Advanced Synthesis & Catalysis

COMMUNICATIONS

DOI: 10.1002/adsc.201600155

Synthesis of 2-Aryl-Substituted Indole-3-acetic Acid Derivatives *via* Intramolecular Imino-Stetter Reaction of Aldimines with Cyanide

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Received: February 4, 2016; Published online: April 15, 2016

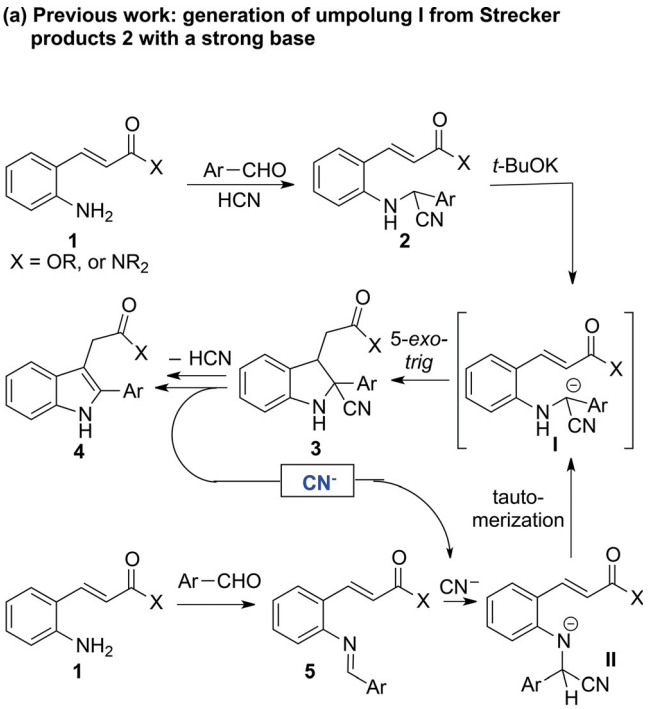
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600155.

Abstract: A general method to generate umpolung of aldimines with cyanide was developed *via* the addition of cyanide to aldimines followed by a proton transfer from the carbon atom to the nitrogen atom in the resulting cyanide adducts. This novel method was successfully applied to the first imino-Stetter reaction of aldimines obtained from 2-aminocinnamic acid derivatives and aromatic aldehydes with cyanide, affording 2-aryl-substituted indole-3-acetic acid derivatives. Furthermore, the usefulness of this method was successfully demonstrated by the synthesis of an FPTase inhibitor, one of the biologically important 2-arylindole-3-acetic acid derivatives.

Keywords: aldimines; 2-arylindole-3-acetic acid derivatives; cyanide; imino-Stetter reaction; umpolung

Since indoles are frequently found in biologically active natural products and pharmaceuticals, the development of new methods for the synthesis of indole scaffolds has been a topic of great importance.[1] Among the indole derivatives, 2-arylindole-3-acetic acid derivatives are key subunits of several biologically active natural products, and thus several protocols to access these important scaffolds have been developed.[2,3] Conventionally, 2-arylindole-3-acetic acid derivatives were prepared *via* either arylation of indole-3-acetic acid derivatives carrying a pre-installed functional group at the 2-position[2] or rhodium-catalyzed C–H functionalization of aniline derivatives with alkynes carrying proper substituents[3].

Alternatively, the Opatz group reported an excellent example of the synthesis of 2-arylindole-3-acetic acid derivatives **4** from Strecker products **2** of 2-aminocinnamic acid derivatives **1** and aromatic aldehydes with a stoichiometric amount of a strong base (Scheme 1a).[4] The treatment of Strecker products **2** with a strong base generated anions **I** that underwent 5-*exo*-*trig* cyclization affording the corresponding indoline products **3**. The subsequent elimination of HCN and aromatization afforded 2-arylindole-3-acetic acid derivatives **4**. Although this method provided a ready access to useful 2-arylindole-3-acetic acid derivatives,[5] it has not been as popular as other conventional methods in the preparation of 2-arylin-



Scheme 1. Synthesis of 2-aryl-substituted indole-3-acetic acid derivatives **4** (a) from Strecker products **2** with a stoichiometric amount of a strong base (previous work) (b) from aldimines **5** with a catalytic amount of cyanide (this work).

dole-3-acetic acid derivatives, presumably due to its drawbacks, particularly in terms of atom-economy.[6] A stoichiometric amount of HCN must be used to prepare the Strecker products, and the same amount of a strong base is required to generate anions **I**, which are umpolung derivatives of aldimines. Moreover, the same amount of HCN is produced as a by-product to regenerate the indole scaffold.

Very recently, we reported a protocol for the synthesis of amides from aldimines *via* cyanide-mediated metal-free aerobic oxidation.[7] The mechanistic studies indicated that amides would be formed from aldimines in the presence of cyanide through the following sequences: (i) the addition of cyanide to aldimines to form cyanide adducts **II**, (ii) a proton transfer from the carbon atom to the nitrogen atom in the resulting cyanide adducts **II** generating umpolung **I**, and (iii) subsequent reaction of **I** with molecular oxygen affording the desired amides.

With this finding in hand, a literature survey was conducted on the generation of umpolung **I** of aldimines with cyanide. Although the generation of umpolung **I** of aldimines with cyanide has been recognized since Strain's seminal report in 1928,[8] and the chemistry of umpolung **I** of aldimines has been demonstrated in dimerization reactions of aldimines *via* the addition of umpolung **I** to the remaining imines,[9,10] the chemistry of **I** with cyanide has been far less investigated compared to that of aldehydes.

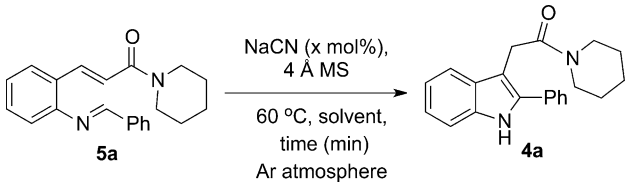
On the basis of our findings[7] in conjunction with the previous reports[8–10] on the facile generation of umpolung of aldimines with cyanide, we hypothesized that 2-arylindole-3-acetic acid derivatives **4** could be prepared from aldimines **5** obtained from 2-aminocinnamic acid derivatives **1** and aromatic aldehydes in the presence of a catalytic amount of cyanide, rather than from the corresponding Strecker products **2** in the presence of a stoichiometric amount of a strong base, although the Opatz group reported that cyclization of aldimines **5** with a catalytic amount of cyanide was unsuccessful.[4] As demonstrated in Scheme 1b, the reaction of aldimines **5** with cyanide would afford cyanide adducts **II**, and the subsequent tautomerization of the resulting cyanide adducts generates anions **I**.[7–10] The resulting anions **I** would follow the same transformation as shown in Scheme 1a, leading to the desired indole derivatives **4**. Because cyanide is released from adducts **3** after the formation of an indole ring, the entire transformation can be expected to be performed with only a catalytic amount of cyanide.

Herein, we report a new protocol for the synthesis of 2-aryl-substituted indole-3-acetic acid derivatives from aldimines obtained from 2-aminocinnamic acid derivatives and aromatic aldehydes with a catalytic amount of cyanide. Various 2-arylindole-3-acetic acid derivatives were obtained in excellent yields in a very short reaction time. The usefulness of this new method was further demonstrated by the syntheses of biologically important 2-arylindole-3-acetic acid derivatives, such as a farnesyl protein transferase (FPTase) inhibitor.[11]

First, the working hypothesis shown in Scheme 1b was tested using aldimine **5a**, obtained from piperidine amide **1a** of 2-aminocinnamic acid and benzaldehyde, as the model compound (Table 1). Cyanide was found to play a crucial role in this transformation; the corresponding indole **4a** was obtained in a high yield in the presence of cyanide (entry 1), whereas no reaction was observed in the absence of cyanide (entry 2). Based on the working hypothesis, this transformation should be possible with a catalytic amount of cyanide; therefore, the effect of the amount of cyanide on this transformation was investigated (entries 1, and 3–7). To our delight, this transformation could be achieved with a catalytic amount of cyanide and the amount of cyanide could be reduced to 5 mol% without any loss of its catalytic efficiency.

Next, the effect of reaction temperature on this transformation was investigated and the reaction tem-

Table 1. Optimization of the reaction conditions.



Entry	NaCN (x mol%)	Solvent	Time [min]	Yield [%][a]
1	100	DMF	10	82
2	–	DMF	240	N.R.[b]
3	50	DMF	10	81
4	20	DMF	10	85
5	10	DMF	10	86
6	5	DMF	10	64
7	<3	DMF	60	trace
8[c]	10	DMF	60	trace
9[d]	10	DMF	60	trace
10[e]	10	DMF	60	78
11[f]	10	DMF	<10	82
12[g]	10	DMF	<10	83
13	10	DMSO	30	81
14	10	MeOH	240	45
15	10	EtOH	240	43
16	10	CH_3CN	240	64
17	10	CH_2Cl_2	240	N.R.[b]
18	10	THF	240	trace

[a] Isolated yield.
[b] No reaction.
[c] At room temperature.
[d] At 40 °C.
[e] At 50 °C.
[f] At 70 °C.
[g] At 80 °C.

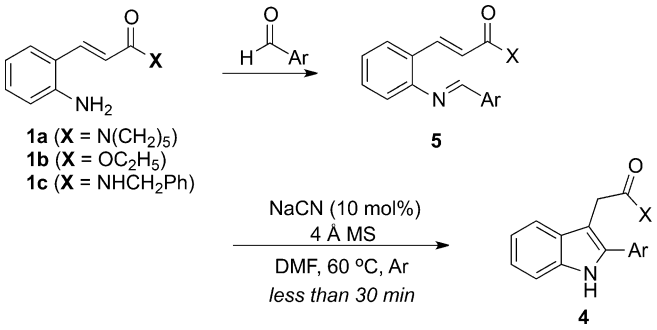
perature was found to significantly affect the efficiency of this transformation (entries 5, and 8–12). The reaction rate increased with reaction temperature; no reaction was observed below 40 °C, but the reaction was completed in less than 10 min when the reaction temperature was above 60 °C. Because the reaction at 60 °C was sufficiently fast, 60 °C was selected for further investigations. The effect of the reaction media on this transformation was investigated (entries 5, and 13–18). The choice of the solvents turned out to have a strong influence on the efficiency of this transformation. Reactions in DMF and DMSO afforded the desired product **4a** in a high yield and in a short reaction time (generally <30 min) (entries 5 and 13), whereas those in other solvents provided **4a** in moderate yields along with 2-aminocinnamic acid piperidine amide **1a** and benzaldehyde *via* hydrolysis of **5a** under the reaction conditions (entries 14–18). Because DMF provided the best result among the solvents tested, DMF was chosen as the optimal solvent for further investigation.

Under these optimized reaction conditions, the substrate scope of this transformation was investigated (Table 2). Aldimines, prepared from various aromatic aldehydes and piperidine amide **1a** of 2-aminocinnamic acid, could be applied to this protocol and the desired products **4** were obtained in high yields in a very short reaction time (generally less than 30 min) regardless of the electronic and steric nature of the aldehydes (entries 1–7). Then, the aldimines obtained from 2-aminocinnamic acid ethyl ester **1b** and aromatic aldehydes were explored in this transformation. To our delight, the aldimines from ethyl ester of 2-aminocinnamic acid could be used in this transformation; the desired indoles **4** were obtained in slightly better yields than the corresponding amides (entries 8–16).[12] Furthermore, fused aromatic aldehydes and heteroaromatic aldehydes were applicable to this protocol to provide the desired indole products **4** in excellent yields (entries 14–16). We attempted to extend this protocol to the synthesis of 2-arylindole-3-acetamides bearing a secondary amide (entry 17). When the aldimine, obtained from benzyl amide **1c** of 2-aminocinnamic acid and benzaldehyde, was subjected to the optimized reaction conditions, the reaction did not go to completion, and the desired indole **4q** was obtained in a low yield. However, when a stoichiometric amount of cyanide was used instead, **4q** was obtained in an excellent yield.

To test the practicality of this protocol, the reaction was performed on a large scale reaction even without the isolation of the corresponding aldimines (Scheme 2). When 2-aminocinnamic acid ethyl ester **1b** and benzaldehyde were subjected to the condensation conditions with a mixture of Na_2SO_4 and $MgSO_4$,[13] and the crude mixture of the resulting aldimine **5h** was concentrated and subjected to the optimized reaction conditions without further purification, the desired product **4h** was obtained in 88% yield on a 20 mmol scale.[14]

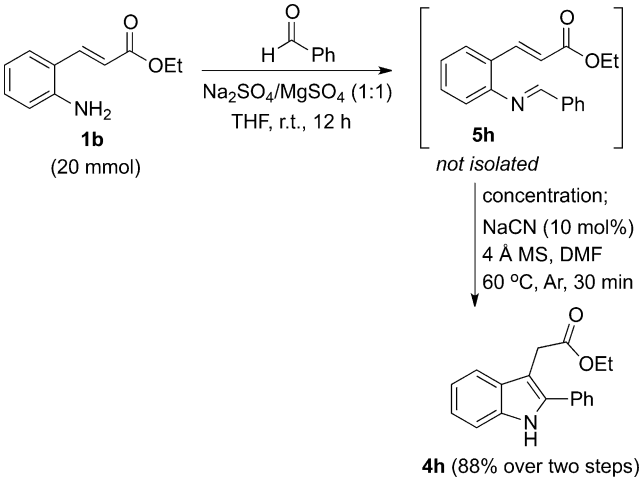
With these results in hand, we further attempted to demonstrate the usefulness of this new protocol in the

Table 2. Substrate scope.

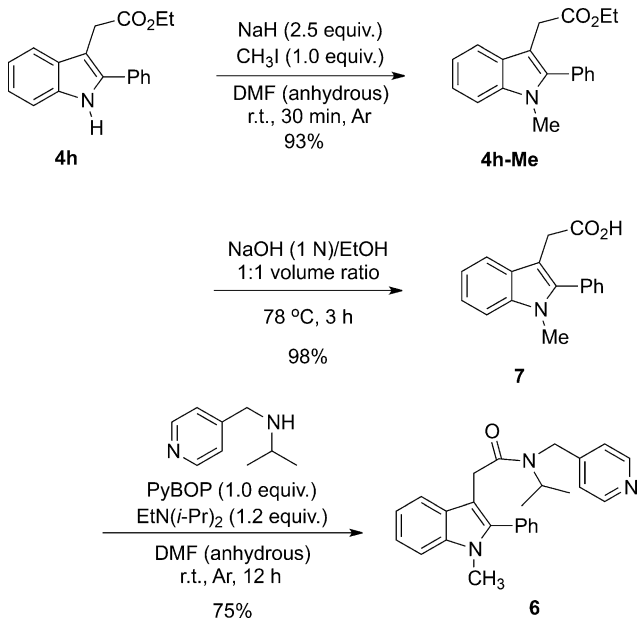


Entry	Indole **4**	X	Ar	Yield [%][a]
1	**4a**	$N(CH_2)_5$	C_6H_5	86
2	**4b**	$N(CH_2)_5$	4-$MeOC_6H_4$	77
3	**4c**	$N(CH_2)_5$	4-MeC_6H_4	87
4	**4d**	$N(CH_2)_5$	4-ClC_6H_4	80
5	**4e**	$N(CH_2)_5$	4-FC_6H_4	88
6	**4f**	$N(CH_2)_5$	2-FC_6H_4	83
7	**4g**	$N(CH_2)_5$	2-naphthyl	86
8	**4h**	OC_2H_5	C_6H_5	98
9	**4i**	OC_2H_5	4-$MeOC_6H_4$	92
10	**4j**	OC_2H_5	4-MeC_6H_4	96
11	**4k**	OC_2H_5	4-ClC_6H_4	96
12	**4l**	OC_2H_5	4-FC_6H_4	81
13	**4m**	OC_2H_5	2-BrC_6H_4	95
14	**4n**	OC_2H_5	2-naphthyl	93
15	**4o**	OC_2H_5	2-furyl	86
16	**4p**	OC_2H_5	2-thienyl	86
17[b]	**4q**	$NHCH_2Ph$	C_6H_5	93

[a] Isolated yield.
[b] A stoichiometric amount of NaCN was used.



Scheme 2. A gram-scale reaction



Scheme 3. Synthesis of FPTase inhibitor **6**

synthesis of biologically important FPTase inhibitor **6** (Scheme 3). The methylation of the free N–H bond in **4h** with methyl iodide, followed by the basic hydrolysis of the ester moiety in **4h-Me** afforded the corresponding carboxylic acid **7**. Amide bond formation of the resulting carboxylic acid **7** with a secondary amine[11] in the presence of a coupling reagent afforded FPTase inhibitor **6** in 68% yield over three steps from readily available indole starting material.

Although there have been several reports in which the umpolung of aldimines could be generated from aldimines with cyanide *via* the cyanide addition to aldimines, followed by a proton transfer in the cyanide adducts,[8–10] the utility of this method has not been fully recognized by the synthetic community for a long time. From our recent findings[7] along with the previous reports,[8–10] we have recognized the facile generation of the umpolung derivatives of aldimines with cyanide and developed a highly efficient protocol for the synthesis of 2-aryl-substituted indole-3-acetic acid derivatives from aldimines, obtained from 2-aminocinnamic acid derivatives and aromatic aldehydes, in the presence of a catalytic amount of cyanide *via* the first imino-Stetter reaction. Various aromatic aldehydes and 2-aminocinnamic acid derivatives could be used in this protocol; the desired 2-aryl-substituted indole-3-acetic acid derivatives were obtained in excellent yields. Furthermore, the usefulness of this protocol was demonstrated in the synthesis of an FPTase inhibitor. Studies on further applications of this umpolung reactivity of aldimines with cyanide to other organic transformations are currently underway in our laboratory and will be reported in due course.

Experimental Section

General Procedure

To a solution of aldimine **5** (1.0 mmol) in DMF (10 mL) in the presence of 4 Å molecular sieves was added sodium cyanide (0.10 mmol) at room temperature. The mixture was stirred at 60 °C under an argon atmosphere and monitored by thin-layer chromatography (TLC). Upon the complete consumption of **5**, the reaction mixture was cooled to room temperature and filtered to remove insoluble molecular sieves. The filtrate was concentrated under vacuum to provide the crude product, indole **4**. The resulting crude mixture was purified by either recrystallization in diethyl ether [when $X=N(CH_2)_5$] or by flash column chromatography on silica (when X = OEt or $NHCH_2Ph$) to provide the desired indole **4**.

Acknowledgements

This work was supported by National Research Foundation of Korea (NRF) grants funded by the Korean Government (NRF-20100020209, NRF-2013R1A1A1008434, and NRF-2015R1D1A1A01057200). C.-H.C. also thanks for a financial support from an NRF grant funded by the Korean Government (NRF-2014-011165, Center for New Directions in Organic Synthesis).

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