



Cyanation of indoles with benzyl cyanide as the cyanide anion surrogate



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ARTICLE INFO

Article history:

Received 3 January 2013

Received in revised form 15 March 2013

Accepted 22 March 2013

Available online 26 March 2013

Keywords:

Copper catalysis

Cyanation

Benzyl cyanide

3-Cyanoindoles

ABSTRACT

A copper-mediated direct cyanation of indoles with benzyl cyanide as the cyanide anion surrogate has been achieved. The cascade reaction furnished 3-cyanoindoles under mild reaction conditions in good to excellent yields with various functional groups tolerance.

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1. Introduction

The importance of indole derivatives comes from their unique presence in natural products and pharmaceutical compounds. Among this field, 3-cyanoindoles particularly functioned as the key intermediates in the preparations of the most fascinating indole containing compounds. For instance, based on the versatile transformations of cyano group, they are useful in the synthesis of indolyl 1,2,4-triazoles¹ and 3,5-bis(indolyl)-1,2,4-thiadiazoles² as potent and selective anticancer agents, indole oxadiazoles as 5-HT₃ antagonists,³ and oxadiazole-5-carboxamide as inhibitors of glycogen-synthase-kinase-3 (GSK-3).⁴ Beyond of these, modification of the N–H bond of 3-cyanoindoles also leads to a great amount of indole containing compounds with special bioactivities, such as indole-3-carbinol analogues,⁵ oncrasin-1 analogues as inhibitors of the C-terminal domain of RNA polymerase II,⁶ 1*H*-benzylindole derivatives as HIV-integrase inhibitors,⁷ and indole-fused piperazinones and piperazines acting as antagonists of the histamine 3 (H₃) receptor.⁸ Further, it is noticeable that 3-cyanoindoles play a key role in the construction of tremendous natural products, such as strychnos alkaloids.⁹ Therefore, the development of new methods leading to simple and rapid introduction of cyano group onto the 3-position of indole remains a challenge in the organic synthesis.

Traditional methods for the preparation of 3-cyanoindoles include two strategies. One is related to the 1C chemistry in which the

cyano group of 3-cyanoindole derives from the relevant aldehyde,¹⁰ aldoxime,¹¹ hydroxymethyl,¹² and ester.¹³ Another one is the direct installation of cyano group through activation of C–H bond of 3-hydroindole or C–X bond of 3-haloindole, which is catalyzed by transition metals. Among these advance methods, cyano source can be a single component, such as MCN (with extremely toxic),¹⁴ K₂Fe(CN)₄ (with solubility obstacle),¹⁵ acetone cyanohydrin (with stability problem),¹⁶ malononitrile,¹⁷ TMSCN,¹⁸ nitromethane,^{19a} DMF^{19b} and so on. Combinations of DMF+NH₃,²⁰ DMSO+NH₄HCO₃,²¹ and DMF+NH₄HCO₃,²² providing ‘C’ and ‘N’, respectively, can also be efficiently used for cyanation of Ar–H or Ar–X.

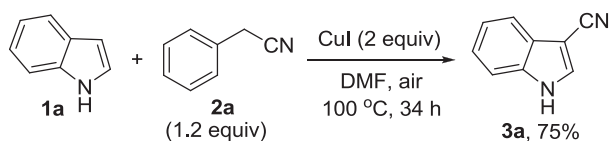
Encouraged by our previous works on benzyl cyanide as an operator-benign cyanation reagent that could be used for palladium-catalyzed cyanation of Ar–X,²³ and copper-catalyzed cyanation of Ar–H with directing group,²⁴ we were interested in exploring the cyanation of electron-rich aromatics with benzyl cyanide through C–H bond activation without directing group. We herein report the detail of this effort.

2. Results and discussion

In our primary investigation, indole was selected as the substrate and tested. As we expected, 3-cyanoindole (**3a**) was isolated in 75% yield when indole (**1a**) reacted with 2 equiv of benzyl cyanide (**2a**) in the presence of 2 equiv of CuI under air in DMF at 100 °C for 34 h (Scheme 1). With the above result, we optimized the reaction conditions (Table 1). By screening the copper sources, CuI presented the best among CuI, CuBr, and CuCl (Table 1, entries 1–3). Other Cu(I) source, such as Cu₂O, provided only a detectable product although

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indole was completely consumed after 34 h (Table 1, entry 4). Cu(II) did not work for this transformation (Table 1, entries 5 and 6). By screening the solvents, DMF was found to be the optimal among polar aprotic solvents, such as DMF, DMAc, DMSO, HMPA, and NMP (Table 1, entries 7–10). Acetonitrile, toluene, *p*-xylene, and 1,4-dioxane did not work for this reaction with the recovery of indole (Table 1, entries 11–14). By decreasing the amount of CuI to 1.2 equiv, 80% yield of **3a** was observed (Table 1, entry 15). Further decreasing the amount of CuI to 1 equiv, indole was consumed completely after reaction and **3a** was isolated in 70% yield (Table 1, entry 16). When the amount of CuI dropped to 0.5 equiv, yield of **3a** was decreased to 36% with a 52% recovery of indole (Table 1, entry 17). When the reaction was carried out with the stoichiometric amount of iodine and catalytic amount of CuI, only trace amount of **3a** could be detected by TLC (Table 1, entry 18). The optimal amount of benzyl cyanide was found to be 1.2 equiv (Table 1, entries 15 and 17–19). Finally the optimal reaction temperature and reaction time were selected to be 100 °C and 34 h (Table 1, entries 15 and 20–23). When the reaction was conducted under nitrogen, no desired product was detected with the recovery of indole (Table 1, entry 24). When the reaction was carried out without benzyl cyanide, 3-formylindole and indolo[2,1-*b*]quinazoline-6,12-dione²⁵ were isolated in 16% and 46% yields, respectively (Scheme 2).



Scheme 1. Cu-catalyzed cyanation of indole with benzyl cyanide.

Table 1
Optimization of the reaction conditions^a

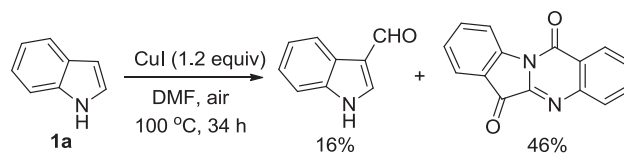
Entry	Catalyst (equiv)	Solvent	Benzyl cyanide (equiv)	Temp (°C)	Time (h)	Yield ^b (%)
1	CuI (2.0)	DMF	1.2	100	34	75
2	CuBr (2.0)	DMF	1.2	100	34	33
3	CuCl (2.0)	DMF	1.2	100	34	27
4	Cu ₂ O (2.0)	DMF	1.2	100	34	Trace
5	CuBr ₂ (2.0)	DMF	1.2	100	34	0
6	Cu(OAc) ₂ (2.0)	DMF	1.2	100	34	0
7	CuI (2.0)	DMAc	1.2	100	34	59
8	CuI (2.0)	DMSO	1.2	100	34	54
9	CuI (2.0)	HMPA	1.2	100	34	35
10	CuI (2.0)	NMP	1.2	100	34	30
11	CuI (2.0)	CH ₃ CN	1.2	81	34	0
12	CuI (2.0)	Toluene	1.2	100	34	0
13	CuI (2.0)	<i>p</i> -Xylene	1.2	100	34	0
14	CuI (2.0)	1,4-Dioxane	1.2	100	34	0
15	CuI (1.2)	DMF	1.2	100	34	80
16	CuI (1.0)	DMF	1.2	100	34	70
17	CuI (0.5)	DMF	1.2	100	34	36
18	CuI (0.5)+I ₂ (1.0)	DMF	1.2	100	34	Trace
19	CuI (1.2)	DMF	1.5	100	34	80
20	CuI (1.2)	DMF	1.0	100	34	75
21	CuI (1.2)	DMF	1.2	120	34	75
22	CuI (1.2)	DMF	1.2	80	34	45
23	CuI (1.2)	DMF	1.2	100	24	62
24	CuI (1.2)	DMF	1.2	100	36	80
25	CuI (1.2)	DMF	1.2	100	34	0 ^c

^a Reaction conditions: **1a** (0.5 mmol), solvent (3 mL), air.

^b Isolated yield.

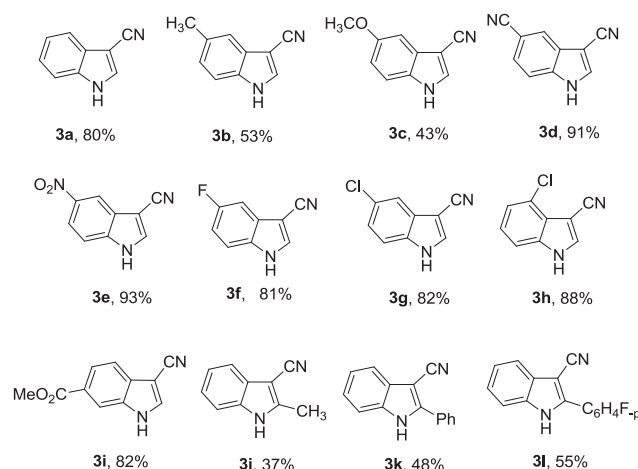
^c Under N₂.

With the optimized reaction conditions in hand, we tested the scope of indoles (Scheme 3). A variety of functional groups tolerated this reaction. Indoles with substituent on 5-position were firstly investigated. With the electron-donating nature of 5-substituent, **3b**



Scheme 2. Reaction of indole without benzyl cyanide.

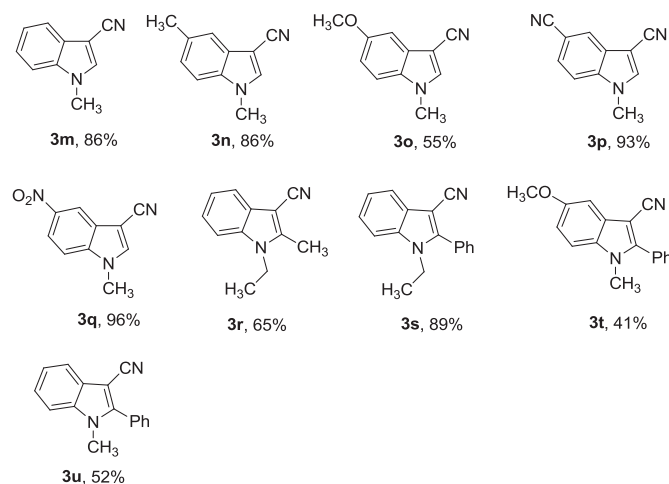
and **3c** were obtained in relatively lower yields. Conversely, substituents with electron-withdrawing property benefitted the reaction. Thus, **3c**, **3d**, **3e**, and **3f** were obtained in good to excellent yields (81–93%). By altering 5-chloroindole to 4-chloroindole, a higher yield of **3h** was observed. With the ester group on 6-position of indole, **3i** was isolated in 82% yield. It was noticeable that cyanation still occurred smoothly on 3-position of 2-substituted indoles. Beyond of these, this transformation could be operated in gram scale. For example, 1.13 g (7 mmol) of 5-nitroindole was cyanated to give 1.15 g of 5-nitroindole-3-carbonitrile (**3e**) in 88% yield.



Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), CuI (0.6 mmol), air, 100 °C, DMF (3 mL), 34 h.

Scheme 3. Structures and yields of prepared 3-cyanoindoles.

When *N*-alkyl indoles were used as the substrates, yields of the cyanation products were significantly improved, especially in the case of 1-ethyl-2-phenyl-1*H*-indole (Scheme 4). From the pair of



Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), CuI (0.6 mmol), air, 100 °C, DMF (3 mL), 34 h.

Scheme 4. Cyanation products of *N*-alkyl indoles.

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