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A ligand-free, copper-catalyzed cascade sequence to indole-2-carboxylic esters

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ABSTRACT

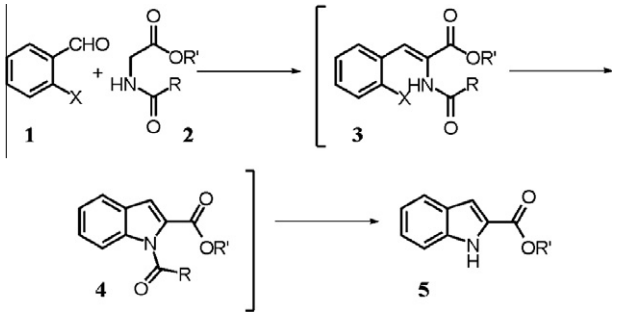
A variety of indole-2-carboxylic esters are accessible in yields up to 61% through a ligand-free, copper-catalyzed reaction of a series of commercially available 2-halo aryl aldehydes with benign glycine amido-esters, including the common reagent ethyl acetamidoacetate. This one-pot, three-reaction format allows ready entry to the desired heterocycles from starting substrates in the reactivity order of iodo > bromo ⩾ chloro substituents. An assortment of functional groups is tolerated, adding to the generality of this methodology.

The indole nucleus, highlighted as a 'biologically privileged structure,'[1] has been targeted with metal-mediated catalysis under a variety of synthetic strategies.[2] A subset of this approach to indoles, copper-catalyzed reactions have proven to be powerful tools to assemble several types of aromatic amines.[3] Though this type of copper chemistry regularly includes a co-ordinating species to accelerate the reaction, some examples of C–N bond formation without the use of such ligands have been reported.[4] In fact, while we were pursuing our research in the area of indole formation, a report was published detailing the ligand-free reaction of ethyl isocyanoacetate and 2-halo aryl aldehydes or ketones.[5] This method, reported by Cai et al., worked under reasonably mild conditions to give the desired heterocyclic systems from an elegant cascade process. However, the transformation benefited from the use of reactive isocyano functionality and the need to handle these foul-smelling and costly compounds is highly undesirable.[6] An alternate coupling partner would be most welcome from a chemical development perspective.

During the course of our work, we became interested in a route to indole-2-carboxylic esters **5** (Scheme 1). In order to avoid using the more direct Hemetsberger-Knittel reaction strategy and the danger associated with azidoacetates[7] or the lower atom economy Horner-Wadsworth-Emmons olefination/cyclization approach,[8] we targeted the indole structures with a Cu(I)-mediated cascade sequence occurring in one-pot under basic conditions. Starting from 2-halobenzaldehydes **1** and ethyl benzamidoacetate **2** (R = Ph, R′ = Et), we were delighted to discover that heterocycle formation proceeded well in this fashion using 2-iodo- or 2-bromobenzaldehyde **1** (X = I or Br) in DMSO at 60 °C (Table 1, entries 1 and 2).

Using CuI with *N,N′*-dimethylethylenediamine,[3a] a frequently used chelating ligand, with **1** (X = I or Br) and **2** (R = Ph, R′ = Et) enabled the reaction to deliver ethyl indole-2-carboxylate **5** in 74% and 55% yields, respectively, as part of a presumed process that included aldol condensation, Cu-catalyzed aryl amidation (Goldberg reaction),[9] and deacylation,[10] with the cascade sequence likely occurring in that order (**1** and **2** → **3** → **4** → **5**, Scheme 1). Curious to see whether the external ligand was necessary for this three-step sequence, we attempted the slurry-based transformation with the more reactive 2-iodobenzaldehyde and ethyl acetamidoacetate **2** (R = Me, R′ = Et) in the absence of the diamine additive. Gratifyingly, this ligand-free reaction proceeded at ambient temperature to give the indole ester **5** in 61% isolated yield, all with a lower catalyst loading (Table 1, entry 4).

In order to explore the scope and limitations of this ligandless reaction, we examined other substrates and conditions. 2-Bromobenzaldehyde provided a slower, but still productive reaction at ambient temperature (47%, Table 1, entry 5) while reacting more efficiently at a moderately elevated temperature (80 °C) to give ethyl indole-2-carboxylate in 53% isolated yield (entry 6). The results with this substrate were particularly encouraging for the generality of such a methodology due to the wide commercial availability of substituted bromobenzaldehydes compared to the iodo-substrates. Meanwhile, 2-chlorobenzaldehyde, which did not react in the presence of the ligand at 60 °C (entry 3), did react in its absence at



Scheme 1. One-pot, three-reaction indole-2-carboxylic ester formation.

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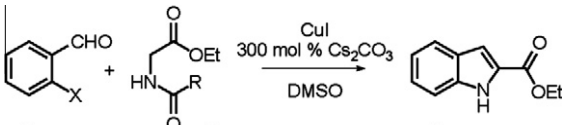
Table 1
Indole-2-carboxylic ester formation



1 2 5

Entry	X=	R=	Cu (mol %)	*T* (°C)	% yield[b]
1[a]	I	Ph	20	60	74
2[a]	Br	Ph	20	60	55
3[a]	Cl	Ph	20	60	ND
4	I	Me	10	25	61
5	Br	Me	20	25	47
6	Br	Me	20	80	53
7	Cl	Me	20	140	16

[a] *N*,*N*′-dimethylethylenediamine (25 mol %) was included as the ligand.
[b] All values are unoptimized, isolated yields from 4.0 mmol reactions with 120 mol % ethyl amidoacetate, 16 h.

Table 2
Screening of conditions with 2-bromobenzaldehyde

Entry	Catalyst	Mol %	Solvent	Mol % base	% yield[a]
1	CuCl	20	DMSO	200	31
2	CuBr	20	DMSO	200	33
3	CuI	20	DMSO	200	50
4	CuI	20	DMSO	150	46
5	CuI	20	DMSO	100	42
6	CuI	10	DMSO	200	50
7	CuI	5	DMSO	200	49
8	CuI	20	DMF	200	45
9	CuI	20	CH_3CN	200	36
10	CuI	20	NMP	200	12
11	CuI	20	EtOH	200	5
12	CuI	20	Toluene	200	21
13	CuI	20	Dioxane	200	19

[a] All unoptimized, isolated yields from 4.0 mmol reactions with 120 mol % ethyl acetamidoacetate, Cs_2CO_3 as base, 80 °C, 16 h.

a higher temperature (140 °C), albeit giving the desired product in only 16% yield from a complex reaction mixture (entry 7). Due to the poor result with the chloro analog and the plentiful supply of bromo-substituted aryl aldehydes, we focused on optimizing the reaction conditions for these latter substrates.

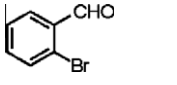
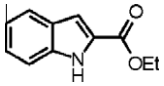
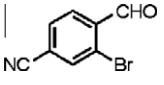
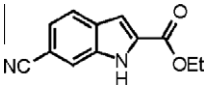
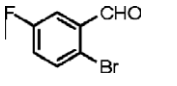
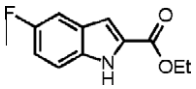
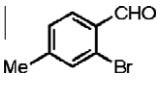
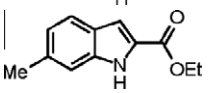
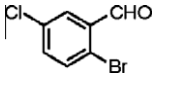
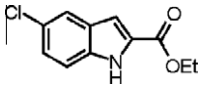
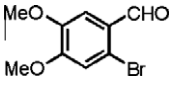
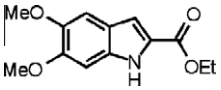
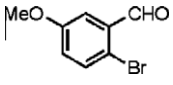
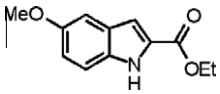
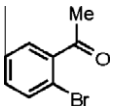
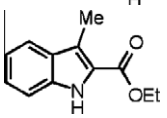
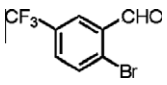
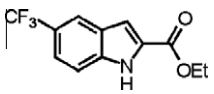
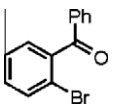
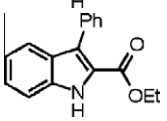
A brief screen of copper complexes showed that CuI was a preferred mediator of the reaction (Table 2, entries 1–3). A screening of bases demonstrated that Cs_2CO_3 was the superior species for this reaction. Other inorganic/insoluble bases, such as K_2CO_3, $KHCO_3$, K_3PO_4, and NaOAc—even when finely ground—as well as organic/soluble species, such as DBU, TMG, EtN(*i*-Pr)$_2$, and pyridine, all failed to provide more than a trace amount of the desired product. Further focus on Cs_2CO_3 showed that levels below 200 mol % were inadequate for the best conversion (entry 3 vs entries 4 and 5). Meanwhile, catalyst loadings of 10 and 5 mol % gave similarly successful results (entries 6 and 7). Not surprisingly, a series of experiments in different media demonstrated that the highly polar aprotic solvents DMSO and DMF were preferred for this transformation (entries 3 and 8 vs entries 9–13).

To further demonstrate the broader generality of this method, we examined a series of 2-bromo-substituted aryl aldehyde substrates with varying substituent groups (Table 3, entries 1–8). With our conditions refined, a series of starting aldehydes were subjected to the reaction in DMSO. All substrates reacted to give the expected indole product in the range of 41–56% yield, encouraging for a three-step cascade process using mild reagents. An array of functionality was tolerated under these conditions, including alkyl, ether, nitrile, and halide groups.

Curiously, aromatic ketones did not react well with this system (Table 3, entries 9 and 10). In the earlier paper using ethyl isocyanoacetate to form indole-2-carboxylic esters, Cai et al. reported that ketones reacted very well, on par with the corresponding aldehydes. It appears that in our case with ethyl acetamidoacetate, the initial aldol condensation does not proceed with the less reactive ketone functionality and thus the crucial intramolecular amidation step cannot occur. This selectivity is indicative of the more benign nature of the glycine amidoesters. Overall, this chemistry presents mild conditions to indole-2-carboxylic esters where the unoccupied 3-position remains available for further derivatization, if necessary.

In conclusion, we have demonstrated that a copper-catalyzed cascade sequence provides ready access to indole-2-carboxylic esters without the use of an external ligand. To our knowledge, this is the first report showing the one-pot formation of indole products

Table 3
CuI-catalyzed formation of various indole-2-carboxylic esters

Entry	Starting material	Desired product	% yield[a]	Entry	Starting material	Desired product	% yield[a]
1			50	6			53
2			53	7			41
3			47	8			55
4			56	9			ND[b,c]
5			44	10			ND[b]

[a] All isolated yields from unoptimized, 4.0 mmol reactions with 120 mol % ethyl acetamidoacetate, 20 mol % CuI, 200 mol % Cs_2CO_3, 80 °C, 16 h.
[b] No desired product was detected from reactions under standard conditions (see previous note) and a majority of the starting material was recovered.
[c] When the reaction was run at 140 °C, the hydrodehalogenated derivative of the starting material, acetophenone, was the major product detected.

starting from 2-halobenzaldehydes and benign glycine amidoesters, particularly ethyl acetamidoacetate, a widely available and inexpensive coupling partner.

Supplementary data

Supplementary data (general experimental and accompanying spectroscopic data for the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.035.

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