EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201301607

Ligand-Free Copper-Catalyzed One-Pot Synthesis of Indole-2-carboxylic Esters

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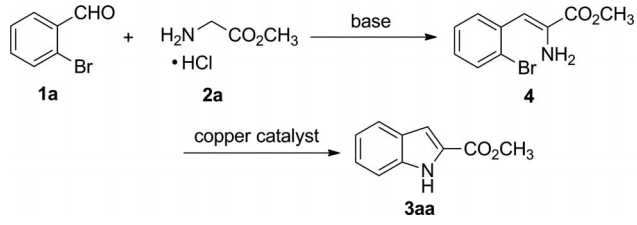
Keywords: Synthetic methods / Domino reactions / Nitrogen heterocycles / Copper

A simple, efficient, and facile synthetic route for the preparation of indole-2-carboxylic esters was described. The cascade reactions of 2-bromobenzaldehyde and glycine ester hydrochloride were promoted by Cu_2O and a base to provide the corresponding products in good yields. Commercially available, inexpensive substrates and reagents were employed under mild reaction conditions in this one-pot operation, which is complementary to existing methods for access to 2-substituted indoles.

Introduction

The indole scaffold as a "biologically privileged structure"[1] represents one of the most significant heterocycles in biologically active and naturally occurring molecules.[2] A great number of methods for the synthesis of indoles have been developed, and this continues to be a very active research area.[3–5] The classic routes for the preparation of indoles include Fischer[6] and Sundberg/Hemetsberger indole synthesis,[4e,7] olefination/cyclization,[8] and some other examples. In this context, transition-metal-catalyzed reactions are the most attractive methods for the facile construction of complicated heterocyclic molecules from readily accessible starting materials under mild conditions.[9–11] Among them, copper catalysis has proven to be increasingly powerful for the synthesis of indoles[12,13] and other nitrogen-containing heterocycles.[14,15] Although much progress has been achieved in the synthesis of indole derivatives, the preparation of some specific substituted patterns remains a challenge.[16] Especially, indole-2-carboxylate esters have been reported to display a wide range of biological functions such as cPLA2 inhibition,[17] histamine H4 receptor antagonism,[18] and HIV-1 inhibition.[19] However, straightforward strategies are relatively rare for the ready and flexible preparation of indole-2-carboxylate esters.[20] While pursuing our research in the area of indole-2-carboxylate synthesis, we found that the Hemetsberger–Knittel reaction, which is associated with dangerous azidoacetates[7,20a] and the Horner–Wadsworth–Emmons olefination/cyclization approach, which has poor atom economy,[11c,20e] are the two most commonly used routes. Cusack et al. described the Cu^I-catalyzed intramolecular cyclization of ene-carbamates to synthesize indole-2-carboxylates.[20e] Nevertheless, ene-carbamates must be first synthesized by Horner–Wadsworth–Emmons condensation of the corresponding aromatic aldehydes and expensive *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester was necessary. Cai et al. demonstrated a ligand-free reaction of ethyl isocyanoacetate and 2-haloaryl aldehydes or ketones to form indole-2-carboxylate esters.[20c] However, the need to handle foul-smelling and costly isocyano compounds is highly undesirable.[21] Another method was reported by Koenig et al. starting from 2-halobenzaldehydes and ethyl benzamidoacetate through a cascade sequence reaction in DMSO.[20b] However, the starting benzamidoacetates are not easy to obtain. Therefore, the development of novel methods to further improve the synthetic efficiency of diversified indole-2-carboxylate esters from inexpensive starting substrates and reagents is still highly desirable. Herein, we present a simple and efficient one-pot synthesis of indole-2-carboxylate esters from 2-bromoarenecarbaldehydes with glycine ester hydrochloride catalyzed by Cu_2O without the addition of any ligand or additive. The reaction pro-



Scheme 1. Possible reaction pathway.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301607.

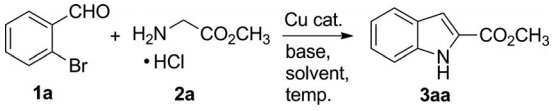
ceeds though a cascade sequence involving an aldol condensation and the Cu-catalyzed intramolecular amidation of aryl bromides (Goldberg reaction, Scheme 1).

Results and Discussion

In our initial studies, the reaction of 2-bromobenzaldehyde (**1a**) with glycine methyl ester hydrochloride (**2a**) was chosen as a model reaction to optimize the reaction conditions. Several parameters including copper catalysts, solvents, and bases were examined at 100 °C under a nitrogen atmosphere (Table 1). First, both monovalent and divalent copper salts, such as CuI, CuBr, CuCl, $CuCl_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, and Cu_2O, were tested in DMF in the presence of Cs_2CO_3 (3 equiv. relative to **1a**) as the base (Table 1, entries 1–7; Tf = trifluoromethanesulfonyl). Cu_2O exhibited the highest activity, for which the target product ethyl indole-2-carboxylate (**3aa**) was obtained in 52% yield (Table 1, entry 5). A control experiment showed that no product was detected by TLC during the reaction process without the addition of a copper catalyst (Table 1, entry 8). Moreover, a new product was observed, which was isolated and identified to be ethyl 2-amino-3-(2′-bromophenyl)acrylate (**4**). This result indicted that the transformation first occurred through a base-promoted aldol condensation and was followed by Cu-catalyzed intramolecular amidation (Scheme 1). Several bases including K_2CO_3, Na_2CO_3, K_3PO_4, and *t*BuOK were then screened, and Cs_2CO_3 was found to be the most effective (Table 1, entries 9–12). The solvent effects were also investigated, and *N*-methylpyrrolidone (NMP) proved to be the best solvent, as it delivered the product in the highest yield (72%; Table 1, entries 13–18). Evaluation of the reaction temperature suggested that 100 °C was the best choice (Table 1, entries 18–20). The yield of desired product **3aa** further improved to 85% if 2 equivalents of Cs_2CO_3 was used (Table 1, entry 22).

The reaction scope was probed under the optimized conditions [Cu_2O (10 mol-%), Cs_2CO_3 (2 equiv.) in NMP under a nitrogen atmosphere at 100 °C], and the results are summarized in Table 2. In general, most of the substrates exam-

Table 1. Optimization of the reaction conditions for the copper-catalyzed cascade synthesis of 1*H*-indole-2-carboxylic methyl ester.[a]

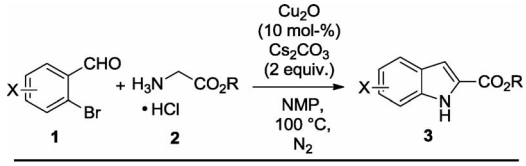


1a 2a 3aa

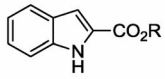
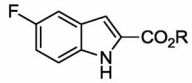
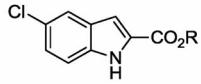
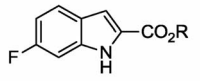
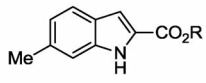
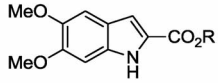
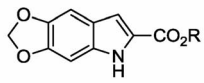
Entry	Catalyst	Base	Solvent	*T* [°C]	Yield [%][b]
1	CuI	Cs_2CO_3	DMF	100	30
2	CuBr	Cs_2CO_3	DMF	100	27
3	CuCl	Cs_2CO_3	DMF	100	37
4	$CuCl_2$	Cs_2CO_3	DMF	100	35
5	Cu_2O	Cs_2CO_3	DMF	100	52
6	$Cu(OAc)_2$	Cs_2CO_3	DMF	100	29
7	$Cu(OTf)_2$	Cs_2CO_3	DMF	100	36
8[c]	–	Cs_2CO_3	DMF	100	–
9	Cu_2O	K_2CO_3	DMF	100	26
10	Cu_2O	Na_2CO_3	DMF	100	15
11	Cu_2O	K_3PO_4	DMF	100	33
12	Cu_2O	*t*BuOK	DMF	100	–
13	Cu_2O	Cs_2CO_3	toluene	100	–
14	Cu_2O	Cs_2CO_3	DCE	100	–
15	Cu_2O	Cs_2CO_3	dioxane	100	–
16	Cu_2O	Cs_2CO_3	DMSO	100	32
17	Cu_2O	Cs_2CO_3	DMA	100	50
18	Cu_2O	Cs_2CO_3	NMP	100	72
19	Cu_2O	Cs_2CO_3	NMP	60	trace
20	Cu_2O	Cs_2CO_3	NMP	80	28
21	Cu_2O	Cs_2CO_3	NMP	120	67
22[d]	Cu_2O	Cs_2CO_3	NMP	100	85

[a] Reaction conditions: 2-bromobenzaldehyde (0.5 mmol), glycine methyl ester hydrochloride (0.75 mmol), catalyst (0.1 mmol), base (1.5 mmol), and solvent (3 mL) under a nitrogen atmosphere. DCE = 1,2-dichloroethane, DMA = dimethylacetamide. [b] Yield of isolated product. [c] In the absence of a copper catalyst. [d] 2 equiv. Cs_2CO_3 was used.

Table 2. Exploration of the substrate scope.[a]



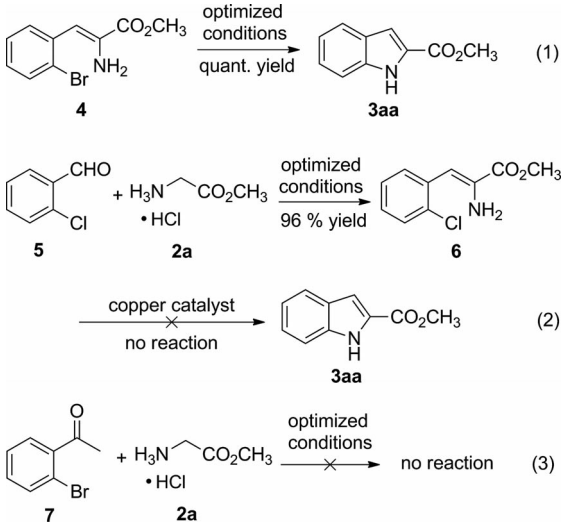
1 2 3

Entry	Product		Yield [%][b]
1		R = Me, **3aa**	85
2		R = Et, **3ab**	82
3		R = Bn, **3ac**	80
4		R = *t*Bu, **3ad**	76
5		R = Me, **3ba**	88
6		R = Et, **3bb**	78
7		R = Bn, **3bc**	74
8		R = *t*Bu, **3bd**	65
9		R = Me, **3ca**	78
10		R = Et, **3cb**	75
11		R = Bn, **3cc**	68
12		R = *t*Bu, **3cd**	62
13		R = Me, **3da**	74
14		R = Et, **3db**	72
15		R = Bn, **3dc**	66
16		R = *t*Bu, **3dd**	61
17		R = Me, **3ea**	65
18		R = Et, **3eb**	66
19		R = Bn, **3ec**	50
20		R = *t*Bu, **3ed**	55
21		R = Me, **3fa**	61
22		R = Et, **3fb**	58
23		R = Bn, **3fc**	60
24		R = *t*Bu, **3fd**	48
25		R = Me, **3ga**	57
26		R = Et, **3gb**	55
27		R = Bn, **3gc**	54
28		R = *t*Bu, **3gd**	35

[a] Reaction conditions: substituted 2-bromobenzaldehyde **1** (0.5 mmol), glycine ester hydrochloride (0.75 mmol), Cu_2O (10 mol-%), Cs_2CO_3 (2 equiv.) in NMP (3 mL) under a nitrogen atmosphere at 100 °C. [b] Yield of isolated product.

ined provided the corresponding indole-2-carboxylate esters products in good to excellent yields. An array of functional groups including alkyl, ether, and halide groups were well tolerated. For various substituted 2-bromobenzaldehydes, the results indicated that electron-poor substrates reacted better than electron-rich ones. The reactions of 5-fluoro-, 5-chloro-, and 4-fluoro-substituted 2-bromobenzaldehydes (i.e., **1b**, **1c**, and **1d**) proceeded smoothly to deliver good results, whereas 4-methyl- and 4,5-dimethoxy-substituted 2-bromobenzaldehydes (i.e., **1e** and **1f**) as well as 6-bromobenzo[1,3]dioxole-5-carbaldehyde (**1g**) only gave moderate yields of the desired products. Notably, the yields decreased slightly as the steric hindrance of the ester was increased.

To verify our proposed reaction mechanism outlined in Scheme 1, **4** was used directly and anticipated product **3aa** was obtained in quantitative yield under the optimized conditions [Scheme 2, Eq. (1)]. Upon replacing 2-bromobenzaldehyde (**1a**) with 2-chlorobenzaldehyde (**5**) under identical reaction conditions, only intermediate ethyl 2-amino-3-(2′-chlorophenyl)acrylate (**6**) was isolated in 96% yield [Scheme 2, Eq. (2)]. This result indicated that the Cu-catalyzed intramolecular amidation did not take place as a result of the lower reactivity of the aryl chloride. At last, in the case of 2-bromoacetophenone (**7**), the reaction did not proceed at all and no new product was noticed [Scheme 2, Eq. (3)].



Scheme 2. Mechanism investigation.

Conclusions

In summary, we have demonstrated a simple, efficient, and facile route for the preparation of indole-2-carboxylic esters through copper-catalyzed cascade reactions of 2-bromobenzaldehyde and glycine ester hydrochloride without the use of any external ligand. Commercially available, inexpensive substrates and reagents were employed under mild reaction conditions in a one-pot operation; this method provides an alternative that can be used to access 2-substituted indoles.

Experimental Section

General Procedure: To a mixture of Cu_2O (7.2 mg, 0.01 mmol) and glycine methyl ester hydrochloride (94.2 mg, 0.75 mmol) was added cesium carbonate (325.6 mg, 1 mmol) and NMP (3 mL). Then, 2-bromobenzaldehyde (0.06 mL, 0.5 mmol) was dropped into the mixture under a nitrogen atmosphere at room temperature. The reaction tube was sealed, and the resulting mixture was heated to 100 °C under a nitrogen atmosphere with good agitation. After 16 h, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and quenched with water (10 mL). After transferring to a separatory funnel with EtOAc and water (30 mL/30 mL), the organic layer was removed. The aqueous layer was extracted with ethyl acetate (2× 5 mL), and the combined organic fraction was washed with water (5 mL) and brine (5 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; EtOAc/petroleum ether, 1:50) to afford desired product **3**.

Supporting Information (see footnote on the first page of this article): Characterization data as well as NMR spectra of the products.

Acknowledgments

The authors are grateful to the National Natural Science Foundation of China (NSFC) (grant numbers 20962010 and 21162012), Jiangxi Provincial Department of Science and Technoloy (for Jiangxi's Key Laboratory of Green Chemistry), and the Science Foundation of Education Department of Jiangxi provice (grant number GJJ10386) for their financial support.

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Received: October 27, 2013
Published Online: December 11, 2013

