Research Paper

Journal of Chemical Research

Journal of Chemical Research
1–5

DOI: 10.1177/1747519820950222
journals.sagepub.com/home/chl
SAGE

Cu-catalyzed cross-coupling of methyl ketones and pyridin-2-amines for the synthesis of N-(2-pyridyl)-α-ketoamides

Ali Chen[1], Daji Yang[1], Yue Yu[1], Xiang Liu[1], Chuixiong Rao[1], Haoming Lin[1] and Pengfeng Guo[1,2]

Abstract

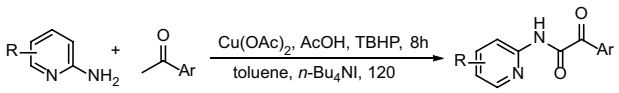
An efficient copper-catalyzed strategy for the synthesis of α-ketoamides via cross-coupling of methyl ketones and pyridin-2-amines is described. This transformation has provided a simple process for the formation of C−N and C=O bonds to prepare α-ketoamides, which are important substrates and intermediates for the preparation of fine chemicals. The reaction mechanism is investigated, which suggests that the reaction proceeds via a radical pathway.

Graphical abstract

Keywords

cross-coupling, Cu-catalyzed, methyl ketones, pyridin-2-amines, α-ketoamides

Date received: 30 May 2020; accepted: 23 July 2020



Introduction

Amides are very common in nature and technology as structural materials, and exhibit a wide range of biological functionalities.[1] Many drugs contain amide moieties, including paracetamol, amoxicillin, penicillin, zolpidem, and cefpimizole (Figure 1). Such compounds have attracted the attention of scientists because of their important applications in pharmaceuticals, natural products, agrochemicals, and biologically active molecules.[2] Therefore, it is not surprising that significant effort has been directed toward developing synthetic transformations[3–5] for the preparation of amides. Several classic and successful synthetic approaches, such as the Beckmann, Ritter, Ugi, and Staudinger reactions, have been developed for the synthesis of amide derivatives. Recently, transition-metal-catalyzed reactions have become powerful tools for the formation of carbon-nitrogen bonds to prepare amides.[6–25] Ahmed and colleagues[26] reported a unique dimethyl sulfoxide (DMSO)-promoted oxidative amidation approach for synthesis of α-ketoamides from 2-oxoaldehydes and aliphatic amines (Scheme 1(a)); Zhang and Wang[27] and Wan and colleagues[28] independently developed a facile TBHP/I_2-promoted oxidative coupling reaction of acetophenones with aliphatic amines for the synthesis of α-ketoamides (Scheme 1(b)); Kaliappan and colleagues[29] has described a one-pot copper-catalyzed biomimetic route to N-heterocyclic amides from methyl ketones and pyridin-2-amines (Scheme 1(c)). Although numerous investigations in this field have been conducted, the development of a new strategy is still highly desirable for the construction of α-ketoamides, which are an important class of amide compounds with the general structure ($R^1COCONR_2$).

Very recently, we have developed approaches for the formation of C–C, C–N, and C–O bonds to synthesize heterocycles.[30–38] Our current interest is focused on the formation of C–N and C–O bonds in order to synthesize

[1]School of Chemistry and Chemical Engineering, Guangdong Pharmaceutical University, Zhongshan, P.R. China
[2]Guangdong Cosmetics Engineering & Technology Research Center, Guangdong Pharmaceutical University, Zhongshan, P.R. China

Corresponding author:
Pengfeng Guo, School of Chemistry and Chemical Engineering, Guangdong Pharmaceutical University, Zhongshan 528458, P.R. China.
Email: guopengfeng@163.com

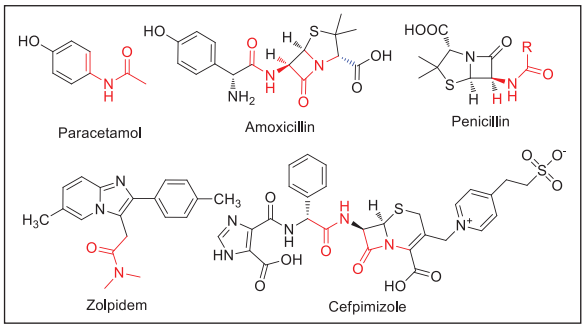
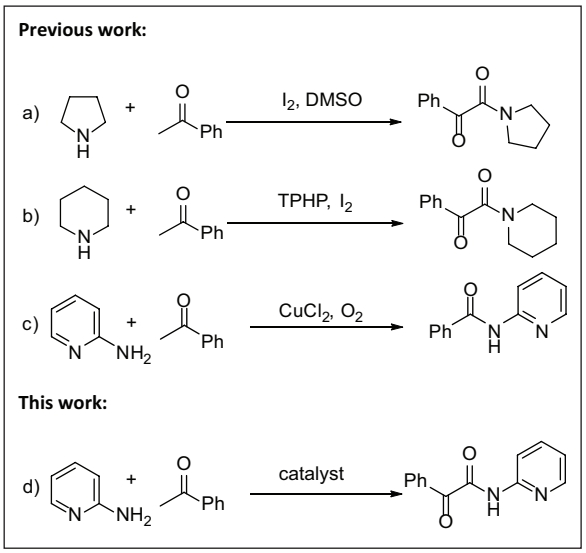


Figure 1. Important amides.



Scheme 1. Methods for the synthesis of amides.

N-(2-pyridyl)-α-ketoamides from methyl ketones and pyridin-2-amines (Scheme 1(d)).

Results and discussion

In our initial study, pyridin-2-amine (**1a**) and acetophenone (**2a**) were chosen as model substrates to optimize the reaction conditions. The results are summarized in Table 1. In a typical procedure, **1a** (0.5 mmol), **2a** (0.6 mmol), $Cu(OAc)_2$ (5 mol%), and AcOH (5 mol%) were stirred in DMSO using O_2 as the oxidant at 120°C for 8 h. Interestingly, the products **3a** and **4a** were formed in 18% and 32% yields, respectively (Table 1, entry 1). We next attempted to improve the yield of **3a** by using different catalysts. Thus, as catalysts $CuCl_2$, $Cu(OTf)_2$, CuI, and CuBr were employed (Table 1, entries 2–5). Among them, $Cu(OAc)_2$ was the most efficient catalyst. Subsequently, our investigation focused on the synthesis of **3a** by testing various additives. The product **3a** was formed in 14% and 11% yields by using trifluoroacetate (TFA) or tosylic acid (TsOH) (Table 1, entries 6 and 7). To our delight, an improved yield was obtained by the addition of KI and acetic acid (AcOH) to the reaction (Table 1, entry 8). When *n*-Bu_4NI, or *n*-Bu_4NBr with AcOH were employed as co-additives, product **3a** was obtained in 34% and 26% yields, respectively (Table 1, entries 9 and 10). Having gained some crucial insight into the effect of various additives, further studies were performed to explore the effect of the oxidant. Interestingly, TBHP proved to be the best oxidant, and the desired product **3a** was obtained in moderate yield, whereas other oxidants such as DDQ and $K_2S_2O_8$ disfavored the reaction to varying degrees (Table 1, entries 11–13). The effect of solvents was then tested. With the results indicating that toluene was the most effective in comparison with DMSO, dioxane, dimethyl formamide (DMF), and dimethyl acetamide (DMA) (Table 1, entries 14–17).

Based on the optimized reaction conditions, the substrate scope of the oxidative coupling reaction for the synthesis of α-ketoamides was then studied. The results are described in Table 2. The oxidative coupling reaction of **1a** with various methyl ketones was initially examined. The reactions were smooth under the optimized conditions in most cases and gave the α-ketoamides in moderate yields. Meanwhile, products **4a–i** were also formed in poor yields. A variety of substituents, such as 4-Et, 3-Me, 2-Me, 4-*n*Bu, 3,4-dimethoxy, 3,4-dimethyl, and 4-F, on the benzene ring of the methyl ketones were well-tolerated for the synthesis of the **3** compounds under the optimized conditions. However, the byproduct **4e** was formed in 43% yield, while only a trace of **3e** was detected. Subsequently, substituted pyridin-2-amines were tested. The product **3j–n** were afforded in 53%–73% yields.

Mechanism

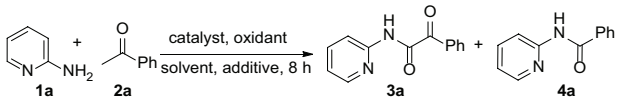
To gain insight into the mechanism of the Cu-catalyzed transformation, control experiments were performed. To prove that an organic radical species was involved in the reaction, we carried out the radical trapping reactions by adding a radical-trapping reagent (TEMPO) (Scheme 2(a)). The result indicated that the reaction had been inhibited and that a radical process was involved in this Cu-catalyzed strategy. In addition, the reaction of **1a** with 2-oxo-2-phenylacetaldehyde was also carried out and the products were detected by gas chromatography–mass spectrometry (GC-MS) analysis. It was found that 2-oxo-2-phenylacetaldehyde may form as an intermediate in the reaction (Scheme 2(b)). Product **3a'** with an ^{18}O in the carbonyl group was not observed in the presence of $H_2{}^{18}O$ (Scheme 2(c)). This result indicated that the oxygen source (CON) of the product was O_2 rather than H_2O.

On the basis of the above experiment results, a plausible mechanism is described in Scheme 3. Initially, radical intermediate **A** is generated from **2a** via a single electron transfer (SET) oxidation in the presence of the Cu(II) species and TBHP, which was further oxidized to intermediate **B**. Next, intermediate **C** is formed by protonation of intermediate **B**; subsequent nucleophilic attack of 1a gave the intermediate **D**. Finally, intermediate **D** underwent dehydrogenation oxidation to give the product **3a**.[39,40]

Conclusions

In conclusion, we have developed a novel and straightforward Cu-catalyzed reaction to prepare amides via oxidative coupling of methyl ketones and pyridin-2-amines. This strategy represents a simple process for the formation

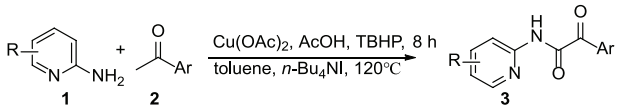
Table 1. Optimization of the reaction conditions.[a].

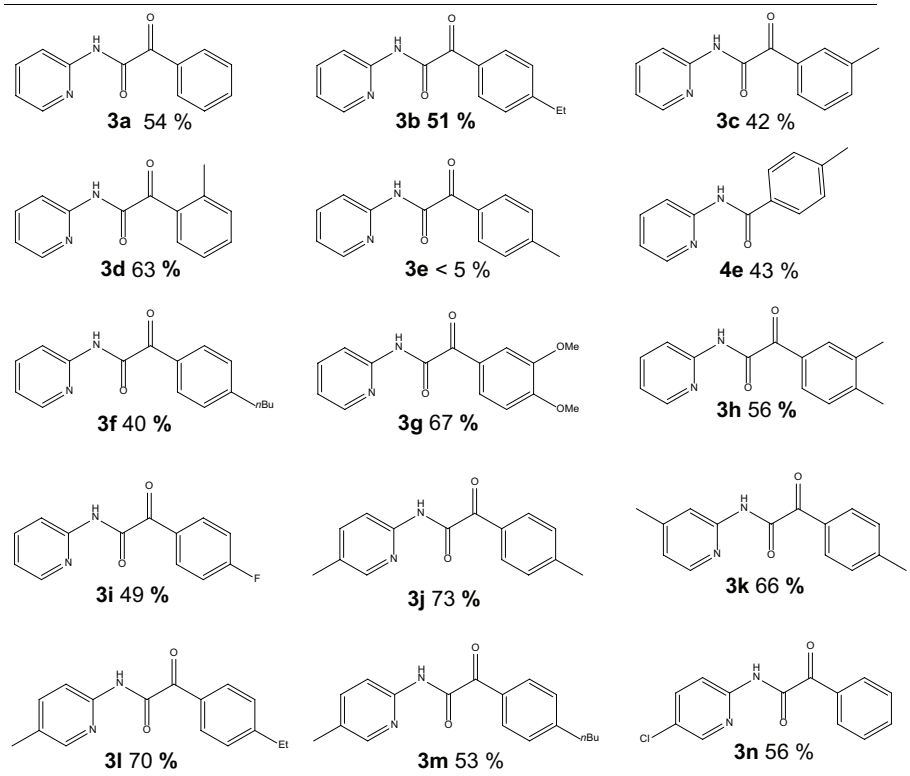


Entry	Catalyst	Additive	Oxidant	Solvent	Yield (%)[b]	
					3a	**4a**
1	$Cu(OAc)_2$	AcOH	O_2	DMSO	18	32
2	$CuCl_2$	AcOH	O_2	DMSO	<5	19
3	$Cu(OTf)_2$	AcOH	O_2	DMSO	trace	16
4	CuI	AcOH	O_2	DMSO	–	–
5	CuBr	AcOH	O_2	DMSO	–	–
6	$Cu(OAc)_2$	TFA	O_2	DMSO	14	27
7	$Cu(OAc)_2$	TsOH	O_2	DMSO	11	30
8	$Cu(OAc)_2$	AcOH/KI	O_2	DMSO	22	25
9	$Cu(OAc)_2$	AcOH/*n*-Bu_4NI	O_2	DMSO	34	13
10	$Cu(OAc)_2$	AcOH/*n*-Bu_4NBr	O_2	DMSO	26	<10
11	$Cu(OAc)_2$	AcOH/*n*-Bu_4NI	TBHP	DMSO	47	20
12	$Cu(OAc)_2$	AcOH/n-Bu_4NI	DDQ	DMSO	trace	trace
13	$Cu(OAc)_2$	AcOH/*n*-Bu_4NI	$K_2S_2O_8$	DMSO	trace	trace
14	$Cu(OAc)_2$	AcOH/*n*-Bu_4NI	TBHP	toluene	62	11
15	$Cu(OAc)_2$	AcOH/*n*-Bu_4NI	TBHP	dioxane	33	15
16	$Cu(OAc)_2$	AcOH/*n*-Bu_4NI	TBHP	DMF	36	18
17	$Cu(OAc)_2$	AcOH/*n*-Bu_4NI	TBHP	DMA	31	23

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (5 mol%), additive (5 mol%), oxidant (2.0 equiv), solvent (2 mL), 120°C, 8 h.
[b]Determined by gas chromatography (GC) analysis.

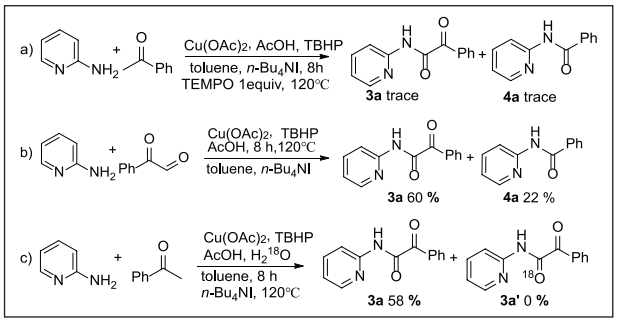
Table 2. Cu-catalyzed synthesis of amides.[a]



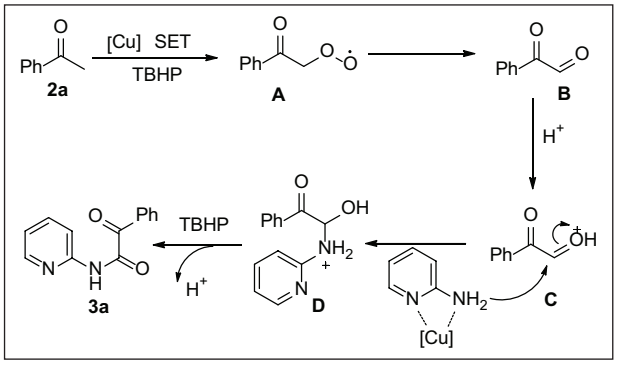


[a] Isolated yields

[a]Isolated yields.



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

of C−N and C=O bonds and provides a new route for the synthesis of α-ketoamides which are common structural motifs in natural products and pharmaceuticals. The mechanism was investigated, which suggested that the reaction occurs via a radical pathway. Further studies on the applications and development of amides are underway in our laboratory.

Experimental section

Commercially available chemicals were purchased from commercial sources and used without further purification. Fourier transform infrared spectra (FTIR) were recorded on a Perkin-Elmer Spectrum 100 Series with pressed KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer (100 MHz for carbon). Mass spectra recorded were obtained on an electrospray ionization mass spectrometry (ESIMS). Elemental analyses were performed with an elemental analyzer. GC-MS was obtained using electron ionization. Thin-layer chromatography (TLC) was performed using commercially prepared 100–400 mesh silica gel plates.

Synthesis of **3a** according to the following procedure: A 25–mL schlenk tube was charged with a stirring bar, and added pyridin-2-amine 1a (0.5 mmol, 1.0 equiv), acetophenone 2a (0.6 mmol, 1.2 equiv), TBHP (2.0 equiv), n-Bu_4NI(5 mol%), AcOH (5 mol%), $Cu(OAc)_2$ (5 mol%), and toluene (2 mL). The reaction was allowed to stir at 120°C until the complete consumption of **3a** was monitored by TLC analysis. The reaction mixture was purified by TLC silica gel plate (eluent: petroleum ether: ethyl acetate, V: V = 4: 1) and then extracted with EtOAc. The solvents were dried in vacuo to afford the pure product.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was financially supported by the National Natural Science Foundation of China (21302023), the Innovation and Strong School Project of Guangdong Pharmaceutical University (2014KTSCX120, 2015cxqx212), the Special Fund for Science and Technology Innovation Strategy of Guangdong Province (pdjh2020a0299), the Project of Innovation for Enhancing Guangdong Pharmaceutical University, Provincial Experimental Teaching Demonstration Center of Chemistry & Chemical Engineering, and Special Funds of Key Disciplines Construction from Guangdong and Zhongshan Cooperating.

ORCID iD

Pengfeng Guo https://orcid.org/0000-0002-9781-3248

Supplemental material

Supplemental material for this article is available online.

References

1. Cupido T, Tulla-Puche J, Spengler J, et al. *Curr Opin Drug Discov Develop* 2007; 10: 768–783.
2. Yamada R, Cao X, Butkevich AN, et al. *J Med Chem* 2011; 54: 2902–2914.
3. Pattabiraman VR and Bode JW. *Nature* 2011; 480: 471–479.
4. Allen CL and Williams JM. *Chem Soc Rev* 2011; 40: 3405–3415.
5. García-Álvarez R, Crochet P and Cadierno V. *Green Chem* 2013; 15: 46–66.
6. Jiang H, Liu B, Li Y, et al. *Org Lett* 2011; 13: 1028–1031.
7. Gunanathan C, Ben-David Y and Milstein D. *Science* 2007; 317: 790–792.
8. Ghosh SC, Muthaiah S, Zhang Y, et al. *Adv Synth Catal* 2009; 351: 2643–2649.
9. Gnanaprakasam B, Balaraman E, Ben-David Y, et al. *Angew Chem Int Ed* 2011; 50: 12240–12244.
10. Srimani D, Balaraman E, Hu P, et al. *Adv Synth Catal* 2013; 355: 2525–2530.
11. Zweifel T, Naubron JV and Grützmacher H. *Angew Chem Int Ed* 2009; 48: 559–563.
12. Vanjari R, Guntreddi T and Singh KN. *Organ Lett* 2013; 15: 4908–4911.
13. Song Q, Feng Q and Yang K. *Organ Lett* 2014; 16: 624–627.
14. Ghosh SC, Ngiam JSY, Seayad AM, et al. *J Organ Chem* 2012; 77: 8007–8015.
15. Bai C, Yao X and Li Y. *ACS Catal* 2015; 5: 884–891.
16. Li Y, Zhu F, Wang Z, et al. *ACS Catal* 2016; 6: 5561–5564.
17. Chandgude AL and Dömling A. *Organ Lett* 2016; 18: 6396–6399.

18. Ren L, Li X and Jiao N. *Organ Lett* 2016; 18: 5852–5855.
19. Ghosh S and Jana CK. *Organ Lett* 2016; 18: 5788–5791.
20. Zhang Z, Su J, Zha Z, et al. *Chem Commun* 2013: 49: 8982–8984.
21. Zultanski SL, Zhao J and Stahl SS. *J Am Chem Soc* 2016; 138: 6416–6419.
22. Mane RS and Bhanage BM. *J Organ Chem* 2016; 81: 1223–1228.
23. Shicheng S, Steven PN and Michal S. *Acc Chem Res* 2018; 51: 2589–2599.
24. Sharma AK, Jaiswal A and Singh KN. *Organ Biomol Chem* 2019; 17(42): 9348–9351.
25. Lv Y, Bao P, Yue H, et al. *Green Chem* 2019; 21(22): 6051–6055.
26. Mupparapu N, Khan S, Battula S, et al. *Organ Lett* 2014; 16: 1152–1155.
27. Zhang X and Wang L. *Green Chem* 2012; 14: 2141–2145.
28. Wei W, Shao Y, Hu H, et al. *J Organ Chem* 2012; 77: 7157–7165.
29. Subramanian P, Indu S and Kaliappan KP. *Organ Lett* 2014; 16: 6212–6215.
30. Cao H, Lei S, Li N, et al. *Chem Commun* 2015; 51: 1823–1825.
31. Cao H, Liu X, Liao J, et al. *J Organ Chem* 2014; 79: 11209–11214.
32. Cao H, Liu XH, Zhao L, et al. *Organ Lett* 2014; 16: 146–149.
33. Cao H, Zhan HY, Cen JH, et al. *Organ Lett* 2013; 15: 1080–1083.
34. Cao H, Zhan HY, Lin YG, et al. *Organ Lett* 2012; 14: 1688–1691.
35. Lei S, Cao H, Chen L, et al. *Adv Synth Catal* 2015; 357: 3109–3144.
36. Lei S, Chen G, Mai Y, et al. *Adv Synth Catal* 2016; 358: 67–73.
37. Lei S, Mai Y, Yan C, et al. *Organ Lett* 2016; 18: 3582–3585.
38. Wang C, Lei S, Cao H, et al. *J Organ Chem* 2015; 80: 12725–12732.
39. Cao H, Jiang H, Yao W, et al. *Organ Lett* 2009; 11: 1931–1933.
40. Becker H-D, Bjórk A and Adler E. *J Organ Chem* 1980; 45: 1596–1600.