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Copper-catalyzed synthesis of α,β-unsaturated acylamides via direct amidation from cinnamic acids and *N*-substituted formamides

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A highly effective synthesis of α,β-unsaturated acylamides is reported for the first time via copper-catalyzed direct amidation between readily available cinnamic acids and *N*-substituted formamides. The protocol was easily accessible and practical.

1. Introduction

α,β-Unsaturated acylamides, such as cinnamamides and their derivatives, possess many biological activities such as anticonvulsant, antidepressant, analgesic, antiestrogenic, and antifungal properties, which have been widely applied in agricultural, pharmaceutical, and synthetic chemistry since the 19th century.[1–7] For example, as shown in Fig. 1, *N*-(2-hydroxyethyl)cinnamamide (**A**) was found to show good anticonvulsant activity and also low toxicity.[2] The natural piperidine derivative (**B**) showed good insecticidal activity against the fall armyworm, *Spodoptera frugiperda*.[3] The genus piperaceae molecules (**C**) have been widely studied, due to the biological properties of secondary metabolites from these plants.[4] Compounds (**D**) represent a novel series of potent small molecule inhibitors that not only have excellent in vitro profiles but also have activity in vivo.[5] In addition, in the course of screening compounds for pharmacological action, it was observed that α-phenyl-*N*,*N*-diethyl cinnamamide potentiated nembutal hypnosis in rats.[6] Furthermore, *N*,*N*-dimethylcinnamamide compounds are potentially antidepressant. It is noteworthy that the trans-isomers possess much more pronounced biological activity than do the cis-isomers.[7] Therefore, the essentially pure trans-isomers are preferred.

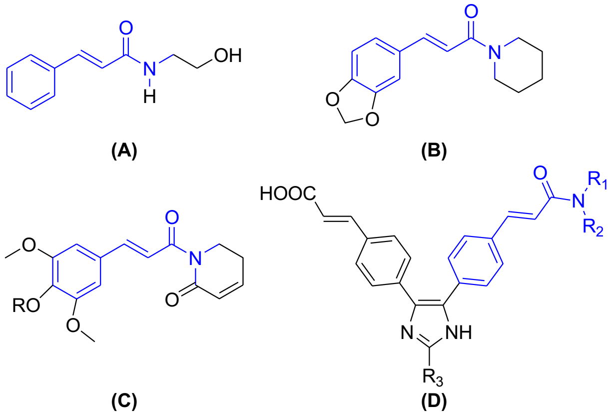

Fig. 1. Examples of molecules containing cinnamamide moiety.

In view of the preparation of cinnamamides, the routine approach is cascade chlorination of cinnamic acid and amination with secondary amines. These chlorination reagents, such as phosphoryl chloride or thionyl chloride, are usually toxic, volatile, irritative, and corrosive. Therefore, a more practical and accessible way to synthesize cinnamamides is highly desirable. Recently, our group reported a copper-catalyzed decarboxylative C–H functionalization between cinnamic acids and benzylic molecules.[8] As a further extension of our work, we have developed an example of copper-catalyzed direct amidation from cinnamic acids and *N*-substituted

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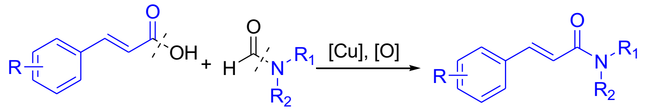
formamides to afford various cinnamamides as shown in Scheme 1. It is noteworthy that in this study, *N*-substituted formamides were used not only as the solvent, but also as an amine source.[9] Actually, *N*,*N*-dimethylformamide (DMF) has been extensively applied to the preparation of amides in different reactions: (a) aminocarbonylation of aryl halides using DMF as an amide source;[10] (b) direct aminocarbonylation of azoles with DMF via C–H activation;[11] (c) tandem chlorination and amidation of carboxylic acids in DMF;[12] (d) direct amidation of alcohols or aldehydes with DMF.[13]



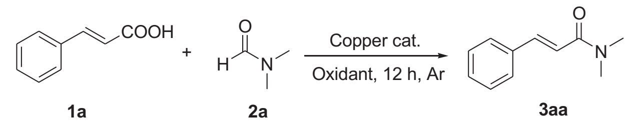
Scheme 1. Our protocol to prepare cinnamamides via coupling between cinnamic acids with *N*-substituted formamides.

2. Results and discussion

Initially, the model reaction of cinnamic acid (0.3 mmol) with 2 mL of DMF was performed in the presence of CuI (20 mol %) and di-*tert*-butyl peroxide (DTBP) (2 equiv) as the oxidant at 140 °C under argon atmosphere and *N*,*N*-dimethylcinnamamide was acquired in the yield of 48% (Table 1, entry 1). Among the copper sources screened, most of the copper salts gave moderate yields (entries 1–12). Notably, $CuSO_4$ and $Cu(OTf)_2$ showed their best catalytic properties for the amidation (entries 11 and 12). In view of the cost of these two salts, we chose readily available $CuSO_4$ as the ideal catalyst. Furthermore, various oxidants were studied, including $(NH_4)_2S_2O_8$, *tert*-butyl hydroperoxide (TBHP), and dicumyl peroxide (DCP) (entries 13–16), and DTBP proved the best. We found that temperatures in the range from 100 to 150 °C did not influence the model reaction greatly (entries 17–20). However, when the reaction was carried out at 80 °C, no reaction was observed (entry 21). Less copper catalyst led to lower yields of the desired product (entries 22 and 23). The reaction performed in air afforded a reduced yield of **3aa** (entry 24). The control experiments showed that $CuSO_4$ or DTBP alone could not catalyze the reaction (entries 25 and 26).

With the optimized conditions in hand, various cinnamic acids were explored for the amidation reactions at 100–140 °C as shown in Table 2. We were pleased to observe that amidation of the cinnamic acids with electron-withdrawing groups such as 4-Cl, 4-F, and 4-CF_3 groups as well as electron-donating groups such as methyl, methoxyl, and isopropyl could offer good to excellent yields of corresponding products (**3ba**–**3la**), and all of the products were the pure trans-isomers. However, it is strange to observe that the reaction of (*E*)-4-nitrocinnamic acid afforded the desired product with mixed isomers (*E*/*Z*=10:1) (**3ma**). 1-Naphthylcrylic acid was also a suitable substrate and the desired product was obtained in 82% yield (**3na**). Subsequently, various heterocyclic acrylic acids were investigated in the reaction. 2-Furylcrylic acid, 2-thienylcrylic acid, and 3-pyridylcrylic acid afforded the corresponding products in moderate to good yields (**3oa**, **3pa**, and **3qa**). When the α-hydrogen of cinnamic acid was substituted by methyl group, the reaction still occurred smoothly (**3ra**).

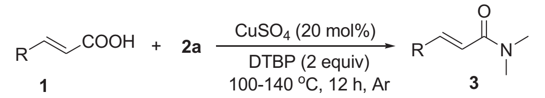
Table 1
Optimization of reaction conditions for the synthesis of cinnamamide (**3aa**)[a]

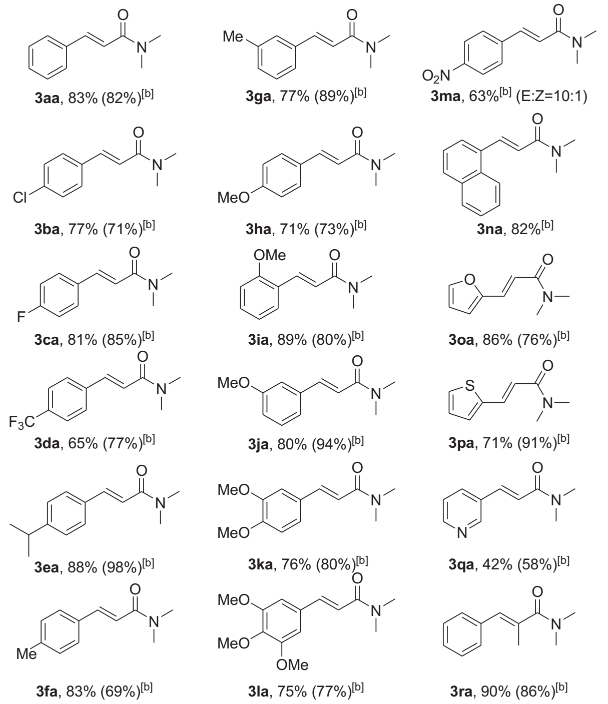


Entry	Copper cat. (mol %)	Oxidant	*T* (°C)	Yield[b] (%)
1	CuI (20)	DTBP	140	48
2	CuBr (20)	DTBP	140	62
3	CuCl (20)	DTBP	140	64
4	Cu_2O (20)	DTBP	140	30
5	Cu powder (20)	DTBP	140	47
6	CuO (20)	DTBP	140	9
7	$CuBr_2$ (20)	DTBP	140	41
8	$CuCl_2\cdot 2H_2O$ (20)	DTBP	140	45
9	$Cu(OAc)_2\cdot H_2O$ (20)	DTBP	140	62
10	$Cu(acac)_2\cdot H_2O$ (20)	DTBP	140	56
11	$CuSO_4$ (20)	DTBP	140	82
12	$Cu(OTf)_2$ (20)	DTBP	140	82
13	$CuSO_4$ (20)	$(NH_4)_2S_2O_8$	140	40
14	$CuSO_4$ (20)	TBHP	140	75
15	$CuSO_4$ (20)	BQ	140	ND
16	$CuSO_4$ (20)	DCP	140	58
17	$CuSO_4$ (20)	DTBP	150	80
18	$CuSO_4$ (20)	DTBP	130	75
19	$CuSO_4$ (20)	DTBP	120	78
20	$CuSO_4$ (20)	DTBP	100	83
21	$CuSO_4$ (20)	DTBP	80	NR
22	$CuSO_4$ (10)	DTBP	100	50
23	$CuSO_4$ (5)	DTBP	100	40
24[c]	$CuSO_4$ (20)	DTBP	100	71
25	—	DTBP	100	NR
26	$CuSO_4$ (20)	—	100	NR

[a] Catalytic conditions: cinnamic acid (**1a**) (0.3 mmol), copper cat., DMF (2 mL), oxidant (2 equiv), 80–140 °C, 12 h, Ar.
[b] Isolated yield based on cinnamic acid.
[c] In air.

Table 2
Copper-catalyzed amidation between different cinnamic acids (**1**) with DMF (**2a**)[a]





3aa, 83% (82%)[b]
3ga, 77% (89%)[b]
3ma, 63%[b] (E:Z=10:1)
3ba, 77% (71%)[b]
3ha, 71% (73%)[b]
3na, 82%[b]
3ca, 81% (85%)[b]
3ia, 89% (80%)[b]
3oa, 86% (76%)[b]
3da, 65% (77%)[b]
3ja, 80% (94%)[b]
3pa, 71% (91%)[b]
3ea, 88% (98%)[b]
3ka, 76% (80%)[b]
3qa, 42% (58%)[b]
3fa, 83% (69%)[b]
3la, 75% (77%)[b]
3ra, 90% (86%)[b]

[b] 140 °C, 12 h.
[a] Catalytic conditions: cinnamic acid (**1a**) (0.3 mmol), DMF (**2a**) (2 mL), $CuSO_4$ (20 mol %), DTBP (2 equiv), 100 °C, 24 h, Ar. Isolated yield based on cinnamic acid. All of the products were pure trans-isomers.

Then, we examined a series of *N*-substituted formamide derivatives and the results were listed in Table 3. It was showed that