



Original article

Copper-catalyzed amide bond formation from formamides and carboxylic acids

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ARTICLE INFO

Article history:

Received 15 May 2014

Received in revised form 30 June 2014

Accepted 14 July 2014

Available online 16 September 2014

Keywords:

Amides

Formamides

Carboxylic acids

Copper

Catalysis

ABSTRACT

A highly efficient copper-catalyzed approach to form amide bonds from formamides and carboxylic acids was developed. This protocol shows broad substrate scopes and high yields in the presence of 1 mol% catalyst and 4.0 equiv. formamides.

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1. Introduction

As one of the most common chemical linkages, the amide bond is ubiquitous in a broad range of organic molecules. By linking amino acids to form proteins, it represents the main chemical bonds in biological system and plays a crucial role in the sustenance of life [1]. Moreover, the amide bond is widely present in drug molecules, agrochemicals, materials, and other natural products [2]. Although a vast array of methods are available for the formation of amide bonds, the most common one involves the coupling reaction of activated carboxylic acids with amines [3]. For this method, carboxylic acids should be preactivated by transforming the hydroxyl groups of the acids into good leaving groups. Unfortunately, the activation of carboxylic acids requires the use of a stoichiometric amount of coupling reagents, and the reactions produce large quantities of potentially hazardous chemical wastes [4]. Due to the great drawbacks of the current methods and the importance of amide bonds, amide bond formation is still the subject of extensive studies and has been voted as the most important synthetic transformation to be improved by the American Chemical Society's (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable (PR) in 2005 [5]. One obvious

strategy to circumvent the problems of the current amide bond formation reactions is to use carboxylic acids as starting materials directly (Fig. 1). Although this strategy is expected to be very challenging, it has still attracted more and more attention due to its great advantages and should be extensively investigated [2d,6].

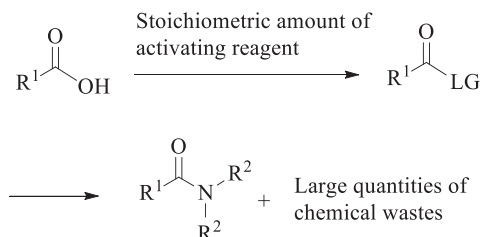
While *N,N*-dimethylformamide (DMF) is primarily used as a polar solvent in chemical reactions, it is a multipurpose reagent and plays various roles in organic synthesis [7]. As a formamide containing an aldehyde and amino group, DMF can serve as a precursor to generate a wide range of intermediates in organic reactions, including $-\text{CONMe}_2$, CHO, $-\text{NMe}_2$, $-\text{CO}$, O, $-\text{Me}$, etc. [8]. Therefore, reactions involving DMF as the reaction precursor has gained considerable interest recently, and its various reactivities have been extensively exploited to develop a wide range of novel organic reactions, especially those enabled by transition metals [7,8].

Herein, we report a copper-catalyzed amide bond formation reaction utilizing carboxylic acids and formamides as the amino source [9]. It should be mentioned that several amidation reactions were reported just when we almost finished this work. The Reddy group disclosed the coupling reaction of carboxylic acids and formamides using $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (10 mol%) as catalyst, *tert*-butyl hydroperoxide (TBHP) (1.5 equiv.) as oxidant and DMF as the solvent and source of the amine [10]. Subsequently, the Song and Li group reported similar amide bond formation reactions under the conditions consisting of CuCl_2 (5 mol%), 1,4-diazabicyclo[2.2.2]octane (DABCO) (10 mol%), TBHP (2 equiv.), and DMF (15 equiv.) in

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Amide bond formation relying on activating reagents



Amide bond formation by direct amidation of carboxylic acids

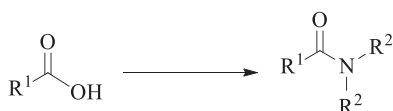


Fig. 1. Two strategies for amide bond formation.

1,2-dichloroethane (DCE) [11]. Coincidentally, the Kantam group developed a similar catalysis system for the synthesis of amides from carboxylic acids and DMF. The catalysis system consists of CuO (10 mol%), TBHP (3 equiv.), and DMF (1.5 mL) [12]. All of these works require the use of an excessive amount of DMF, either 15 equiv. or as the solvent. Actually, this drawback is found in many reactions involving DMF as the reactants, which is not only against atom-economic strategy, but also restricts the reactions to those volatile formamides. In addition, the similar amidation of α -oxocarboxylic acids with formamides have been reported [13]. Although the reactions yielded the amidation products in good yield in the presence of only 5 equiv. of formamides in Wang's work [13a], 10 mol% copper catalyst was used. In our work

presented here, only 4 equiv. of DMF and 1 mol% copper catalyst are enough to achieve high yields.

2. Experimental

^1H NMR and ^{13}C NMR spectra were recorded on Bruker ARX400. High resolution mass spectra were measured on Bruker MicroTOF II ESI-TOF mass spectrometer. All solvents were distilled prior to use unless otherwise noted. ^1H NMR spectra were recorded in CDCl_3 and referenced to residual CHCl_3 at 7.26 ppm, and ^{13}C NMR spectra were referenced to the central peak of CDCl_3 at 77.0 ppm.

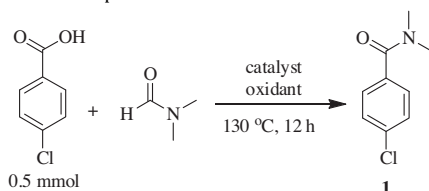
General procedure for the amidation of benzoic acids: A 50 mL sealed tube (with a Teflon high pressure valve) equipped with a magnetic stir bar was charged with $\text{Cu}(\text{OTf})_2$ (0.05 mmol), followed by carboxylic acid (0.5 mmol), formamide (2.0 mmol), *tert*-butyl peroxide (DTBP, 1 mmol), and DCE (1 mL). After the reaction mixture was stirred at 130 °C for 12 h, it was allowed to cool to ambient temperature. The reaction mixture was diluted with ethyl acetate, and then filtered through a small pad of Celite. The filtrate was washed with saturated aqueous NaHCO_3 (5 mL) and brine (5 mL, twice). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel preparative TLC to give the corresponding product.

3. Results and discussion

Our research started with the investigation of the amidation of 4-chlorobenzoic acid. In the presence of CuI (10 mol%) as the catalyst and $\text{K}_2\text{S}_2\text{O}_8$ (2.0 equiv.) as the oxidant, the reaction generated desired product **1** in a very low yield in DMF at 130 °C (Table 1, entry 1). Screening oxidants showed that DTBP was the comparatively better oxidant than the other peroxides (entry 4), and thus, DTBP was chosen as the oxidant for further studies. Among the surveyed copper catalysts, $\text{Cu}(\text{OTf})_2$ proved to be the most efficient, and the yield reached 89% (entry 8). It should be

Table 1

Condition optimization for the amidation of 4-chlorobenzoic acid with DMF.



Entry	Catalyst (mol%)	Oxidant (2.0 equiv.)	Solvent (1.0 mL)	Yield (%) ^a
1	CuI (10)	$\text{K}_2\text{S}_2\text{O}_8$	DMF	9
2	CuI (10)	Oxone	DMF	/
3	CuI (10)	TBHP	DMF	13
4	CuI (10)	DTBP	DMF	45
5	CuI (10)	DTBP	DMF	58
6	CuBr_2 (10)	DTBP	DMF	70
7	$\text{Cu}(\text{OAc})_2$ (10)	DTBP	DMF	73
8	$\text{Cu}(\text{OTf})_2$ (10)	DTBP	DMF	89
9	$\text{Cu}(\text{OTf})_2$ (10)	DTBP	DMA	21 ^b
10	$\text{Cu}(\text{OTf})_2$ (10)	DTBP	DMSO	48 ^b
11	$\text{Cu}(\text{OTf})_2$ (10)	DTBP	CH_3CN	18 ^b
12	$\text{Cu}(\text{OTf})_2$ (10)	DTBP	Dioxane	45 ^b
13	$\text{Cu}(\text{OTf})_2$ (10)	DTBP	DCE	87 ^b
14	$\text{Cu}(\text{OTf})_2$ (10)	DTBP	DCE	85 ^c
15	$\text{Cu}(\text{OTf})_2$ (10)	DTBP	DCE	69 ^d
16	$\text{Cu}(\text{OTf})_2$ (5)	DTBP	DCE	84
17	$\text{Cu}(\text{OTf})_2$ (1)	DTBP	DCE	84 (80 ^e)
18	/	DTBP	DCE	<5

^a The yields were determined by ^1H NMR analysis of crude products using DCE as the internal standard.

^b DMF 10 equiv.

^c DMF 4 equiv.

^d DMF 3 equiv.

^e Isolated yield.

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