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A Simple Copper-Catalyzed Cascade Synthesis of 2-Amino-1*H*-indole-3-carboxylate Derivatives

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Abstract: We have developed a simple and efficient copper-catalyzed method for the synthesis of 2-amino-1*H*-indole-3-carboxylate derivatives *via* cascade reactions of substituted *N*-(2-halophenyl)-2,2,2-trifluoroacetamide with alkyl 2-cyanoacetate or malononitrile under mild conditions, and the method is of wide practical application.

Keywords: 2-amino-1*H*-indole-3-carboxylates; cascade reactions; copper; nitrogen heterocycles; synthetic methods

Introduction

Nitrogen-containing heterocyclic compounds in the form of biologically active drugs or agents play an important role in the pharmaceutical and agrochemical industries.[1] The indole core is a privileged structural motif found in both designed medicinal agents and in natural products. As shown in Figure 1, the neurotransmitter serotonin [**1**, 5-hydroxytryptamine, (5-HT)], the antihypertensive reserpine (**2**),[2] and the antibiotic indolmycin (**3**)[3] are indole derivatives. Some approved drugs have this core in their structures, for example, the 5-HT3 receptor antagonist ondansetron (**4**) used for the treatment of chemotherapy-induced nausea and vomiting,[4] the 5HT1 receptor agonist sumatriptan (**5**) used for the treatment of cluster headache.[5] The diversity of indole-based molecules found in naturally occurring alkaloids as well as their biological and pharmaceutical relevance have stimulated research into the development of new strategies for the synthesis of readily functionalized indole ring systems.[6] In comparison to classical

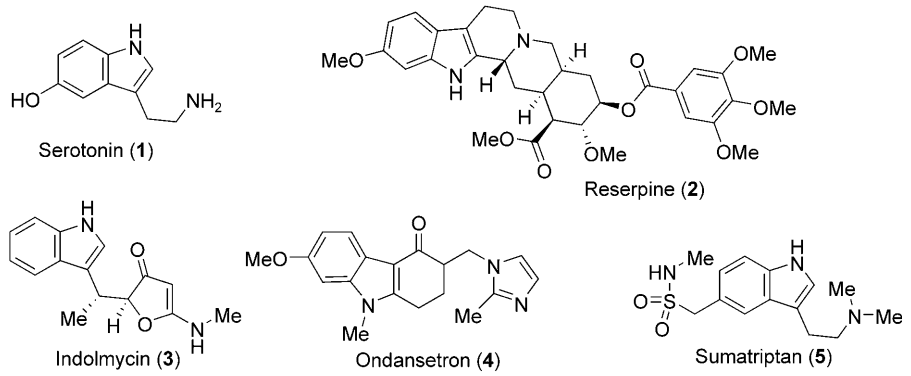


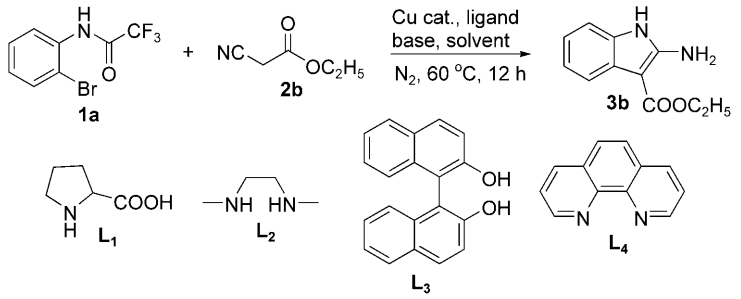
Figure 1. Relevant biologically active molecules with an indole moiety.

indole synthetic methods,[7] the transition metal-catalyzed strategy has the advantages of increased functional group tolerance, as well as providing indoles with greater structural diversity and often higher overall yields.[8,9] The 2-amino-1*H*-indole-3-carboxylate derivatives are found to be biologically active molecules and important intermediates for construction of medicinal molecules.[10,11] Unfortunately, only a few of examples were reported for their synthesis,[11a,12] and the starting materials often are not readily available and difficult to prepare. Volovenko et al. attempted a synthesis of 2-amino-6-nitroindoles *via* the reaction of 2-halo-5-nitroanilines and substituted acetonitriles,[13] the result showed that only 2-fluoro-5-nitroaniline containing a strong electron-withdrawing group (nitro) was effective, however, other 2-haloanilines did not work, so the method could not construct diverse 2-amino-1*H*-indole derivatives. Recently, great progress for copper-catalyzed Ullmann-type couplings has been made,[14] and we have also developed some copper catalyst systems that were used in *N*-arlyations.[15] Some N-heterocycles have been constructed *via* the Ullmann-type couplings by us[16] and other research groups.[17] Herein, we report a simple, convenient one-pot copper-catalyzed cascade method for the synthesis of 2-amino-1*H*-indole-3-carboxylate derivatives under mild conditions.

Results and Discussion

Initially, *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide and ethyl 2-cyanoacetate were chosen as the model substrates to optimize reaction conditions including the catalysts, bases and solvents under nitrogen atmosphere. As shown in Table 1, four copper catalysts (10 mol% amount) were tested at 60 °C using 20 mol% L-proline as the ligand, 2 equiv. of K_2CO_3 as the base [relative to the amount of *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide] in the mixed solvent of DMSO and water (volume ratio 1:1) (entries 1–4), and CuI showed the highest activity (entry 1). We attempted other ligands (entries 5–7), and L-proline was proved to be the most effective. A 61% yield of the

Table 1. Copper-catalyzed cascade coupling of *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide with ethyl 2-cyanoacetate to ethyl 2-amino-1*H*-indole-3-carboxylate: optimization of the reaction conditions.[a]

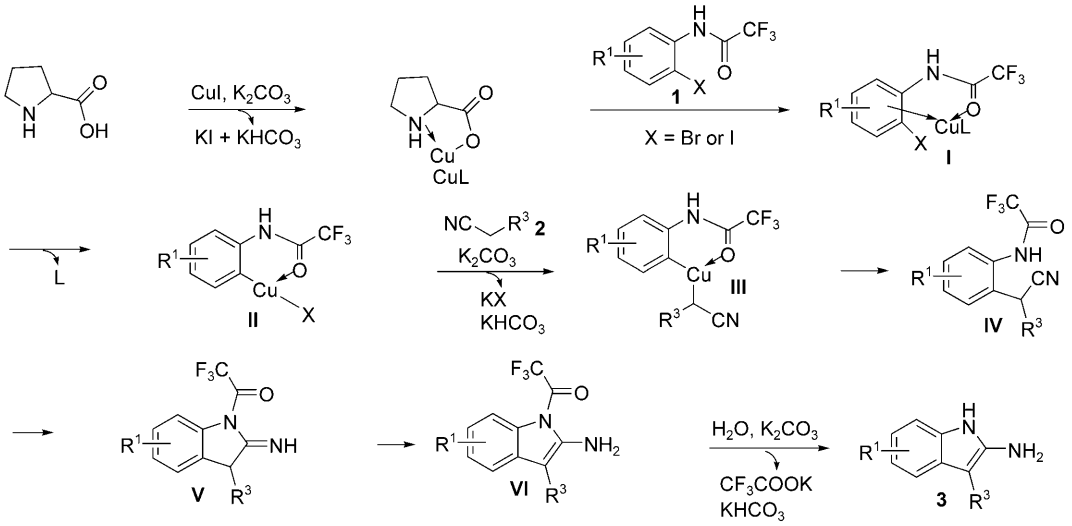


Entry	Cu catalyst	Ligand	Base	Solvent	Yield [%][b]
1	**CuI**	**L_1**	**K_2CO_3**	**DMSO/H_2O**	**84**
2	CuBr	L_1	K_2CO_3	DMSO/H_2O	67
3	$Cu(OAc)_2$	L_1	K_2CO_3	DMSO/H_2O	45
4	Cu	L_1	K_2CO_3	DMSO/H_2O	39
5	CuI	L_2	K_2CO_3	DMSO/H_2O	69
6	CuI	L_3	K_2CO_3	DMSO/H_2O	26
7	CuI	L_4	K_2CO_3	DMSO/H_2O	16
8	CuI	–	K_2CO_3	DMSO/H_2O	61
9	–	L_1	K_2CO_3	DMSO/H_2O	0
10	–	–	K_2CO_3	DMSO/H_2O	0
11	CuI	L_1	Cs_2CO_3	DMSO/H_2O	82
12	CuI	L_1	K_2CO_3	DMF/H_2O	43
13	CuI	L_1	K_2CO_3	CH_3CN/H_2O	29
14	CuI	L_1	K_2CO_3	dioxane/H_2O	27
15	CuI	L_1	K_2CO_3	toluene/H_2O	trace
16	CuI	L_1	K_2CO_3	DMSO/H_2O	trace[c]

[a] *Reaction conditions: N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (0.5 mmol), ethyl 2-cyanoacetate (0.6 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1 mmol), water (0.5 mL), the other solvent (0.5 mL), reaction temperature (60 °C) under nitrogen atmosphere, reaction time (12 h).

[b] Isolated yield.

[c] Using *N*-(2-bromophenyl)acetamide as the substrate.



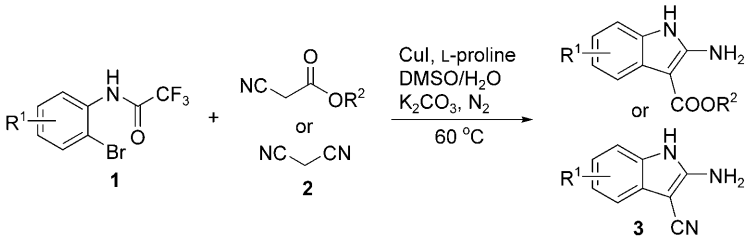
Scheme 1. Possible mechanism of formation of 2-amino-1*H*-indole-3-carboxylate derivatives.

target product was obtained in the absence of ligand (entry 8), which implies an *ortho*-substituent effect of the $-NHCOCF_3$ group (see reaction mechanism in Scheme 1). However, no target product was observed in the absence of copper catalyst (entry 9) or copper catalyst/ligand (entry 10). The reactivity slightly decreased when K_2CO_3 was replaced with Cs_2CO_3 as the base (compare entries 1 and 11). Several mixed solvents, DMF/H_2O, CH_3CN/H_2O, dioxane/H_2O and toluene/H_2O, were screened, and DMSO/H_2O was found to be the most effective (compare entries 1, 12–15). The reaction temperature was also changed, and 60 °C was the best choice. When the group $-NHCOCF_3$ in the *N*-(2-halophenyl)-2,2,2-trifluoroacetamide was replaced with $-NHCOMe$ (entry 16), only a trace amount of the target product was observed. A possible reason is that group $-COCF_3$ is of stronger electron-withdrawing power compared with $-COCH_3$, which is helpful for *C*-arylation (see intermediate **IV** in Scheme 1), and deprotection of the group $-COCF_3$ is easier than for $-COCH_3$ in aqueous base medium after intermediate **VI** in Scheme 1 is formed.

The scope of the copper-catalyzed cascade reactions of substituted *N*-(2-halophenyl)-2,2,2-trifluoroacetamides with alkyl 2-cyanoacetates or malononitrile was investigated under optimized condition (10 mol% CuI as the catalyst, 20 mol% L-proline as the ligand, 2 equiv. of K_2CO_3 as the base). As shown in Table 2, most of the substrates examined provided good yields at 60 °C. For the substituted *N*-(2-halophenyl)-2,2,2-trifluoroacetamides, the electronic effect of the substituent groups could affect the reactivity of the substrates. For example, *N*-[2-bromo-5-(trifluoromethyl)-phenyl]-2,2,2-trifluoroacetamide containing an electron-withdrawing group (CF_3) showed higher reaction rates than the substrates containing electron-rich, neutral groups. *N*-(2-Iodophenyl)-2,2,2-trifluoroacetamide provided higher yields than *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (compare entries 1–4 and 17–20). Interestingly, reactions of *N*-(2,4-dibromophenyl)-2,2,2-trifluoroacetamide with alkyl 2-cyanoacetates or malononitrile only occurred at the *ortho*-sited C–Br bond of the $-NHCOCF_3$ group which indicated a copper-catalyzed *ortho*-substituent effect (see reaction mechanism in Scheme 1). For alkyl 2-cyanoacetates and malononitrile, malononitrile showed higher reactive activity than alkyl 2-cyanoacetates. It is worthwhile to note that water was not added until the Ullmann-type coupling was completed (TLC determination) when methyl 2-cyanoacetate was used as the substrate because a small amount of the methyl ester could be hydrolyzed under a long-term incubation of an aqueous base system.

We attempted the reaction of 2-bromoaniline (**4**) with ethyl 2-cyanoacetate (**2b**) under our standard conditions, but it did not work even when the reaction temperature was raised to 100 °C (Figure 2). Therefore, a possible formation mechanism of 2-amino-1*H*-indole-3-carboxylate derivatives was proposed in Scheme 1 according to the results mentioned above and the *ortho*-substituent effect.[18] Complexation of L-proline with CuI in the presence of base (K_2CO_3) forms the coordinated CuL, and treatment of CuL with substituted *N*-(2-halophenyl)-2,2,2-trifluoroacetamide forms complex **I**. The oxidative adduct of **I** gives **II** releasing the ligand. Conjugation of **II** with deprotonated alkyl 2-cyanoacetate or malononitrile in the presence of base provides **III**, and reductive elimination of **III** gives the coupling product **IV**. Addition of N–H of $NHCOCF_3$ to CN in **IV** produces intermediate **V**, isomerization of **V** leads to **VI**, and hydrolysis of **VI** in the presence of base affords the desired target product (**3**).

Table 2. Copper-catalyzed synthesis of 2-amino-1*H*-indole-3-carboxylate derivatives.[a]



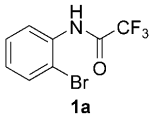
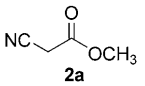
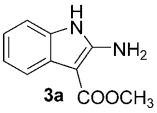
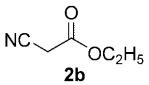
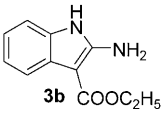
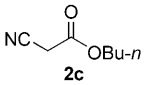
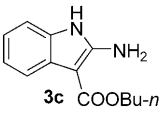
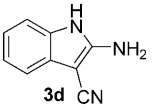
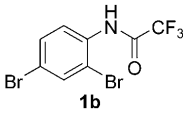
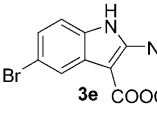
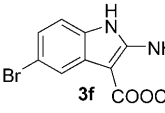
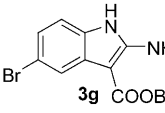
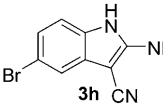
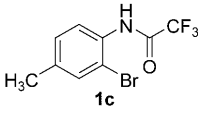
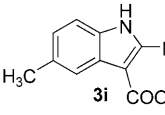
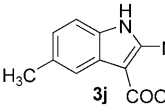
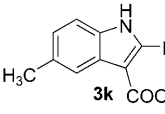
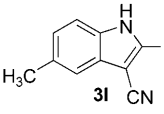
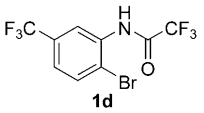
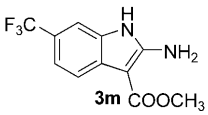
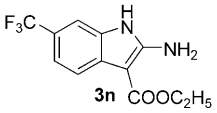
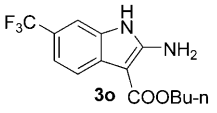
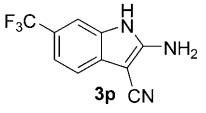
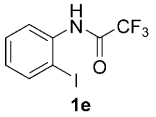
Entry	1	2	Product (3)	Yield [%][b]
1	 **1a**	 **2a**	 **3a**	71
2	**1a**	 **2b**	 **3b**	84
3	**1a**	 **2c**	 **3c**	81
4	**1a**	 **2d**	 **3d**	85
5	 **1b**	**2a**	 **3e**	75
6	**1b**	**2b**	 **3f**	87
7	**1b**	**2c**	 **3g**	74
8	**1b**	**2d**	 **3h**	92
9	 **1c**	**2a**	 **3i**	65
10	**1c**	**2b**	 **3j**	73
11	**1c**	**2c**	 **3k**	73
12	**1c**	**2d**	 **3l**	72

Table 2. (Continued)

Entry	1	2	Product (3)	Yield [%][b]
13	 **1d**	**2a**	 **3m**	72
14	**1d**	**2b**	 **3n**	85
15	**1d**	**2c**	 **3o**	79
16	**1d**	**2d**	 **3p**	93
17	 **1e**	**2a**	**3a**	73
18	**1e**	**2b**	**3b**	87
19	**1e**	**2c**	**3c**	83
20	**1e**	**2d**	**3d**	97

[a] *Reaction conditions:* substituted *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (0.5 mmol), alkyl 2-cyanoacetate (0.6 mmol), malononitrile (0.6 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), K_2CO_3 (1 mmol), DMSO (0.5 mL), H_2O (0.5 mL), reaction temperature (60 °C), reaction time (12 h for entries 1–12 and 17–20; 9 h for entries 13–16).
[b] Isolated yield.

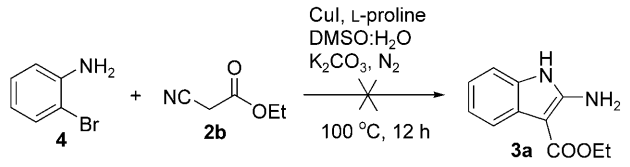


Figure 2. Reaction of 2-bromoaniline (**4**) with ethyl 2-cyanoacetate (**2b**) under our standard conditions.

Conclusions

We have developed a simple and efficient method for the synthesis of 2-amino-1*H*-indole-3-carboxylate derivatives. The cascade reactions of substituted *N*-(2-halophenyl)-2,2,2-trifluoroacetamide with alkyl 2-cyanoacetate or malononitrile were performed well under mild conditions, the corresponding indole derivatives containing amino and carboxylate groups were obtained in good yields, and they are biologically active molecules and important intermediates for the construction of medicinal molecules. The present method shows practical advantages over the previous methods and its starting materials are readily available, so it will provide an opportunity for the construction of diverse and useful molecules in organic chemistry and medicinal chemistry.

Experimental Section

General Procedure for Synthesis of Compounds 3a–p

A 10-mL round-bottom flask was charged with a magnetic stirrer and DMSO (0.5 mL) and water (0.5 mL) [water was not added until the Ullmann-type coupling was completed (TLC determination) when methyl 2-cyanoacetate was used as the substrate], substituted *N*-(2-halophenyl)-2,2,2-trifluoroacetamide (**1**) (0.5 mmol), alkyl 2-cyanoacetates or malononitrile (**2**) (0.6 mmol), L-proline (0.1 mmol, 12 mg) and K_2CO_3 (1 mmol, 138 mg), after stirring of the mixture for 15 min under nitrogen atmosphere, and CuI (0.05 mmol, 10 mg) was added to the flask. The mixture was stirred at 60 °C for 9 h or 12 h under a nitrogen atmosphere. The resulting mixture was cooled to room temperature and filtered. The solid was washed with methanol two times (2 × 3 mL), and the combined filtrate was concentrated on the rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1:1 to 1:2) as eluent to give the desired product.

Acknowledgements

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2007AA02Z160, 2006DFA43030) and the Key Subject Foundation from Beijing Department of Education (XK100030514).

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