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Synthesis of 3-indole derivatives by copper sulfonato Salen catalyzed three-component reactions in water[†]

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An efficient three-component reaction of indole, aldehyde, and malononitrile in water catalyzed by a copper(11) sulfonato Salen complex afforded 3-indole derivatives in good to excellent yields up to 97%.

Multi-component reactions (MCRs), by virtue of their convergence, ease of execution and generally high yields of products, have attracted considerable attention^{1,2} and emerged as a powerful tool in the synthesis of biologically important compounds for reducing operative steps and enhancing synthesis efficiency.³

Indole frameworks have been widely known as prominent agents in compounds of high biological, agrochemical and pharmacological relevance.^{4,5} Several MCR methods have been reported for the synthesis of substituted indoles.⁶ However, the development of simple, efficient and environmentally benign synthetic approaches remains a challenging task, especially for 3-substituted indole derivatives, which represent important building blocks in many synthetic plans.

Normally, MCRs are carried out in organic solvents. Owing to its low cost, non-flammability and environmental friendliness, water is now witnessing a sort of renaissance, which has become of growing interest both in industry and academia.⁷ In continuation of our efforts in aqueous catalysis,⁸ we wish to report here three-component reactions involving indoles, aldehydes, and malononitrile to afford 2-((1*H*-indol-3-yl)(aryl)methyl)malononitriles in water.⁹

Our initial efforts were focused on searching for an efficient catalytic system based on indole, benzaldehyde, and malononitrile as model substrates. As shown in Table 1, among the different transition metals tested in the catalysis with the same ligand L^1 (Scheme 1), Cu(OAc)₂ exhibited higher catalytic ability than others, including Mn(II), Ni(II) and Co(II) (Table 1, entries 1–5). Control experiments indicated the necessity of metal and ligand, only 12% and 23% yields were obtained in the absence

 Table 1
 Screening of catalysts and reaction conditions for the catalytic three-component reaction

CH0 + NC CN	+ Catalyst H ₂ O CCN

Entry	Metal (mol%)	L (mol%)	Base/acid	Yield $(\%)^b$
1	$Mn(OAc)_2(5)$	$L^{1}(5)$	_	63
2	$Ni(OAc)_2(5)$	$L^{1}(5)$	_	49
3	$Co(OAc)_2$ (5)	$L^{1}(5)$		60
4	$Cu(OAc)_2$ (5)	$L^{1}(5)$	_	80
5	CuI (5)	$L^{1}(5)$	_	74
6	$Cu(OAc)_2$ (5)		_	23
7		$L^{1}(5)$	_	12
8	$Cu(OAc)_2$ (5)	$L^{1}(5)$	K_2CO_3	43
9	$Cu(OAc)_2$ (5)	$L^{1}(5)$	K ₃ PO ₄	34
10	$Cu(OAc)_2$ (5)	$L^{1}(5)$	KOAc	70
11	$Cu(OAc)_2$ (5)	$L^{1}(5)$	KHCO ₃	24
12	$Cu(OAc)_2$ (5)	$L^{1}(5)$	KH_2PO_4	90
13	$Cu(OAc)_2$ (5)	$L^{2}(5)$	KH_2PO_4	75
14	$Cu(OAc)_2$ (5)	$L^{3}(5)$	KH_2PO_4	61
15	$Cu(OAc)_2$ (5)	$L^{4}(5)$	KH_2PO_4	78
16	$Cu(OAc)_2$ (5)	$L^{5}(5)$	KH_2PO_4	58
17	$Cu(OAc)_2$ (5)	$L^{6}(5)$	KH_2PO_4	83
18	$Cu(OAc)_2(5)$	$L^{7}(5)$	KH_2PO_4	74
19	$Cu(OAc)_2(5)$	$L^{8}(5)$	KH_2PO_4	79
20^c	$Cu(OAc)_2(5)$	$L^{1}(5)$	KH_2PO_4	63
21	$Cu(OAc)_2$ (2)	$L^{1}(2)$	KH_2PO_4	88
22	$Cu(OAc)_2(1)$	$L^{1}(1)$	KH_2PO_4	87
23	$Cu(OAc)_2$ (0.5)	$L^{1}(0.5)$	KH_2PO_4	82

^{*a*} Unless otherwise specified, all reactions were carried out using benzaldehyde (0.1 mmol), malononitrile (0.11 mmol), indole (0.11 mmol) and 1.0 equiv. of acid/base in water (3 mL) at 60 °C for 6 h. ^{*b*} Isolated yield. ^{*c*} The reaction temperature was 40 °C.

of them (Table 1, entries 6 and 7). Different bases/acids were screened, and the weak acid KH_2PO_4 was indicated to be beneficial to the reaction, while normal bases showed negative effects on the results (Table 1, entries 8–12). Then, a series of water-soluble Salen ligands L^1-L^8 (Scheme 1) were tested.¹⁰ L^1 was found to be superior to the others, with a 90% yield (Table 1, entries 12–19). Further experiments suggested that it was not good for the reaction if the reaction temperature was lower than 60 °C. Finally, when the catalyst loading was dropped from 5% to 2%, 1% and 0.5%, the yields decreased from 90% to 88%, 87% and 82%, respectively

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Scheme 1 Different water soluble Salen ligands used in this work.







Table 2

(continued)

^{*a*} Unless otherwise noted, all reactions were performed with aldehyde (0.1 mmol), malononitrile (0.11 mmol), 1*H*-benzopyrrole (0.11 mmol), Cu–L¹ (1 mol%), KH₂PO₄ (1.0 equiv.), water (3 mL) at 60 °C for 6 h. ^{*b*} Isolated yield.

(Table 1, entries 12, 21–23). Thus, the optimal catalytic conditions consist of 1 mol% Cu(OAc)₂ and L^1 , with KH₂PO₄ as an additive, at 60 °C.

Then, a variety of aldehydes were tested under the optimized reaction conditions, to explore the scope of this methodology. As shown in Table 2, aromatic aldehydes bearing electron-withdrawing substituents seemed to be beneficial to the catalysis, and the steric hindrance seemed to have few effects on the results (Table 2, entries 2–4). Aliphatic aldehydes, such as pivalaldehyde also formed the desired products in 78% yield.

To extend the scope of the methodology, two other kinds of indoles were tested. As shown in Table 3, 2-methyl indole reacted well with various aldehydes and malononitrile to give the corresponding products in excellent yields ranging from 82–96% (Table 3, entries 1–6). Meanwhile, *N*-methyl indole gave slightly lower yields, around 77–83% (Table 3, entries 7–9).

In conclusion, we have developed an efficient three-component reaction of indoles, aldehydes, and malononitrile in a simple one-pot procedure. In this catalytic system, water is



Table 3 Catalytic three-component reaction for other indole

substrates

^{*a*} Unless otherwise noted, all reactions were performed with aldehyde (0.1 mmol), malononitrile (0.11 mmol), indole (0.11 mmol), $Cu-L^1$ (1 mol%), KH_2PO_4 (1.0 equiv.), 3 mL water at 60 °C for 6 h. ^{*b*} Isolated yield.

used in place of commonly-used volatile organic solvents without adding any surfactant. The catalyses can be easily performed in air with low catalyst loading. Furthermore, the tolerance with diverse functional groups makes the present methodology attractive.

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