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One-Pot Synthesis of 2-Amino-indole-3-carboxamide and Analogous

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Abstract

An efficient one-pot, two-step solution-phase synthetic method was developed to synthesize twenty-three 2-amino-indole-3-carboxamides (**3**) from 2-halonitrobenzene (**1**) or heterocyclic analogous and cyanoacetamides (**2**). In this sequence, first, intermediate 2-cyano-2-(2-nitrophenyl)-acetamide (**4**) was generated under basic condition via S_NAr reaction; after direct addition of hydrochloric acid solution, FeCl₃, and Zn powder, indole **3** was generated via reduction/cyclization process.

Keywords

reductive cyclisation; cyanoacetamide; 2-aminoindole; one-pot; solution phase

INTRODUCTION

The indole fragment is one of the most important heterocycles for drug discovery, with a broad range of biological activities. In addition, many endogenous biologically active substances, such as tryptophan, 5-hydroxytryptophan, melatonin, and brassinin, and many clinical used drugs, such as nonsteroidal anti-inflammatory indomethacin, antiemetic ondansetron, and antimigraine sumatriptan, are indole based. For example, in the recent

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Author Contributions

A.D. conceived and designed the experiments. K.W. performed the experiments. E.H. performed the X-ray diffraction.

Supporting Information. Experimental methods of the products, NMR data of all new compounds, and X-ray data of compound **3–20**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

discovery of new p53/MDM2/MDMX antagonist for cancer treatment, the indole unit is critical for binding MDM2 and MDMX as a mimic of tryptophan residue (Figure 1).¹⁻³

2-Aminoindoles, on the other hand, are key fragments in a multitude of biologically active compounds including IK β -kinase,⁴ phosphodiesterase-V inhibitors,⁵ hypotensives, diuretics, and appetite suppressants,⁶ and many other important biological active compounds. Notably, the 2-aminoindole chemotype is aromatic planar and comprises two adjacent hydrogen bond donors to interact with a protein target (Figure 2). Amidine moieties can widely interact with acid side chains in proteins (Asp, Glu), however also form pi-pi interactions with aromatic side chains. Therefore amidines are very often found in druglike molecules. On the other hand, the strong basic character of this functional group makes permeation through biological membranes very difficult, and oral bioavailability and blood brain barrier penetration is rarely achieved. Therefore prodrug approaches are often used to solve these issues, for example, in the recently approved anticoagulant dabigatran, an amidine carbamate prodrug.⁷⁻⁹ Another successful approach is the incorporation of the basic amidine moiety into aromatic heterocycles.^{10,11} By delocalizing the amidinemoiety in an aromatic scaffold, the charge is partially delocalized and the basicity can be adjusted by the introduction of appropriate substituents and ring. With these significant observations, it is very attractive to develop practical and efficient methods of generating a diversity of 2-aminoindole derivatives.

Herein, we would like to report a novel, straightforward, and one-pot synthesis of highly substituted 2-amino (hetero)-indole-3-carboxamides. 2-Amino-indole-3-carboxamides in the past have been synthesized by several step processes, for example, by [3,3]-sigmatropic rearrangement and intramolecular cyclization from *N*-arylhydroxamic acids and malononitrile,¹⁵ by nucleophilic aromatic substitution reaction¹⁶ with malondinitrile or cyanoacetic acid esters, followed by reduction (eq 1, Scheme 1),¹⁷⁻²⁴ or by a four-component reaction of pyridine or 3-picoline, chloroacetonitrile, malononitrile, and aromatic aldehydes,²⁵ by the Nenitzescu reaction of primary ketene amins and 1,4-benzoquinones,²⁶ by the reaction of 2-haloanilines and substituted acetonitriles,²⁷⁻²⁹ and other methods.³⁰ Our synthetic approach involves a nucleophilic aromatic substitution reaction of a suitable *o*-halo-nitro-(hetero)aromatic with a cyanoacetamide and a subsequent reductive cyclization. To the best of our knowledge, no such transformation has been described in a one-pot manner. Together with our recently described experimentally very simple one-pot access to hundreds of cyanoacetamides,³¹⁻³³ we believe this is a valuable procedure of general interest to medicinal and organic chemists.

Generally, cyanoacetic acid derivatives react with 2-halonitrobenzene in a nucleophilic aromatic substitution; then, the intermediates were isolated and reduced under different conditions, commonly, Zn/HOAc, Fe/HOAc, or Pd/C/H₂, etc., to generate 2-aminoindole esters; finally, these esters would be saponified and coupled with appropriate amines to generate corresponding 2-aminoindole amides, although no such precedents have been reported yet. Herein, a convenient two-step, one-pot method is reported to prepare 2-aminoindole-3-carboxamide (**3**) from 2-fluoronitrobenzene or its heterocycle analogous and cyanoacetamides (eq 2, Scheme 1).

RESULT AND DISCUSSION

In an easily and gram-scale accessible model reaction, *n*-butylcyanoacetamide (**1a**) was reacted to find the optimal conditions. Sodium hydride was selected as a base in this reaction because it is a strong base with weak nucleophilicity. First, sodium hydride in excess was added to a solution of cyanoacetamides (**1a**) in DMF. After 10 min, 2-fluoronitrobenzene (**2a**) was added, and the reaction becomes deep purple. After 1 h, the corresponding

substitution intermediate (**4a**) was monitored with LC-MS. Next, 1 N HCl was added to the reaction to acidify the excess NaH; then, FeCl₃ (3 equiv) and Zn (10 equiv) were added.³⁴ The reduction conditions were optimized and different Fe/Zn ratios or iron powder for example did not give the expected products. After 1 h at 100 °C, the desired 2-aminoindole product was isolated with high yield (Scheme 2).

Next different cyanoacetamide (**1a–u**, Scheme 3) and different 2-halonitrobenzene (**2a–e**, Scheme 4) were treated under this condition. All these reactions work fine to afford desired 2-aminoindole products (**3-1–3-23**) in good yields. It is interesting to note that unprotected alcohol in cyanoacetamide (**1h**) give good reaction as well. Different heterocycles, such as, indole (**1p**), morpholine (**1c, i, s**), piperazine (**1q, r**), pyridine (**1o**), are compatible with the reaction. Alkene (**1d**) or alkyne (**1g**) functionalities can be introduced without problems and might be of value for further transformations. Bis-cyanoacetamide (**1u**) reacts smoothly with two equivalents of 2-fluoronitrobenzene (**1a**) to afford the corresponding compounds (**3-23**) in good yields.

In addition to 2-fluoronitrobenzene derivatives, some heterocyclic starting materials, such as 2-fluoro-3-nitropyridine (**2d**) and 4-chloro-3-nitropyridine (**2e**), offer easy access to pyrrolo-[3,2-*b*]pyridines (**3-18–3-21**) and pyrrolo[2,3-*c*]pyridine (**3-22**) products as well. This result indicates that this two-step, one-pot reaction is a quite general protocol. All products with their structures and isolated yields are listed in the Table 1.

To prove the identity of the products, we characterized all compounds by NMR and HR-MS and also crystallized 2-amino-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxamide derivative (**3-20**) in a quality suitable for X-ray diffraction. The structure of **3-20** in the solid state is shown in Figure 3 and in Supporting Information. There are several noteworthy observations regarding the crystal structure. There are two crystallographically independent molecules (**3-20**) in the unit cell. One (conformation **A**) is forming an intramolecular hydrogen bridge between the amide and the pyridine nitrogen, whereas the morpholinoethyl side chain is stretched. In the second molecule (conformation **B**) the morpholinoethyl side chain is bent back to the amide group to form a bifurcated hydrogen bond; the NH comprises a bifurcated hydrogen bond donor. Such intramolecular hydrogen bonds can be actively used in drug design and have a pronounced effect on key compound parameters such as membrane permeability, water solubility, and lipophilicity.³⁵

Not surprisingly the amidine substructure in **3-20** forms an intermolecular hydrogen bond to the amide carbonyl but also intermolecular and trifurcated hydrogen bonds to carbonyls of adjacent molecules.

CONCLUSION

In summary, we have described a highly efficient one-pot sequence toward 2-amino indole-type molecules involving an aromatic substitution and a subsequent reduction/cyclization process. Significantly, heteroaromatics are substrates for this reaction sequence. Scope and limitation of the sequence are described. Further work is being performed in our laboratory to investigate the extraordinary biological activities of these molecules and will be reported in due course.

EXPERIMENTAL PROCEDURES

General Two-Step, One-Pot Procedure for Preparing 2-Amino-*N*-butyl-1*H*-indole-3-carboxamide (3-1)

Cyanoacetamide (**1a**, 2.0 mmol, 1.0 equiv.) in dry DMF (0.5 M) and NaH (60% dispersion in mineral oil, 2.2 mmol, 2.2 equiv) were added to a 50 mL flask equipped with stir bar. After 10 min, 2-fluoronitrobenzene (**2a**, 2.0 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture became deep purple. Then 1.0 N HCl (4.0 mmol, 2.0 equiv) was added, following FeCl₃ (6.0 mmol, 3 equiv.) and Zn dust (20 mmol, 10 equiv.). The reaction mixture was heated to 100 °C for 1 h. The reaction mixture was cooled down, and 20 mL of water was added to the crude reaction mixture. The crude reaction mixture was filtered, washed with 25 mL of ethyl acetate. The solution was extracted with ethyl acetate (20 mL × 2). The combined organic phase was washed by saturated sodium bicarbonate solution (10 mL) and brine (10 mL). The organic phase was dried with anhydrous sodium sulfate and the solvent was removed. The crude product was purified by short silica gel column chromatography with 5% methanol in ethyl acetate to generate 393 mg (85%) the title compound as a yellow solid. HRMS ESL-TOF for C₁₃H₁₇N₃ONa (M + Na⁺) Found: *m/z* 254.1288. Calcd Mass: 254.1269. ¹H NMR (DMSO-*d*₆, 600MHz): δ 10.54 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.85 (t, *J* = 7.8 Hz, 1H), 6.70 (s, 2H), 6.67 (t, *J* = 6.6 Hz, 1H), 3.27 (m, 2H), 1.51 (m, 2H), 1.32 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm. ¹³CNMR(DMSO-*d*₆, 150 MHz): δ 167.2, 152.8, 132.7, 125.7, 120.2, 118.8, 116.8, 110.1, 86.8, 38.5, 32.5, 20.2, 14.3 ppm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Indole unit is critical for potent p53/MDM2 antagonists. Alignment of three MDM2 structures, the native p53 MDM2 interaction (PDB ID 1YCR), MDM2 in complex with van Leusen (vL) imidazole (top compound, PDB ID 3LBK), and spirooxindole (bottom compound, PDB ID 3LBL). The MDM2 binding site is shown as blue surface, the key indole side chain (Trp23) as turquoise sticks, the van Leusen imidazole as red sticks, and the oxindole as yellow sticks. Notably, there is perfect alignment of the three indole fragments.

Figure 2.

Top: Different representative binding modes of heterocyclic amidines and guanidines in proteins. (left) Etravirine in complex with the HIV reverse transcriptase (PDB ID 3M8Q) forms an extended hydrogen bond network with Lys101 and a crystal water.¹² (middle) 5-Hydroxy-2-aminobenzimidazole (PDB ID 1FV9) in complex with urokinase and forming a charge-charge interaction with Asp191 in addition to a bifurcated hydrogen bond with the backbone carbonyl of Gly220.¹³ (right) A 3-amino-1,2,4-triazole in complex with the active site of *Mycobacterium tuberculosis* methionine aminopeptidase (PDB ID 1DGH);¹⁴ the geminal nitrogens of the triazole unit form a bridging ligand to the active site bimetal center, whereas the exo amino group makes a water hydrogen bridge and the 3-amino group makes a contact to His114. Bottom: Pharmacophore model interactions of 2-aminoindoles with amino acid side chains.

Figure 3. Top left: ORTEP drawing with 50% ellipsoids for **3–20**. Top right: Schematic drawing of the mono- and bifurcated hydrogen bridge. Bottom: Complex intra- and intermolecular hydrogen bond network in the crystal (visualization using Mercury software).

Scheme 1.
Two Synthetic Pathways to 2-Aminoindole Derivatives

Scheme 2.
Two-Step, One-Pot Synthesis of 2-Aminoindole-3-carboxamide

Scheme 3.
Cyanoacetamide Starting Materials

Scheme 4.
2-Halonitrobenzene or Pyridine Starting Materials

Table 1

is of 2-Amino-indole-carboxamides (3-1–3–23)

yield %	77
structure	3-3
structure	3-2
yield %	85

yield %	69
<p>3-6</p>	structure
<p>3-5</p>	yield %	74
<p>3-6</p>	structure
<p>3-5</p>	yield %	72
<p>3-6</p>	structure	

	yield %	64	<div data-bbox="414 147 894 483"> </div> <div data-bbox="414 483 894 861">3-9</div>
	yield %	52	<div data-bbox="414 861 894 1218"> </div> <div data-bbox="414 1218 894 1564">3-8</div>
	yield %	56

yield %	71	<p>3-12</p>	yield %	79	<p>3-11</p>	yield %	85	<p>ACS Comb Sci. Author manuscript; available in PMC 2011 June 27.</p>
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yield %	55	<p>3-15</p>
	yield %	76	<p>3-14</p>
	yield %	64

yield %	45

yield %	75

yield %	76

<p>yield %</p>	<p>56</p>	<p>structure</p> <p>3-21</p>
<p>3-20</p>	<p>yield %</p>	<p>77</p>	<p>structure</p>
<p>3-20</p>	<p>yield %</p>	<p>54</p>	<p>3-20</p>

yield %	48
structure	yield %	42
structure	yield %	42
structure	yield %	42
structure	yield %	42
structure	yield %	42
structure	yield %	42
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