MeOH).

*1-((2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-phenyl-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**6f**).* Eluent: dichloromethane−methanol (10:1). White solid (82 mg, 68%). Mp: 207−208 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.16−2.20 (m, 1H), 2.53 (br s, 2H), 2.81−2.86 (m, 1H), 3.86−3.98 (m, 3H), 4.70 (t, *J* = 3.6 Hz, 1H), 6.19 (t, *J* = 7.2 Hz, 1H), 7.55 (s, 6H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.2, 61.7, 70.7, 85.6, 88.4, 114.1, 115.2, 117.3 (q, $^3J_{C-F}$ = 3.9 Hz), 120.9 (q, $^3J_{C-F}$ = 3.0 Hz), 124.5 (q, $^1J_{C-F}$ = 271.35 Hz), 125.4 (q, $^2J_{C-F}$ = 32.1 Hz), 127.8, 127.9, 129.3, 129.7, 130.7, 135.6, 149.8. HRMS calcd for $C_{21}H_{18}F_3N_2O_3$: 403.1264 $[M + H]^+$, found 403.1255. $[\alpha]_D^{20}$ = +49.7 (*c* = 0.35, MeOH).

*1-((2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-(4-methoxyphenyl)-5-(trifluoromethyl)-1H-indole-3-carbonitrile (**6g**).* Eluent: dichloromethane−methanol (10:1). White solid (87 mg, 67%). Mp: 195−196 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.17−2.20 (m, 1H), 2.47 (br s, 2H), 2.84−2.89 (m, 1H), 3.88 (s, 3H), 3.92−4.00 (m, 3H), 4.72 (t, *J* = 10.2 Hz, 1H), 6.21 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 39.2, 55.5, 61.8, 70.8, 85.6, 88.0, 113.9, 114.78, 114.83, 115.4, 117.3 (q, $^3J_{C-F}$ = 4.8 Hz), 120.0, 120.7 (q, $^4J_{C-F}$ = 2.85 Hz), 124.5 (q, $^1J_{C-F}$ = 270.0 Hz), 125.3 (q, $^2J_{C-F}$ = 33.6 Hz), 127.9, 131.19, 131.23, 150.0, 161.4. HRMS calcd for $C_{22}H_{20}F_3N_2O_4$: 433.1370 $[M + H]^+$, found 433.1366. $[\alpha]_D^{20}$ = +32.0 (*c* = 0.35, MeOH).

4. Procedure for the Preparation of 2-(2-Bromophenyl)-3-phenylacrylonitrile (A). To a tube containing a solution of 2-(2-bromophenyl)acetonitrile (**1a**, 98 mg, 0.5 mmol) in DMSO (2 mL) were added CuI (9.5 mg, 0.05 mmol), K_2CO_3 (69 mg, 0.5 mmol), L-proline (11.5 mg, 0.1 mmol), and benzaldehyde (**2a**, 80 mg, 0.75 mmol). Then the tube was sealed, and the mixture was stirred at 100 °C under an air atmosphere for 2 h. Upon completion, it was

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J. Org. Chem. 2016, 81, 9530−9538

quenched with water and extracted with ethyl acetate (8 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether−ethyl acetate (100:1) as the eluent to give 2-(2-bromophenyl)-3-phenylacrylonitrile (**A**, 128 mg, 90%).

*2-(2-Bromophenyl)-3-phenylacrylonitrile (**A**).* Eluent: petroleum ether−ethyl acetate (100:1). White solid (128 mg, 90%). Mp: 80−82 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.09 (s, 1H), 7.13 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.24−7.26 (m, 1H), 7.27−7.30 (m, 1H), 7.34−7.36 (m, 3H), 7.53 (d, J = 6.6 Hz, 1H), 7.77−7.79 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 110.7, 117.3, 122.8, 128.1, 129.1, 129.4, 130.6, 131.0, 131.1, 133.2, 133.7, 136.4, 148.3. HRMS calcd for $C_{15}H_{11}BrN$: 284.0069 $[M + H]^+$, found 284.0077.

5. Procedure for the Preparation of 2-Phenylindoline-3-carbonitrile (E). To a tube containing a solution of 2-(2-bromophenyl)acetonitrile (**1a**, 98 mg, 0.5 mmol) in DMSO (2 mL) were added CuI (9.5 mg, 0.05 mmol), K_2CO_3 (69 mg, 0.5 mmol), L-proline (11.5 mg, 0.1 mmol), benzaldehyde (**2a**, 80 mg, 0.75 mmol), and aqueous ammonia (**3**, 26%, 0.5 mL). After being flushed with nitrogen, the tube was sealed, and the mixture was stirred at 100 °C under a nitrogen atmosphere for 18 h. Upon completion, it was quenched with water and extracted with ethyl acetate (8 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether−ethyl acetate (20:1) as the eluent to give 2-phenylindoline-3-carbonitrile (**E**, 91 mg, 83%).

*2-Phenylindoline-3-carbonitrile (**E**).* Eluent: dichloromethane−methanol (20:1). Colorless liquid (99 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.03 (d, J = 10.8 Hz, 1H), 4.24 (d, J = 2.8 Hz, 1H), 5.10 (dd, J_1 = 10.4 Hz, J_2 = 3.6 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.84 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.23−7.28 (m, 1H), 7.36−7.42 (m, 3H), 7.53 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.3, 68.8, 110.1, 119.1, 120.0, 122.5, 124.5, 126.6, 128.9, 129.1, 130.0, 139.9, 149.8. HRMS calcd for $C_{15}H_{13}N_2$: 221.1073 $[M + H]^+$, found 221.1062.

6. Preparation of 4a from Intermediate A. To a tube containing a solution of 2-(2-bromophenyl)-3-phenylacrylonitrile (**A**, 128 mg, 0.45 mmol) in DMSO (2 mL) were added CuI (8.6 mg, 0.045 mmol), K_2CO_3 (62 mg, 0.45 mmol), L-proline (10.4 mg, 0.09 mmol), and aqueous ammonia (**3**, 26%, 0.5 mL). Then the tube was sealed, and the mixture was stirred at 100 °C under an air atmosphere for 15 h. After being cooled to room temperature, it was quenched with water, and extracted with ethyl acetate (8 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether−ethyl acetate (5:1) as the eluent to give 2-phenyl-1*H*-indole-3-carbonitrile (**4a**, 89 mg, 91%).

7. Preparation of 4a from Intermediate E. To a tube containing a solution of 2-phenylindoline-3-carbonitrile (**E**, 88 mg, 0.4 mmol) in DMSO (2 mL) were added CuI (7.6 mg, 0.04 mmol), K_2CO_3 (55 mg, 0.4 mmol), and L-proline (9.2 mg, 0.08 mmol). Then the mixture was stirred at 100 °C under an air atmosphere for 1 h. After being cooled to room temperature, it was quenched with water and extracted with ethyl acetate (8 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether−ethyl acetate (5:1) as the eluent to give 2-phenyl-1*H*-indole-3-carbonitrile (**4a**, 85 mg, 97%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01612.

^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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