Assembly of indole-2-carboxylic acid esters through a ligand-free copper-catalysed cascade process†

Qian Cai,*[a] Zhengqiu Li,[b] Jiajia Wei,[a] Chengyong Ha,[b] Duanqing Pei[a] and Ke Ding*[a]

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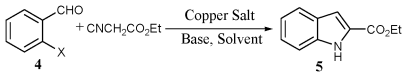
A straightforward synthesis of indole-2-carboxylic esters was developed through a ligand-free copper-catalysed condensation/coupling/deformylation cascade process from 2-halo aryl aldehydes or ketones with ethyl isocyanoacetate. The reactions proceeded well for most of the 2-iodo-, bromo-, and chloro-subtrates under room temperature or mild conditions.

The indole ring systems represent one class of the most abundant and ubiquitous heterocycles in nature.[1] Owing to their structural diversity and remarkable biological functions,[2] great efforts have been devoted to the development of methods for synthesizing indoles during the last decade.[3] The classic approaches include Japp–Klingemann and Fischer indole synthesis,[4] reduction cyclization,[5] metal-catalysed hetero-annulation[6] and others. Recently, copper-catalysed Ullmann-type reactions have been extensively explored[7] to assemble indoles[8–12] and other nitrogen-containing heterocycles.[13] For instance, 2,3-disubstituted indoles have been efficiently synthesized by using copper-catalysed coupling of 2-haloaniline or 2-halotrifluroacetanilides with β-keto esters or amides.[8a,b,9] Despite much progress achieved for the synthesis of indole derivatives, the preparation of some specific substituted patterns remains difficult. It is still highly desirable to develop new methods to further improve the synthetic efficiency for the highly diversified indoles. Indole-2-carboxylic acid derivatives have been reported to display a wide range of biological functions such as cPLA2 inhibition (acid **1**),[14] histamine H4 receptor antagonism (amide **2**),[15] and HIV-1 inhibition (amide **3**) (Fig. 1).[16] But straightforward methods are relatively rare for readily and flexibly preparing indole-2-carboxylic acid derivatives.[12a,b] In this paper, we describe an efficient method for the synthesis of indole-2-carboxylic acid esters from 2-halo aryl aldehydes or ketones catalysed condensation/coupling/deformylation cascade process under mild conditions.

The investigation was initiated by using the reaction of 2-iodo benzenealdehyde with ethyl isocyanoacetate as a model (Table 1). We were pleased to find that 1*H*-indole-2-carboxylate ethyl ester **5** was obtained in 77% yield under the catalysis of 10 mol% CuI. However, only the condensated olefin was isolated as the major byproduct and no desired product was detected with the absence of CuI. Among several copper sources examined, CuBr displayed a similar catalytic potency to that of CuI. Others such as CuCl, Cu_2O and $CuSO_4$ were less active (entries 4–6). Further investigation revealed that DMSO was the optimal solvent (entries 2, 7–10). Condition screening also suggested that both NaOH and Cs_2CO_3 were highly efficient for the coupling reaction of 2-iodo or 2-bromo benzenealdehyde at room temperature (entries 11–15). Although 10 mol% CuI was sufficient to promote the room-temperature cascade process for 2-iodo aryl aldehydes or ketones,[17] 20 mol% CuI was required for the less active 2-bromo substrates to obtain a good yield in 24 h (entries 14, 15). It is worth mentioning that the reaction was significantly accelerated under an elevating temperature of 50 °C (entry 16).

Table 1 Reaction of 2-iodo- or 2-bromo benzenealdehyde with ethyl isocyanoacetate[a]



4 5

Entry	X	Copper Salts	Base	Solvent	Time/h	Yield (%)[b]
1	I	—	NaOH	DMSO	6	n.d.[c,d]
2	I	CuI	NaOH	DMSO	6	77
3	I	CuBr	NaOH	DMSO	6	73
4	I	CuCl	NaOH	DMSO	6	45
5	I	Cu_2O	NaOH	DMSO	6	<10[e]
6	I	$CuSO_4$	NaOH	DMSO	6	<10
7	I	CuI	NaOH	DMF	12	25
8	I	CuI	NaOH	Toluene	12	n.d.[d]
9	I	CuI	NaOH	Dioxane	12	n.d.[d]
10	I	CuI	NaOH	IPrOH	12	n.d.[d]
11	I	CuI	Cs_2CO_3	DMSO	24	81
12	I	CuI	K_3PO_4	DMSO	24	31
13	I	CuI	K_2CO_3	DMSO	24	45
14	Br	CuI	NaOH	DMSO	24	60[f]
15	Br	CuI	Cs_2CO_3	DMSO	24	66[f]
16	Br	CuI	Cs_2CO_3	DMSO	4	70[f,g]

[a] Reaction conditions: Cu salts (0.1 mmol), base (2.0 mmol), 2-iodobenzene aldehyde (1.0 mmol), ethyl isocyanoacetate (1.1 mmol), solvent (1.0 mL), N_2 atmosphere, room temperature. [b] Isolated yields. [c] No copper salt was added. [d] No desired products. [e] 0.05 mmol Cu_2O. [f] 20% CuI was added. [g] 50 °C.

Under optimized conditions, the scope of the cascade process was explored with various 2-bromo aryl aldehydes or ketones.[18] In general, almost all the tested substrates successfully yielded the corresponding products with good to excellent yields (Table 2). Interestingly, obviously better yields were obtained for the ketone substrates. The reaction was well tolerated with many other functional groups such as

[a] *Key Laboratory of Regenerative Biology, Institute of Chemical Biology, Guangzhou Institute of Biomedicine, Health, Chinese Academy of Sciences, Guangzhou International Business Incubator D-10, Guangzhou Science Park, Guangzhou, 510663, China. E-mail: cai_qian@gibh.ac.cn, ding_ke@gibh.ac.cn; Fax: (+)86-20-32290606*
[b] *Key Laboratory of Cellulose and Lignocellulosics Chemistry, Guangzhou Institute of Chemistry, Chinese Academy of Sciences, China*

† Electronic supplementary information (ESI) available: Experimental Section, ^1H NMR, ^{13}C NMR and HRMS spectra of all new compounds. See DOI: 10.1039/b918345k

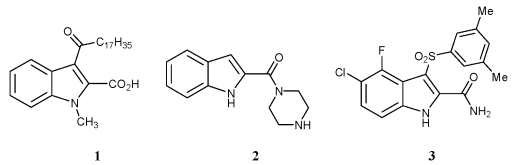
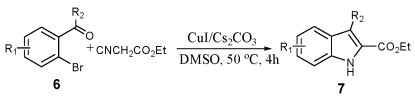


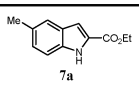
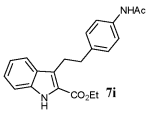
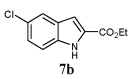
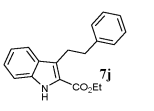
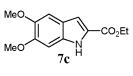
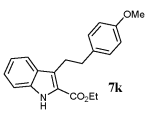
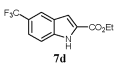
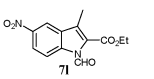
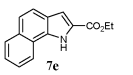
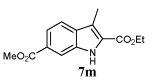
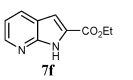
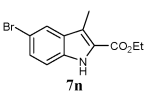
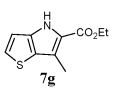
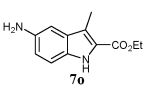
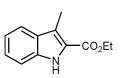
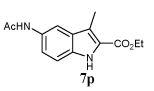
Fig. 1 Structures of representatives of pharmaceutically important indole-2-carboxylic acid derivatives.

carboxylic ester, amide, halo, trifluromethyl group or nitro groups *etc*. (Table 2, entries 4, 13, 14, 15 and 16). When 2,5-dibromobezne acetone was used as the substrate, only 5-bromo-3-methyl indole-2-carboxyliac acid ethyl ester **7n** was isolated (Table 2, entry 14). This may be due to the fact that an intramolecular coupling was much more favoured. The primary amine group or free hydroxyl group was detrimental to the copper-catalysed cascade reaction, but it could be compensated by a simple protection of the free amine or hydroxyl groups (Table 2, entries 11 and 16). It is also noteworthy that the corresponding products **7f** and **7g**, which contained heteroatoms were successfully produced when 2-bromo heteroaryl aldehydes or ketones were applied (Table 2, entries 6, 7).

Although ligand-free conditions have recently been explored in copper-catalysed cascade reactions to construct quinazolinones,[19a] benzimidazoles[19b] and benzothiazoles,[20] there are only a few successful examples for the use of aryl chlorides as substrates.[7] We further investigated the potential reactivity of 2-chloro aryl aldehydes or ketones with ethyl isocyanoacetate. As shown in Table 3, only a trace amount of indole-2-carboxylic acid ester was detected when *o*-chlorobenzene aldehyde **8a** reacted with ethyl isocyanoacetate at room temperature or 50 °C under the optimized combinations. However, a 20% isolated yield was obtained when the temperature was elevated to 80 °C (Table 3, entry 1). Poly-substituted aldehyde **8b** also gave a similar result

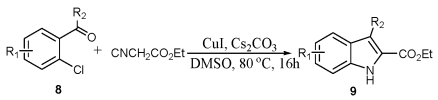
Table 2 Reactions of 2-bromo aryl aldehydes or ketones with ethyl isocyanoacetate[a]

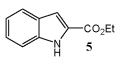
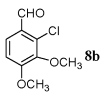
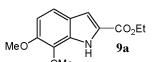
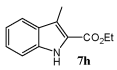
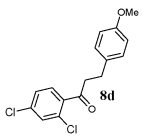
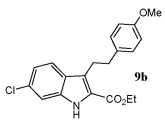
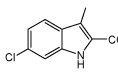
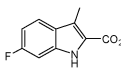
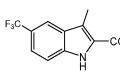
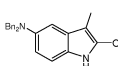
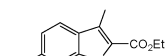
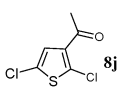
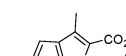


Entry	Product	Yield (%)	Entry	Product	Yield (%)[b]
1		75	9		65
2		63	10		83
3		74	11		85[c]
4		60	12		45[d]
5		72	13		87
6		60	14		90
7		92	15		32[e]
8		94	16		91

[a] Reaction conditions: CuI (0.1 mmol), Cs_2CO_3 (2.0 mmol), aryl bromides (1.0 mmol), ethyl isocyanoacetate (1.1 mmol), DMSO (1.0 mL), N_2 atmosphere, 50 °C, 4 h. [b] Isolated yields. [c] Trace product for the substrate with free hydroxyl on the aryl ring. [d] Performed at room temperature. [e] Similar result was available at room temperature.

Table 3 Reaction of 2-chloro aryl aldehydes and ketones with ethyl isocyanoacetate[a]



Entry	Substrate	Product	Yield (%)[b]
1			20[c]
2			20
3			45
4			56
5			57
6			56
7			60
8			42
9			45
10			66
11			77

[a] Reaction conditions: CuI (0.2 mmol), Cs_2CO_3 (2.0 mmol), aryl chlorides (1.0 mmol), ethyl isocyanoacetate (1.1 mmol), DMSO (1 mL), N_2, 80 °C. [b] Isolated yields. [c] Trace product at R.T. or 50 °C.

(Table 3, entry 2). Similar to that of 2-iodo or 2-bromo substrates, the ketones gave much better results (Table 3, entries 3–11). For example, 45% of ethyl 3-methyl-1*H*-indole-2-carboxylate (**7h**) was obtained when 1-(2-chlorophenyl)-ethanone (**8c**) was used as the substrate. The unusual thienopyrrole carboxyliac acid esters (**9h** and **7g**) were also successfully synthesized by using 1-(2-chlorothiophen-3-yl) ketones as the substrates (Table 3, entries 10 and 11). Of note, thienopyrroles have been used as templates for the discovery of selective human histamine H4 antagonists or other bio-active molecules,[21a] which required several separated steps to construct the core structure.[21]

In summary, an efficient ligand-free copper-catalysed condensation/coupling/deformylation cascade process of 2-halo aryl aldehydes or ketones with ethyl isocyanoacetates was described. The reactions performed well at room temperature or 50 °C for iodo- and bromo-substituted substrates. Chloride substituted substrates also successfully yielded the desired indole-2-carboxylic acid esters with acceptable yields when the temperature was elevated to 80 °C. Furthermore, the reaction displayed excellent functional group compatibility and high chemical selectivity in the presence of a broad range of functional groups. Our report provides a highly straightforward method for the preparation of indole-2-carboxylic acid esters under mild reaction conditions.

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Notes and references

1 For recent reviews of indole containing natural products, see: (*a*) T. Kawasaki and K. Higuchi, *Nat. Prod. Rep.*, 2005, **22**, 761; (*b*) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2004, **21**, 278; (*c*) M. Lounasmaa and A. Tolvanen, *Nat. Prod. Rep.*, 2000, **17**, 175.
2 For a review, see: D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.
3 (*a*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875; (*b*) S. Patil and J. K. Buolamwini, *Curr. Org. Synth.*, 2006, **3**, 477.
4 (*a*) B. Robinson, *The Fiscer Indole Synthesis*, Wiley-Interscience, New York, 1982; (*b*) R. R. Phillips, *Org. React.*, 1959, **10**, 143.
5 (*a*) P. G. Tsoungas and A. I. Diplas, *Curr. Org. Chem.*, 2004, **8**, 1579; (*b*) B. C. G. Söderberg, *Curr. Org. Chem.*, 2000, **4**, 727.
6 (*a*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644; (*b*) I. Ojima, M. Tzamarioudaki, Z. Li and R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635.
7 For recent reviews about copper-catalysed Ullmann-type coupling reactions, see: (*a*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*b*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337–2364; (*c*) J. Lindley, *Tetrahedron*, 1984, **40**, 1433; (*d*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054.
8 (*a*) Y. Chen, Y. Wang, Z. Sun and D. Ma, *Org. Lett.*, 2008, **10**, 625; (*b*) Y. Chen, X. Xie and D. Ma, *J. Org. Chem.*, 2007, **72**, 9329; (*c*) F. Liu and D. Ma, *J. Org. Chem.*, 2007, **72**, 4844.
9 S. Tanimori, H. Ura and M. Kirihata, *Eur. J. Org. Chem.*, 2007, 3977.
10 C. Cacchi, G. Fabrizi and L. M. Parisi, *Org. Lett.*, 2003, **5**, 3843.
11 (*a*) Y. Ohta, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2009, **11**, 1979; (*b*) Y. Ohta, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2008, **10**, 3535.
12 (*a*) C. Barberis, T. D. Gordon, C. Thomas, X. Zhang and K. P. Cusack, *Tetrahedron Lett.*, 2005, **46**, 8877; (*b*) K. Okano, H. Tokuyama and T. Fukuyama, *J. Am. Chem. Soc.*, 2006, **128**, 7136; (*c*) S. Wang, J. Sun, G. Yu, X. Hu, J. O. Liu and Y. Hu, *Org. Biomol. Chem.*, 2004, **2**, 1573.
13 For some recent studies on the syntheses of *N*-heterocycles by using Ullmann-type couplings, see: (*a*) B. Zou, Q. Yuan and D. Ma, *Angew. Chem., Int. Ed.*, 2007, **46**, 2598; (*b*) X. Yuan, X. Xu, X. Zhou, J. Yuan, L. Mai and Y. Li, *J. Org. Chem.*, 2007, **72**, 1510; (*c*) F. Bonnaterre, M. Bois-Choussy and J. Zhu, *Org. Lett.*, 2006, **8**, 4351; (*d*) R. Martin, R. Rodriguez and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7079; (*e*) G. Evindar and R. A. Batey, *J. Org. Chem.*, 2006, **71**, 1802; (*f*) T. Yang, C. Lin, H. Fu, Y. Jiang and Y. Zhao, *Org. Lett.*, 2005, **7**, 4781.
14 (*a*) M. Lehr, *Arch. Pharm.*, 1996, **329**, 386; (*b*) M. Lehr, *J. Med. Chem.*, 1997, **40**, 2694.
15 J. A. Jablonowski, C. A. Grice, W. Chai, C. A. Dvorak, J. D. Venable, A. K. Kwok, K. S. Ly, J. Wei, S. M. Baker, P. J. Desai, W. Jiang, S. J. Wilson, R. L. Thurmond, L. Karlsson, J. P. Edwards, T. W. Lovenberg and N. I. Carruthers, *J. Med. Chem.*, 2003, **46**, 3957.
16 G. La Regina, A. Coluccia, F. Piscitelli, A. Bergamini, A. Sinistro, A. Covazza, G. Maga, A. Samuele, S. Zanoli, E. Novellino, M. Artico and R. Silverstri, *J. Med. Chem.*, 2007, **50**, 5034.
17 We also explored 2-iodobenzene ethyl ketone, which delivers the corresponding product **7h** with 78% yield at room temperature for 6 h.
18 All the aryl bromides tested in Table 2 were also tested at room temperature and deliver the corresponding products with moderate yields from 40–70% in 24 h, while 1-(5-amino-2-bromophenyl) ethanone gave the product **7o** at about 30% at room temperature.
19 (*a*) X. Liu, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 348; (*b*) D. Yang, H. Fu, L. Hu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2008, **73**, 7841.
20 D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong and Y. Jiang, *Angew. Chem., Int. Ed.*, 2009, **48**, 4222.
21 (*a*) J. D. Venable, H. Cai, W. Chai, C. A. Dvorak, C. A. Grice, J. A. Jablonowski, C. R. Shah, A. K. Kwok, K. S. Ly, B. Pio, J. Wei, P. J. Desai, W. Jiang, S. Nguyen, P. Ling, S. J. Wilson, P. J. Dunford, R. L. Thunmond, T. W. Lovenberg, L. Karlsson, N. I. Carruthers and J. P. Edwards, *J. Med. Chem.*, 2005, **48**, 8289; (*b*) W. W. Gale, A. N. Scott and H. R. Snyder, *J. Org. Chem.*, 1964, **29**, 2160; (*c*) R. W. Friesen and J. A. Mancini, *J. Med. Chem.*, 2008, **51**, 4059–4067; (*d*) J. B. Blair, D. Marona-Levicka, A. Kanthasamy, V. L. Lucaites, D. L. Nelson and D. E. Nichols, *J. Med. Chem.*, 1999, **42**, 1106–1111.