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# Copper(I)-catalyzed N-Carboxamidation of Indoles with Isocyanates: Facile and General Method for Synthesis of Indole-1-carboxamides

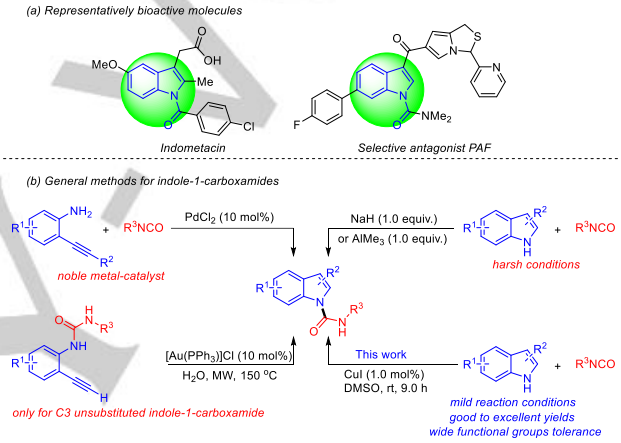
Jinyang Chen,* Li Hu, Haiying Wang, Lingrong Liu, Binyang Yuan*

**Abstract:** A facile and general method for synthesis of indole-1-carboxamides was developed *via* copper(I)-catalyzed N-caboxamidation of indoles with isocyanates under mild reaction conditions. This process is scalable and tolerates a wide spectrum of indoles and isocyanates to deliver corresponding products in good to excellent yields, providing a viable synthetic approach to indole-1-carboxamides**,** which can be used for the treatment of inflammatory diseases and diabetes.

## Introduction

Indole derivatives have become attractively synthetic goal in organic chemistry,[1] because the indole skeleton is an important element of both natural products and synthetic molecules that exhibit a wide range of bioactivities,[2] such as monoterpene indole alkaloids,[3] indole alkaloids[4] and tryptophan-derived substances,[5] and their application as tubulin polymerization inhibitors was also studied.[6] The development of efficient methods for their generation has attracted increasingly attentions.[7] Transition metal-catalyzed (such as Pd-[8], Cu-[9] or Rh-[10] catalysts) intramolecular cyclization of functionalized *o*-alkynylanilines is one of the most efficient approaches for synthesis of indoles. Other cyclization reactions for indoles were also described including Fischer,[11] Hemetsberger,[12] Sundberg,[13] and Madelung[14] reactions.

Moreover, indole-1-carboxamides have been used as important drugs for the treatment of inflammatory diseases[15] and diabetes[16] (Scheme 1, a). The N-arylcarboxamide groups of indole-1-carboxamides can also be used as good protecting or directing groups in various transformation.[17] However, only few methods for synthesis of indole-1-carboxamides have been reported so far.[18] Although the N-carboxamidation of indoles with isocyanates was the most direct method for indole-1-carboxamides, these N-carboxamidation reactions always occurred under harsh conditions, due to the use of NaH[17c] or $AlMe_3$[19] (Scheme 1, b). Transition metal-catalyzed cyclization of 1-(2-ethynylphenyl)-3-alkylurea or 2-alkynylbenzenamides with isocyanates to form indole-1-carboxamides was also described. These reactions were performed in the presence of 10 mol% of noble metal-catalysts ($PdCl_2$[20] or Au-complex[21]), and both cyclization reactions were only suitable for C3-unsubstituted indoles. Other procedures for indole-1-carboxamides have also been reported,[22,7d] however, challenges still exist in developing more facile and general methods for their generation. Herein, an efficient route to indole-1-carboxamides *via* the N-carboxamidation of indoles with isocyanates catalyzed by 1.0 mol% of copper iodide (CuI) under mild conditions is proposed.




**Scheme 1** (a) Representatively bioactive molecules containing indole-1-carboxamides. (b) General methods for synthesis of indole-1-carboxamides.

## Results and Discussion

This work was initiated with the reaction of indole (**1a)** with *p*-tolylisocyanate (**2a**) catalysed by 10 mol% of $Pd(AcO)_2$ in DMF at rt for 6.0 h, and the desired product (**3a**) was obtained in the yield of 62% (Table 1, entry 1). Then, the influence of different catalysts on the N-carboxamidation was studied systematically (Table 1, entries 1-6), and the results showed that CuI was the most suitable catalyst for giving the desired product (**3a**) in the highest yield of 84% (Table 1, entry 2). However, 2.0 equiv. of *p*-tolylisocyanate (**2a**) must be used to promote the N-carboxamidation efficiently, mainly due to the self-decomposition of *p*-tolylisocyanate (**2a**) in the presence of CuI (Table 1, entry 8). A series of solvents (such as DMF, DMSO, $CH_3CN$, acetone, EtOH, THF, 1,4-dioxane, toluene and DCM) were also examined to promote the N-carboxamidation (Table 1, entries 7-16), and results indicated that DMSO was the best solvent, affording the desired product (**3a**) in the yield of 95% within 6.0 hours (Table 1, entry 9). Then the influence of the catalyst amount on the N-carboxamidation was explored, and the results demonstrated that 1.0 mmol% of CuI was enough to promote the N-carboxamidation effectively by extending the reaction time to 9.0 h (95%, Table 1, entry 20). No desired product was detected

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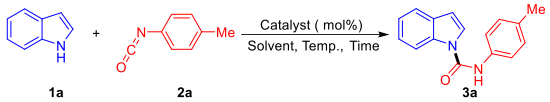
without catalysts (Table 1, entry 22). In addition, the effect of temperature on the reaction was also examined, and it concluded that no increase in yield was observed by increasing the temperature to 50 °C (Table 1, entries 23). Furthermore, the N-carboxamidation was affect inapparently by the atmosphere of air or nitrogen. After extensive screening, it was satisfactory that the reaction of indole (**1a**) with *p*-tolyl isocyanate (**2a**) in DMSO catalyzed by 1.0 mmol% of CuI in air provided the desired product (**3a**) in the excellent yield of 95% within 9.0 hours (Table 1, entry 20).

**Table 1.** Optimization of the reaction conditions[a].

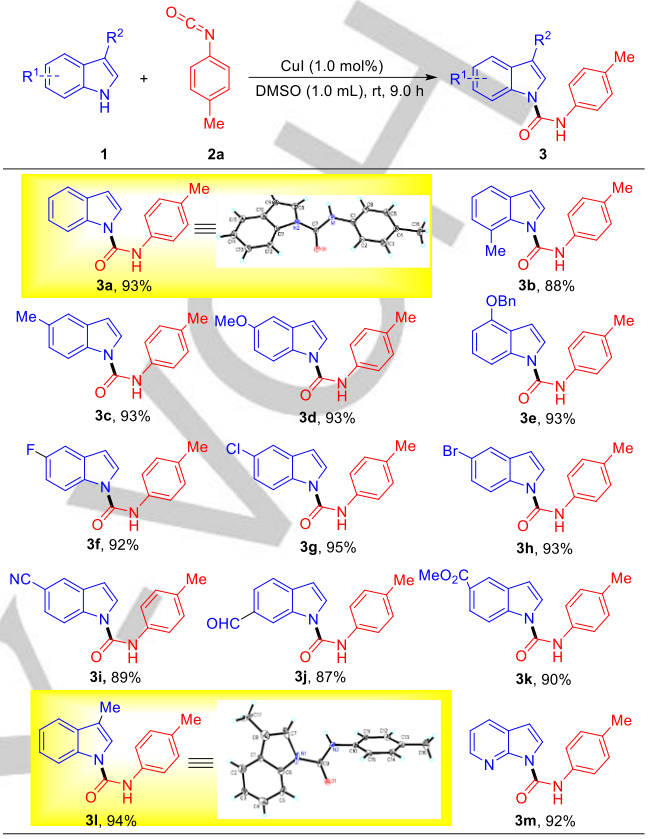



| Entry | Cat. (mol%) | $n_{1a}$:$n_{2a}$ | Solvent | Temp. | Time (h) | Yields [b] (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(AcO)_2$ (10 mol%) | 1:1.2 | DMF | r.t. | 6.0 | 62% |
| 2 | CuI (10 mol%) | 1:1.2 | DMF | r.t. | 6.0 | 84% |
| 3 | $Ni(AcO)_2$ (10 mol%) | 1:1.2 | DMF | r.t. | 6.0 | 25% |
| 4 | $CuBr_2$ (10 mol%) | 1:1.2 | DMF | r.t. | 6.0 | 18% |
| 5 | $Ni(acac)_2$ (10 mol%) | 1:1.2 | DMF | r.t. | 6.0 | 13% |
| 6 | $Cu_2O$ (10 mol%) | 1:1.2 | DMF | r.t. | 6.0 | 32% |
| 7 | CuI (10 mol%) | 1:1.5 | DMF | r.t. | 6.0 | 86% |
| 8 | CuI (10 mol%) | 1:2.0 | DMF | r.t. | 6.0 | 88% |
| 9 | CuI (10 mol%) | 1:2.0 | DMSO | r.t. | 6.0 | 95% |
| 10 | CuI (10 mol%) | 1:2.0 | $CH_3CN$ | r.t. | 6.0 | 28% |
| 11 | CuI (10 mol%) | 1:2.0 | Actone | r.t. | 6.0 | 24% |
| 12 | CuI (10 mol%) | 1:2.0 | EtOH | r.t. | 6.0 | trace |
| 13 | CuI (10 mol%) | 1:2.0 | THF | r.t. | 6.0 | 58% |
| 14 | CuI (10 mol%) | 1:2.0 | 1,4-dioxane | r.t. | 6.0 | 25% |
| 15 | CuI (10 mol%) | 1:2.0 | Toluene | r.t. | 6.0 | 18% |
| 16 | CuI (10 mol%) | 1:2.0 | $CH_2Cl_2$ | r.t. | 6.0 | 13% |
| 17 | CuI (5.0 mol%) | 1:2.0 | DMSO | r.t. | 6.0 | 95% |
| 18 | CuI (2.5 mol%) | 1:2.0 | DMSO | r.t. | 6.0 | 95% |
| 19 | CuI (1.0 mol%) | 1:2.0 | DMSO | r.t. | 6.0 | 88% |
| **20** | **CuI (1.0 mol%)** | **1:2.0** | **DMSO** | **r.t.** | **9.0** | **95%** (93%)[c] |
| 21 | CuI (1.0 mol%) | 1:2.0 | DMSO | r.t. | 12 | 95% |
| 22 | None | 1:2.0 | DMSO | r.t. | 9.0 | N.D. |
| 23 | CuI (1.0 mol%) | 1:2.0 | DMSO | 50 °C | 9.0 | 95% |
| 24[d] | CuI (1.0 mol%) | 1:2.0 | DMSO | r.t. | 9.0 | 95% |

[a] Reaction conditions: indoles **1a**, *p*-tolyl isocyanate **2a**, catalyst, solvent (1.0 mL). [b] GC yields base on indole **1a**. [c] Isolated yields base on indole **1a**. [d] The reaction was performed under nitrogen atmosphere.

With the optimal conditions in hand, the scope of the N-carboxamidation was investigated, and results are summarized in Table 2. As shown in Table 2, a variety of indole derivatives could efficiently undergo N-carboxamidation to afford corresponding products in good to excellent yields. Electron-donating (Me, OMe and OBn) and electron-withdrawing (F, Cl, Br and CN) functional groups at the 4, 5, 6 or 7-positions of indole derivatives affected the N-carboxamidation slightly, affording all corresponding products in excellent yields (**3b**-**3j**, 90%-96%). The N-carboxamidation of 4-benzyloxy indole with *p*-tolyl isocyanate proceeded well with good yield (**3e**, 93%), suggesting that the steric effect of substituted group present in the C4 of indole on the reaction was insignificant. The optimized conditions were also suitable for the N-carboxamidation of 1H-indole-6-carbaldehyde and methyl 1H-indole-5-carboxylate, the corresponding products (**3j**, **3k**) were obtained in 91% and 93% yields, respectively. And the functional groups (Me) presenting at the C3 of the indoles only slightly affected the N-carboxamidation (**3l**, 94%). Good yield was also obtained, when 1H-pyrrolo[2,3-*b*] pyridine was treated with *p*-tolyl isocyanate under the optimal conditions (**3m**, 92%). The structures of products **3a** (CCDC:1908851) and **3l** (CCDC:1918544) were determined by X-Ray as shown in Table 2.

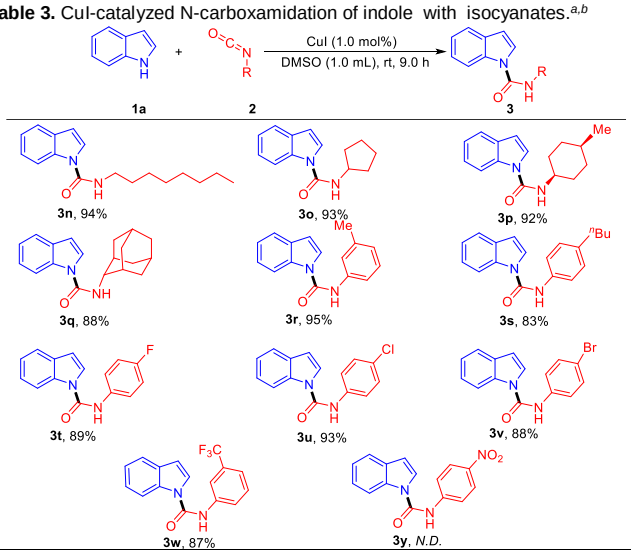
**Table 2.** CuI-catalyzed N-carboxamidation of indole derivatives with *p*-tolyl isocyanate.[a,b]




[a] Reaction conditions: substituted indoles **1** (0.5 mmol), 4-methylphenyl isocyanate **2a** (1.0 mmol), CuI (0.005 mmol), DMSO (1.0 mL), rt, under air atmosphere, 9.0 h. [b] Isolated yields base on substituted indoles.

Next, this approach was applied to examine the viability of various isocyanates under the optimized reaction conditions, and results are summerized in Table 3.

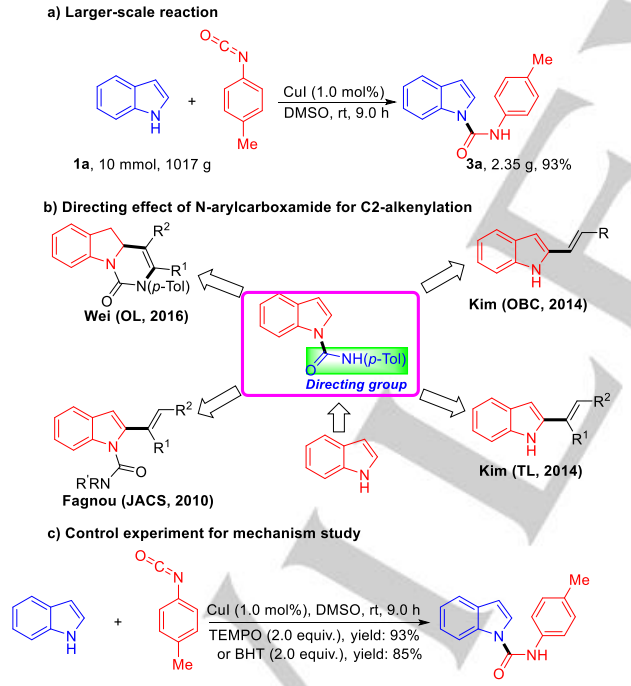
**Table 3.** CuI-catalyzed N-carboxamidation of indole with isocyanates.[a,b]




[a] Reaction conditions: indole **1a** (0.5 mmol), isocyanates **2** (1.0 mmol), CuI (0.005 mmol), DMSO (1.0 mL), rt, under air atmosphere, 9.0 h. [b] Isolated yields base on indole.

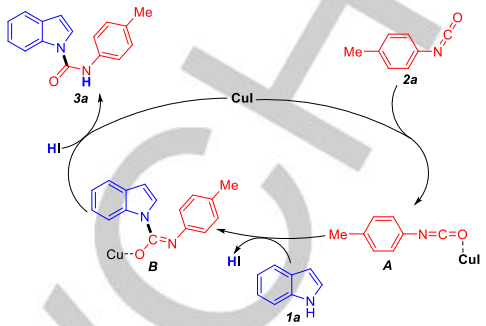
By analyzing Table 3, it concluded that the N-carboxamidation of isocyanates with both aliphatic and aromatic groups gave desired products in good to excellent yields. And the steric hindrance (**3n**-**3q**, 88%-94%) of the aliphatic groups affected the reaction slightly. In addition, the reactions showed good tolerance toward aromatic isocyanates with electron-donating (e.g., *m*-Me and *p*-$^n$Bu) or electron-withdrawing groups (e.g., *p*-F, *p*-Cl, *p*-Br and *m*-$CF_3$), leading to corresponding products in good to excellent yields (**3r**-**3w**, 83%-95%). Unfortunately, no desired product was obtained, when indole was treated with 1-nitro-4-isocyanatobenzene under the above conditions.

The N-carboxamidation can also be carried out on a larger scale reaction, and the desired paroduct (**3a**) were obtained in the yield of 93%, when 10 mmol of indole (**1a**) was treated with 20 mmol of *p*-tolyl isocyanate (**2a**) under the standard conditions (Scheme 2, a). Moreover, the N-arylcarboxamide group of desired product **3a** could be used as efficient directing group for some C2-alkenylation of indoles (Scheme 2, b).[17c-17f] To shed light on the mechanism of the N-carboxamidation, indole (**1a**) was treated with *p*-tolyl isocyanate (**2a**) under standard conditions by using 2.0 equiv. of TEMPO or BHT as radical scavengers (Scheme 2, c), and the desired product (**3a**) was obtained in the yields of 93% and 85% respectively, suggesting that no single-electron transfer process was involved through the whole reaction.




**Scheme 2**. (a) Larger-scale synthesis of **3a**. (b) Directing effect of N-arylcarboxamide for C2-alkenylation. (c) Control experiment for mechanism study.

On the basis of the above experimental results and previous works,[17d,23] a possible mechanism has been depicted in Scheme 3. The first step of the N-carboxamidation is the generation of the intermediate ***A*** by the coordination of *p*-tolylisocyanate (**2a**) with **CuI**. Then, the nucleophilic addition of indole (**1a**) with intermediate ***A*** yields intermediate ***B*** with concomitant loss of a **HI**. Finally, **HI** attacked copper-complex ***B*** to form desired product (**3a**) and **CuI**, which promotes the N-carboxamidation effectively.




**Scheme 3**. Proposed mechanism of the N-carboxamidation.

## Conclusions

In summary, a facile protocol for the synthesis of indole-1-carboxamides *via* the N-carboxamidation of substituted indoles with isocyanates catalyzed by 1.0 mmol% of CuI under mild reaction conditions has been proposed. A broad range of substituted indoles and isocyanates were tolerated, and all the desired products could be obtained in good to excellent yields. Comparing to the reported results, the present strategy has the advantages of high efficiency, simple operation, and mild reaction conditions, providing a convenient and general method for indole-1-carboxamides.

## Experimental Section

Unless noted, all reactions were conducted in Schlenk tubes under an atmosphere of air using commercial solvents. Indole and its derivatives (such as 5-methoxylindole, 5-methylindole, 7-methylindole, 4-benzyloxyindole, 5-fluoroindole, 5-chloroindole, 5-bromoindole, indole-5-methyl formate, 5-nitroindole, indole-5-aldehyde, 3-methylindole, 1H-pyrrolo[2,3-b]pyridine) and isocyanates (ethyl isocyanate, *n*-buthyl isocyanate, *n*-octyl isocyanate, cyclopentyl isocyanate, 2-methylphenyl isocyanate, 4-(*n*-butylphenyl) isocyanate, 4-fluorophenyl isocyanate, 4-chlorophenyl isocyanate, 4-bromophenyl isocyanate, 3-(trifluromethylphenyl) isocyanate, benzyl isocyanate, 4-nitrophenyl isocyanate, trans-4-methycyclohexyl isocyanate, 1-adamantyl isocyanate) were purchased from Energy Company (China) and used as received. Thin-layer chromatography (TLC) analysis was carried out using gel 60 F254 pre-coated plates. Visualization was accomplished with UV lamp or $I_2$ stain. Silica gel 300-400 mesh size was used for column chromatography using the combination of ethyl acetate and hexane as an eluent. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded at 400 MHz (or 500 MHz). Chemical shift was recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). $^1$ HNMR splitting patterns are designated as singlet (s), doublet (d), double doublet (dd), triplet (t) or multiplet (m). Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded

at 100 MHz (or 125 MHz). $^1$H NMR and $^{13}$C NMR spectra were recorded using residue solvent peaks as internal standards ($CHCl_3$, δ = 7.26 ppm for $^1$H, δ = 77.0 ppm for $^{13}$C). Coupling constants are given in hertz. Mass spectra (MS) were obtained using EI mass spectrometer.

**General Procedure for the prepration of compounds 3a−3w**: Substituted indoles (0.5 mmol) and isocyanates (1.0 mmol) were added to a solution of CuI (0.005 mmol) in DMSO (1.0 mL). The resulting solution was stirred at room temperature, under air condition for 9.0 hours. And then, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phase was dried with $Na_2SO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel to afford corresponding products **3a**-**3w**.

***N-(p-tolyl)-1H-indole-1-carboxamide*** **(3a)**[21]: (White amorphous solid, 116.25 mg, 93%); m. p. 120-122 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.6 Hz , 1H), 7.53-7.52 (m, 1H), 7.43-7.30 (m, 4H), 7.24 (t, *J* = 7.4 Hz,1H), 7.16-7.13 (m, 2H), 6.64-6.62 (m, 1H), 2.32 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 149.84, 135.17, 134.64, 134.40, 130.36, 129.75, 124.43, 124.17, 122.60, 121.40, 120.76, 114.10, 107.59, 20.91; MS(EI) *m*/*z* 250 ($M^+$).

***7-methyl-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3b)**[17c]**:** (White amorphous solid, 116.16 mg, 88%); m. p. 126-128 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 3.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.16 (s, 1H), 7.10 (d, *J* = 8.0 Hz, 3H), 7.05-7.03 (m, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 2.46 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.84, 134.61, 134.48, 134.34, 131.24, 129.84, 127.07, 126.80, 123.66, 122.76, 119.74, 119.06, 106.74, 20.88, 20.46; MS(EI) *m*/*z* 264 ($M^+$).

***5-methyl-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3c):** (White amorphous solid, 122.76 mg, 93%); m. p. 125-127 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ. 7.95 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 1H), 7.41 (d, *J* = 3.2 Hz, 1H), 7.30 (t, *J* = 8.4 Hz, 3H), 7.08-7.04 (m, 3H), 6.45 (d, *J* = 3.2 Hz, 1H), 2.40 (s, 3H), 2.27 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 150.16, 134.56, 134.46, 133.53, 132.01, 130.60, 129.65, 125.78, 124.27, 121.14, 121.00, 113.95, 107.20, 21.35, 20.91; MS(EI) *m*/*z* 264 ($M^+$); HRMS calc. for $C_{17}H_{16}N_2O$ 264.1335, found 264.1335.

***5-methoyl-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3d)** [17c]**:** (White amorphous solid, 130.2 mg, 93%); m. p. 128-130 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ. 8.04 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 3.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.00-6.97 (m, 1H), 6.60 (d, *J* = 3.2 Hz, 1H), 3.88 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.76, 149.74, 134.53, 134.46, 131.13, 130.07, 129.74, 124.58, 120.70, 114.98, 113.48, 107.45, 103.60, 55.71, 20.91; MS(EI) *m*/*z* 280 ($M^+$).

***4-(benzyloxy)-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3e):** (White amorphous solid, 165.54 mg, 93%); m. p. 132-134 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ. 7.72 (d, *J* = 8.4 Hz, 1H), 7.54-7.49 (m, 3H), 7.46-7.42 (m, 5H), 7.39-7.36 (m, 1H), 7.30-7.25 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 3.6 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.25 (s, 2H), 2.38 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 152.46, 149.74, 137.10, 136.40, 134.58, 134.40, 129.77, 128.59, 127.96, 127.38, 125.38, 122.79, 121.14, 120.58, 107.22, 104.83, 104.23, 70.08, 20.92, 0.04; MS(EI) *m*/*z* 356 ($M^+$); HRMS calc. for $C_{23}H_{20}N_2O_2$ 356.1525, found 356.1529.

***5-fluoro-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3f):** (White amorphous solid, 123.28 mg, 92%); m. p. 134-136 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ. 8.13 (dd, $J_{F-H}$ = 9.0 Hz, $J_{H-H}$ = 4.5 Hz, 1H), 7.54 (d, *J* = 4.0 Hz, 1H), 7.48 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.26 (dd, $J_{F-H}$ = 8.5 Hz, $J_{H-H}$ = 2.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.06 (td, $J_{F-H}$ = 9.0 Hz, $J_{H-H}$ = 2.5 Hz, 1H), 6.59 (d, *J* = 3.5 Hz, 1H), 2.35(s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.12 (d, $J_{F-C}$ = 237.5 Hz), 149.73, 134.80, 134.22, 131.90, 130.93 (d, $J_{F-C}$ = 10.2 Hz), 129.72, 125.22, 120.96, 115.51 (d, $J_{F-C}$ = 9.2 Hz), 112.48 (d, $J_{F-C}$ = 25.4 Hz), 107.39 (t, $J_{F-C}$ = 3.9 Hz), 106.41 (d, $J_{F-C}$ = 23.5 Hz), 20.89; MS(EI) *m*/*z* 268 ($M^+$); HRMS calc. for $C_{16}H_{13}FNO_2$ 268.1012, found 268.1012.

***5-chloro-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3g)**[17c] (White amorphous solid, 134.9 mg, 95%); m. p. 137-139 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.8 Hz, 1H ), 7.52-7.51 (m, 2H), 7.45 (d, *J* = 3.2 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.50 (d, *J* = 3.6 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.72, 134.87, 134.15, 133.82, 131.23, 129.73, 128.19, 125.03, 124.58, 121.04, 120.68, 115.56, 106.95, 20.90; MS(EI) *m*/*z* 284 ($M^+$).

***5-bromo-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3h)**[17c]**:** (White amorphous solid, 152.52 mg, 93%); m. p. 144-146 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H), 7.47-7.44 (m, 2H), 7.36-7.31 (m, 3H), 7.11-7.07 (m, 2H), 6.50 (s, 1H), 2.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.65, 134.88, 134.14, 131.78, 129.74, 127.22, 124.89, 123.77, 120.99, 115.95, 115.86, 106.84, 20.91; MS(EI) *m*/*z* 328 ($M^+$).

***5-cyano-N-(p-tolyl)-1H-indole-1-carboxamide*** (**3i**): (White amorphous solid, 122.38 mg, 89%). m. p. 130-132 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 3.5 Hz, 1H), 7.52 (d, *J* = 6.0 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 3H), 7.24 (s, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 3.5 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.98, 135.47, 135.24, 133.87, 131.55, 129.91, 127.42, 125.92, 124.39, 120.87, 119.52, 117.83, 106.06, 104.02, 20.92; MS(EI) *m*/*z* 275 ($M^+$); HRMS calc. for $C_{17}H_{13}N_3O$ 275.1059, found 275.1061.

***6-formyl-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3j)** (White amorphous solid, 120.93 mg, 87%). m. p. 132-134 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 10.08 (s, 1H), 8.78 (s, 1H), 8.30 (d, *J* = 3.6 Hz, 1H), 7.75-7.74 (m, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 3.6 Hz, 1H), 2.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 193.41, 149.86, 135.94, 135.52, 135.03, 133.71, 132.75, 130.21, 129.67, 122.83, 121.88, 121.47, 118.55, 106.93, 20.94; MS(EI) *m*/*z* 278 ($M^+$); HRMS calc. for $C_{17}H_{13}N_3O$ 278.1128, found 278.1131.

***methyl-1-(p-tolylcarbamoyl)-1H-indole-5-carboxylate*** **(3k)** (White amorphous solid, 138.60 mg, 90%). m. p. 138-140 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 1.0 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 9.0 Hz, *J* = 1.5 Hz,1H), 7.51 (d, *J* = 4.0 Hz, 1H), 7.39 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 6.64 (d, *J* = 3.5 Hz, 1H), 3.86 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.55, 149.38, 137.92, 134.94, 134.16, 129.88, 129.81, 125.65, 125.16, 124.57, 123.70, 120.80, 114.06, 108.22, 52.09, 20.89; MS(EI) *m*/*z* 308 ($M^+$); HRMS calc. for $C_{18}H_{16}N_2O_3$ 308.1161, found 308.1164.

***5-methyl-N-(p-tolyl)-1H-indole-1-carboxamide*** **(3l)**[17c]**:** (White amorphous solid, 124.08 mg, 94%); m. p. 112-114 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H ), 7.51 (d, *J* = 7.6 Hz, 1H), 7.36-7.22 (m, 6H), 7.12 (d, *J* = 8.0 Hz, 2H), 2.30 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.90, 135.61, 134.63, 134.37, 131.12, 129.68, 124.49, 122.23, 121.05, 120.73, 119.29, 116.95, 114.36, 20.89, 9.64; MS(EI) *m*/*z* 264 ($M^+$).

***N-(p-tolyl)-1H-pyrrolo[2,3-b]pyridine-1-carboxamide*** **(3m):** (White amorphous solid, 115.46 mg, 92%), m. p. 125-127 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H), 8.85-8.34 (m, 1H), 8.07-8.06(m, 1H), 7.95-7.93 (m, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.23-7.20 (m, 3H), 6.58-6.56 (m, 1H), 2.36 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.74, 146.33, 142.25, 135.26, 133.69, 130.10, 129.59, 126.09, 123.64, 120.21, 118.10, 103.34, 20.94; MS(EI) *m*/*z* 251 ($M^+$); HRMS calc. for $C_{15}H_{13}N_3O$ 251.1131, found 251.1138.

***N-heptyl-1H-indole-1-carboxamide*** **(3n):** (White amorphous solid, 127.84 mg, 94%), m. p. 119-120 °C;$^1$H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 3.2 Hz, 1H), 7.46-7.45 (m, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.59-6.58 (m, 1H), 6.70 (s, 1H), 3.45-3.42 (m, 2H), 1.66-1.62 (m, 2H), 1.34-1.23 (m, 10H), 0.88 (t, *J* = 8.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.19, 135.05, 130.22, 124.20, 124.12, 122.19, 121.22, 113.95, 106.81, 41.05, 31.80, 29.77, 29.27, 29.22, 26.96, 22.65, 14.10; MS(EI) *m*/*z* 272 ($M^+$); HRMS calc. for $C_{17}H_{24}N_2O$ 272.1961, found 272.1966.

***N-cyclopentyl-1H-indole-1-carboxamide*** **(3o):** (White amorphous solid, 106.0 mg, 93%), m. p. 120-122 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 3.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.59-6.58 (m, 1H), 5.52 (s, 1H), 2.15-2.10 (m, 2H), 1.78-1.68 (m, 4H), 1.59-1.54 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.69, 134.95, 130.29, 124.33, 124.09, 122.17, 121.29, 113.75, 106.70, 52.84, 33.29, 23.72; MS(EI) *m*/*z* 228 ($M^+$); HRMS calc. for $C_{14}H_{16}N_2O$ 228.1263, found 228.1263.

***N-((1r,4r)-4-methylcyclohexyl)-1H-indole-1-carboxamide*** **(3p)**: (White amorphous solid, 117.76 mg, 92%); m. p. 122-124 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14-8.13 (m, 1H),7.68-7.65 (m, 1H), 7.54-7.53 (m, 1H), 7.38-7.26 (m, 2H), 6.66-6.65 (m, 1H), 5.61 (s, 1H); 3.92-3.83 (m, 1H) 2.20 (d, *J* = 12 Hz ,2H) 1.83 (t, *J* = 8 Hz ,2H) 1.47-1.30 (m, 4H) 1.20-1.14 (m, 2H) 0.10-0.97 (m, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 151.38, 135.03, 130.26, 124.29, 124.06, 122.15, 121.24, 113.91, 106.67, 50.23, 33.80, 33.35, 31.95, 22.13; MS(EI) *m*/*z* 256 ($M^+$); HRMS calc. for $C_{16}H_{20}N_2O$ 256.1648, found 256.1656.

***N-((1R,3S,5r)-adamantan-2-yl)-1H-indole-1-carboxamide*** **(3q)**: (White amorphous solid, 129.36 mg, 88%); m. p. 142-144 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03-7.98 (m, 1H),7.65-7.63 (m, 1H), 7.51-7.47 (m, 1H), 7.36-7.23 (m, 2H), 6.64-6.61 (m,1H), 5.39 (s, 1H), 2.20-2.17 (m, 10 H), 1.79-1.76 (m, 5H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 150.23, 134.87, 130.35, 124.69, 123.89, 121.99, 121.30, 113.63, 106.24, 52.58, 41.91, 36.32, 29.53; MS(EI) *m*/*z* 294 ($M^+$); HRMS calc. for $C_{19}H_{22}N_2O$ 294.1732, found 294.1734.

***N-(m-tolyl)-1H-indole-1-carboxamide*** **(3r):** (White amorphous solid, 118.75 mg, 95%); m. p. 122-124 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H ), 7.59-7.48 (m, 3H ), 7.31-7.16 (m, 5H ), 6.93 (d, *J* = 7.6 Hz, 1H ), 6.58 (s, 1H ), 2.29 (s, 3H ); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.88, 139.22, 136.97, 135.23, 130.36, 129.02, 125.68, 124.44, 124.17, 122.64, 121.37, 121.33, 117.76, 114.23, 107.63, 21.48; MS(EI) *m*/*z* 250 ($M^+$); HRMS calc. for $C_{16}H_{14}N_2O$ 250.1179, found 250.1173.

***N-(4-butylphenyl)-1H-indole-1-carboxamide*** **(3s):** (White amorphous solid, 121.18 mg, 83%); m. p. 128-130 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.49-7.48 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.58-6.57 (m, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.60-1.52 (m, 2H), 1.36-1.27 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.98, 139.71, 135.21, 134.56, 130.35, 129.10, 124.40, 124.21, 122.59, 121.36, 120.86, 114.19, 107.55, 35.07, 33.65, 22.34, 14.00; MS(EI) *m*/*z* 292 ($M^+$); HRMS calc. for $C_{19}H_{20}N_2O$ 292.1648, found 292.1648.

***N-(4-fluorophenyl)-1H-indole-1-carboxamide*** **(3t)** [21]**:** (White amorphous solid, 113.03 mg, 89%); m. p. 136-138 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.41 (dd, $J_{F\text{-}H}$ = 9.0 Hz, $J_{H\text{-}H}$ = 5.0 Hz, 1H), 7.00 (T, *J* = 8.5 Hz, 2H), 6.61 (d, *J* = 3.5 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.85 (d, $J_{F\text{-}C}$ = 243.2 Hz), 149.76, 135.12, 132.94 (d, $J_{F\text{-}C}$ = 2.8 Hz), 130.38, 124.57, 123.94, 122.75, 122.55 (d, $J_{F\text{-}C}$ = 8.0 Hz), 121.49, 115.89 (d, $J_{F\text{-}C}$ = 22.6 Hz), 114.02, 107.92; MS(EI) *m*/*z* 254 ($M^+$).

***N-(4-chlorophenyl)-1H-indole-1-carboxamide*** **(3u):** (White amorphous solid, 125.55 mg, 93%); m. p. 138-140 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H ), 7.63 (d, *J* = 8.0 Hz, 1H ), 7.55-7.51 (m, 1H), 7.50-7.48 (m, 2H), 7.41-7.34 (m, 4H), 7.29-7.27 (m, 1H), 6.70-6.69 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.43, 135.65, 135.08, 130.37, 129.95, 129.31, 124.65, 123.90, 122.84, 121.63, 121.53, 114.03, 108.08; MS(EI) *m*/*z* 270 ($M^+$); HRMS calc. for $C_{15}H_{11}ClN_2O$ 270.0633, found 270.0638.

***N-(4-bromophenyl)-1H-indole-1-carboxamide*** **(3v)** [21] **:** (White amorphous solid, 118.8 mg, 88%); m. p. 142-144 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H ), 7.65 (d, *J* = 7.6 Hz, 1H ), 7.56 (d, *J* = 7.6 Hz, 1H ), 7.53-7.45 (m, 5H), 7.38 (t, *J* =7.8 Hz, 1H), 7.31-7.29 (m, 1H), 6.71 (d, *J* = 3.6 Hz, 1H); $^{13}$C NMR

(100 MHz, $CDCl_3$) δ 149.40, 136.20, 135.09, 132.24, 130.36, 124.65, 123.89, 122.85, 121.94, 121.52, 117.53, 114.06, 108.10; MS(EI) *m*/*z* 270 ($M^+$).

***N-(3-(trifluoromethyl)phenyl)-1H-indole-1-carboxamide* (3w):** (White amorphous solid, 132.24 mg, 87%); m. p. 139-141 °C; $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.74 (s, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.47 (s, 1H), 7.40 (t, *J* = 9.0 Hz, 1H), 7.35-7.33 (m, 1H), 7.27 (td, $J_{F-H}$ = 8.0 Hz, $J_{H-H}$ = 1.0 Hz, 1H), 7.19 (td, $J_{F-H}$ = 8.0 Hz, $J_{H-H}$ = 1.0 Hz, 1H), 6.59 (d, *J* = 3.5 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 149.45, 137.71, 135.13, 131.72 (q, $J_{F-C}$ = 32.6 Hz), 130.40, 129.80, 124.74, 123.75, 123.43, 122.96, 122.67, 121.54, 121.34 (q, $J_{F-C}$ = 3.6 Hz), 117.09 (q, $J_{F-C}$ = 3.6 Hz), 114.11, 108.33; MS(EI) *m*/*z* 304 ($M^+$); HRMS calc. for $C_{16}H_{11}F_3N_2O$ 304.0896, found 304.0894.

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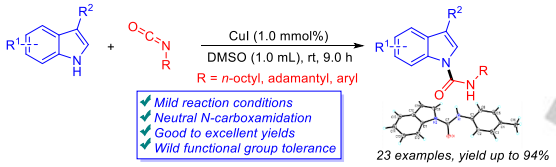
# COMMUNICATION

A general method for synthesis of indole-1-carboxamides was developed *via* copper(I)-catalyzed N-caboxamidation of indoles with isocyanates under mild reaction conditions. This process was scalable and tolerates a wide spectrum of indoles and isocyanates to deliver corresponding products in good to excellent yields, providing a viable synthetic approach to indole-1-carboxamides.




**Neutral N-carboxamidation, Mild conditions, Wild functional group tolerance***

*Jinyang Chen,* Li Hu, Haiying Wang, Lingrong Liu, Binfang Yuan**

***Page No.1 – Page No.4***
**Copper(I)-catalyzed N-Carboxamidation of Indoles with Isocyanates: Facile and General Method for Synthesis of Indole-1-carboxamides**