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Easy conjugations between molecules *via* copper-catalyzed reactions of *ortho*-aromatic diamines with ketones†

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It is a great challenge to achieve a useful reaction under benign conditions. In this paper, a highly efficient method for copper-catalyzed conjugations of *o*-aromatic diamines with ketones has been developed using benign chemistry. Interestingly, the conjugation between the biological small molecules worked very well.

Introduction

It is highly desirable to develop site-selective coupling or conjugation between molecules, especially biomolecules for chemists and biologists *via* a benign chemistry process. Benign chemistry was defined as "click chemistry" by Sharpless *et al.*, and it includes simple reaction conditions (insensitive to oxygen and water), readily available starting materials and reagents, wide scope of substrates, the use of no solvent or environmentally friendly solvent, high selectivity, high yields, only inoffensive byproducts, and simple product isolation.[1] The conjugation between biomolecules was defined as bioorthogonal chemistry by Bertozzi *et al.*[2] However, it is a great challenge to achieve a useful reaction under such benign conditions. *o*-Aromatic diamines and ketones are common chemicals, and their coupling can provide 2,2-disubstituted 2*H*-benzo[*d*]imidazole derivatives that have been used in materials[3] and biological molecules.[4] However, traditional methods for the synthesis of 2,2-disubstituted 2*H*-benzo[*d*]-imidazole derivatives usually use large quantities of hazardous MnO_2, K_2MnO_4 [3] or $Cu(ClO_4)_2$ [5] as oxidant, and a high temperature is often required,[3] so the reactions under the conditions are far from those of click chemistry and bioorthogonal chemistry. Molecular oxygen is the ideal oxidant for its abundance, low cost and lack of toxic by-products, and it has been used in the selective transition metal-catalyzed aerobic oxidative formation of bonds.[6] Recently, copper-catalyzed reactions with inexpensive and low toxic copper-catalysts have shown wide application with high tolerance of functional groups.[7] Herein, we report a highly efficient copper-catalyzed conjugation of *o*-aromatic diamines with ketones under benign conditions. It is worth noting that some biological small molecules can be selectively conjugated *via* coupling of *o*-aromatic diamines with ketones in aqueous medium.

Results and discussion

At first, copper-catalyzed conjugation of 1,2-phenylenediamine (**1a**) with acetone (**2a**) under air leading to 2,2-dimethyl-2*H*-benzo[*d*]-imidazole (**3a**) was chosen as the model reaction to optimize the conditions including the catalysts and solvents. As shown in Table 1, various copper catalysts (5 mol%, relative to amount of **1a**) were screened (entries 1–11) using ethanol as the solvent at room temperature (~25 °C) under air, and $Cu(OAc)_2$ showed the highest catalytic activity (entry 7). The conjugation did not work in the absence of copper-catalyst (entry 12). Various solvents were attempted, and ethanol provided the highest yield (compare entries 7, 13–21). The reaction provided a small amount of product in the absence of air (entry 22). Therefore, the copper-catalyzed optimum conditions are as follows: 5 mol% Cu(OAc) as the catalyst, ethanol as the solvent under air at room temperature (~25 °C).

With the optimum reaction conditions in hand, we investigated the scope of copper-catalyzed conjugations of *o*-aromatic diamines with ketones. As shown in Table 2, the examined substrates provided good to excellent yields. For ketones, their reactivity depended on their electronic effect and steric hindrance, the substrates with higher charge density on the carbon of the carbonyl and bigger steric hindrance provided lower yields. For example, 5-nonanone (**3g**), cyclopentadecanone (**3q**) and 1-(4-nitrophenyl)-ethanone (**3r**) showed lower reactivity

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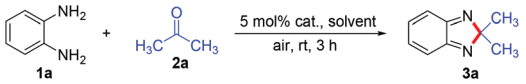
†Electronic supplementary information (ESI) available: Full experimental details, characterization and NMR spectra of the target products are provided. See DOI: 10.1039/c3gc41585f

Table 1 Copper-catalyzed conjugation of 1,2-phenylenediamine (**1a**) with acetone (**2a**) under air leading to 2,2-dimethyl-2*H*-benzo[*d*]imidazole (**3a**): optimization of conditions[a]



1a + **2a** → **3a**

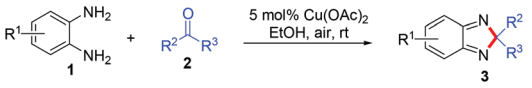
Entry	Cat.	Solvent	Yield[b] (%)
1	CuI	EtOH	55
2	CuBr	EtOH	58
3	CuCl	EtOH	63
4	Cu_2O	EtOH	Trace
5	CuO	EtOH	Trace
6	$CuCl_2$	EtOH	49
7	**$Cu(OAc)_2$**	**EtOH**	**91**
8	$Cu(O_2CCF_3)_2$	EtOH	77
9	$Cu(OTf)_2$	EtOH	72
10	Copper acetylacetonate	EtOH	Trace
11	Copper 2-ethylhexanoate	EtOH	85
12	—	EtOH	0
13	$Cu(OAc)_2$	MeOH	90
14	$Cu(OAc)_2$	*n*-PrOH	90
15	$Cu(OAc)_2$	i-PrOH	89
16	$Cu(OAc)_2$	DMF	Trace
17	$Cu(OAc)_2$	DMSO	Trace
18	$Cu(OAc)_2$	THF	Trace
19	$Cu(OAc)_2$	CH_3CN	Trace
20	$Cu(OAc)_2$	Toluene	Trace
21	$Cu(OAc)_2$	Acetone	13
22	$Cu(OAc)_2$	EtOH	15[c]

[a] Reaction conditions: under air (1 atm.), 1,2-phenylenediamine (**1a**) (1 mmol), acetone (**2a**) (1.2 mmol), catalyst (0.05 mmol), solvent (2 mL), reaction temperature (rt, ~25 °C), reaction time (3 h). [b] Isolated yield. [c] Under nitrogen atmosphere.

than other ketones. For *o*-aromatic diamines, the substrates containing electron-donating groups exhibited higher reactivity than the others. The copper-catalyzed conjugations could tolerate some functional groups including esters (**3m**, **3v**, **3c′–e′**), nitro (**3r**), ethers (**3x–z**, **3a′**, **3c′–e′**), C–Br bond (**3b′**).

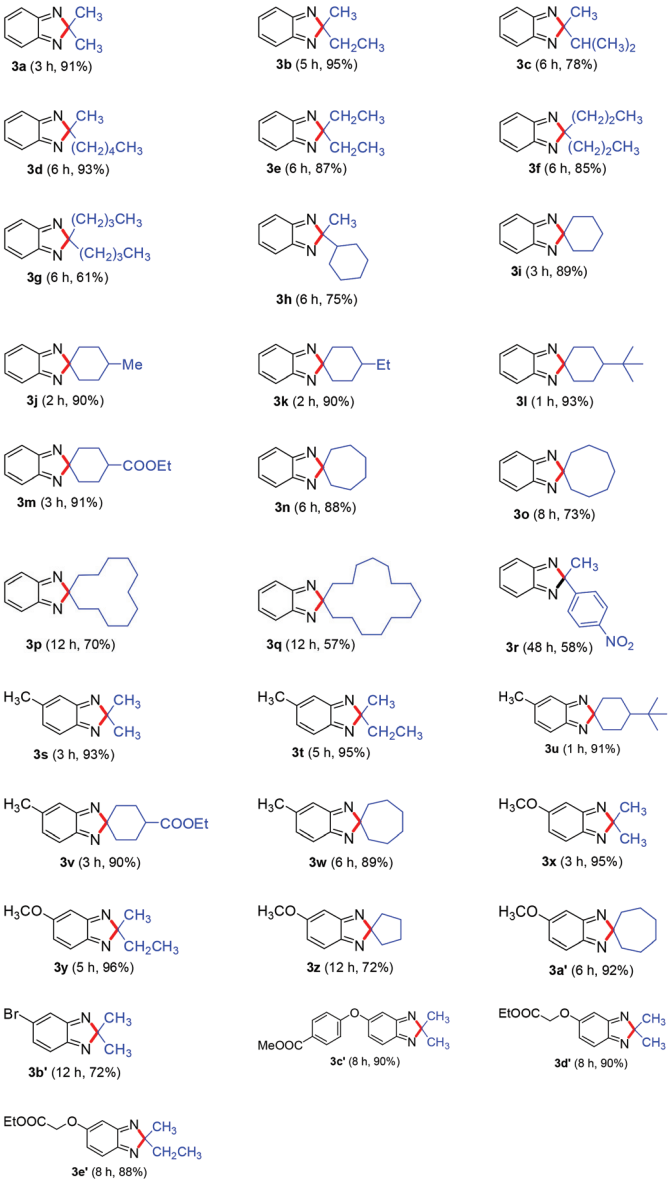
Inspired by the excellent results above, we applied this copper-catalyzed method to direct conjugation of biological small molecules. As shown in Scheme 1, conjugation of 1,2-phenylenediamine (**1a**) with ketone (**4**) containing a nucleoside provided **3f′** in 74% yield under the standard conditions. In order to develop further application of the present method, we prepared a new *o*-aromatic diamine (**10**) with dipeptide. As shown in Scheme 2, reaction of 4-amino-3-nitrophenol with ethyl 2-bromoacetate in the presence of base (K_2CO_3) provided **6** in 98% yield, and hydrolysis of **6** gave **7** (96% yield). Coupling of **7** with dipeptide (**8**) afforded **9** (95% yield), and reduction of **9** led to **10** (93% yield). We attempted conjugation of **10** with acetone (**2a**) in aqueous medium, and 2,2-dimethyl 2*H*-benzo[*d*]imidazole derivative (**3g′**) containing dipeptide was obtained in 80% yield. Finally, treatment of the *o*-aromatic diamine (**10**) containing a dipeptide with ketone (**4**) containing a nucleoside was performed in aqueous medium (Scheme 3), and we were very happy to get the desired target product (**3h′**) containing a dipeptide and nucleoside. The reaction showed wide tolerance of functional

Table 2 Copper-catalyzed conjugations of *o*-aromatic diamines with ketones[a]

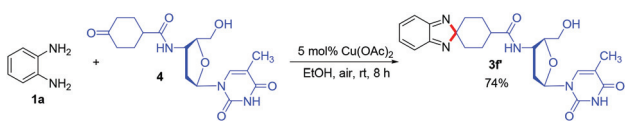


1 + **2** → **3**

3 (Time, yield[b])

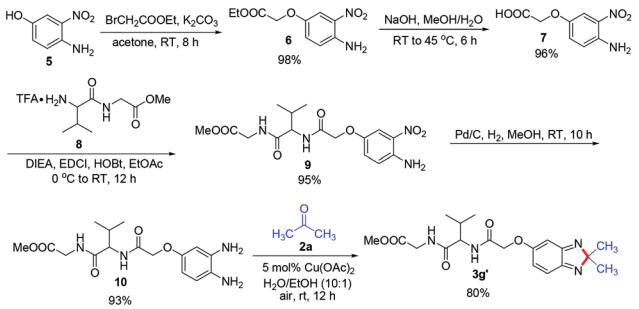


[a] Reaction conditions: under air (1 atm.), *o*-aromatic diamine (**1**) (1.0 mmol), ketone (**2**) (1.2 mmol), $Cu(OAc)_2$ (0.05 mmol), EtOH (2 mL), reaction temperature (rt, ~25 °C), reaction time (1–48 h). [b] Isolated yield.

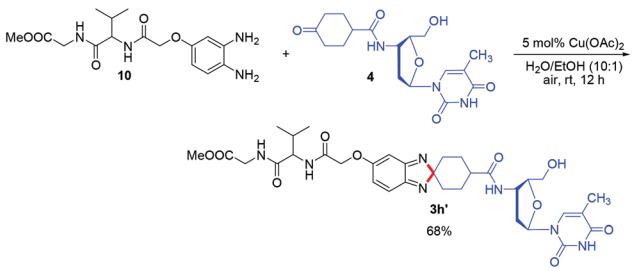


1a + **4** → **3f′**

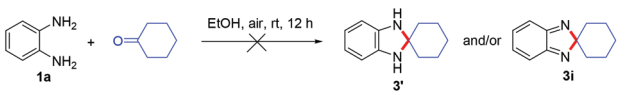
Scheme 1 Conjugation of 1,2-phenylenediamine (**1a**) with ketone (**4**) containing nucleoside under the standard conditions.



Scheme 2 Synthesis of 2,2-methyl 2*H*-benzo[*d*]imidazole derivative (**3g′**) containing dipeptide in aqueous medium (DIEA = *N*,*N*-diisopropylethylamine, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt = *N*-hydroxybenzotriazole).



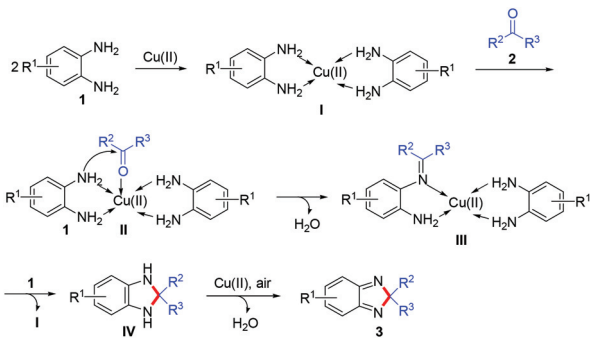
Scheme 3 Conjugation of *o*-aromatic diamine (**10**) containing dipeptide with ketone (**4**) containing nucleoside in aqueous medium.



Scheme 4 Treatment of 1,2-phenylenediamine (**1a**) with cyclohexanone in the absence of the copper-catalyst.

groups in biological small molecules, so the present method that was carried out under the benign conditions should provide a novel strategy for conjugation of biological molecules.

In order to explore the mechanism of the copper-catalyzed conjugation of *o*-aromatic diamines with ketones, a control experiment was performed as shown in Scheme 4. Treatment of 1,2-phenylenediamine (**1a**) with cyclohexanone in the absence of copper catalyst was carried out at room temperature under air for 12 h, and no reaction occurred (**3′** and **3i** were not observed). The result showed that the copper catalyst was involved in the formation of the intermediate **3′** under the standard conditions. Therefore, a possible mechanism for the copper-catalyzed conjugation is proposed in Scheme 5. First, coordination of the *o*-aromatic diamine with $Cu(OAc)_2$ provides complex **I**, and treatment of **I** with ketone leads to **II**. Nucleophilic attack of the amino group to the carbonyl in **II** and dehydration gives the imine-copper complex **III**,



Scheme 5 Possible mechanism for copper-catalyzed conjugations of *o*-aromatic diamines with ketones.

and intramolecular addition of the *ortho*-amino group to the imine in **III** in the presence of **1** affords **IV** leaving **I**. Copper-catalyzed aerobic oxidation of **IV** provides the target product (**3**).

Conclusions

In conclusion, we have developed a highly efficient copper-catalyzed method for the conjugation of *o*-aromatic diamines with ketones leading to 2,2-disubstituted 2*H*-benzo[*d*]imidazole derivatives. Interestingly, the conjugation between the biological small molecules worked very well. The method is of the following advantages: (a) inexpensive $Cu(OAc)_2$ as the catalyst; (b) economical and environmentally friendly air as the terminal oxidant; (c) environmentally friendly ethanol or water as the solvent; (d) without the addition of any acid, base or additive; (e) high reaction yields; (f) high selectivity; (g) all the reactions were performed at room temperature; (h) water was the only byproduct; (i) outstanding tolerance of functional groups; (j) easy workup procedure. All these results meet the requirements of benign chemistry, so the present method will be of widely practical application in various fields. Further investigation on application of this method is in progress.

Experimental section

General procedure for copper-catalyzed conjugations of *ortho*-aromatic diamines with ketones

A 25 mL flask was charged with a magnetic stirrer and ethanol (2.0 mL) or water–ethanol (v/v = 10 : 1) (3.3 mL) (for **3g′** and **3h′**), *o*-aromatic diamine (**1**) (1.0 mmol), ketone (**2**) (1.2 mmol) and $Cu(OAc)_2$ (0.05 mmol, 9.1 mg) were added to the flask. The mixture was stirred at room temperature (~25 °C) under air. After the conjugation was completed (TLC determination), the resulting solution was concentrated by a rotary evaporator, and the residue was purified by column chromatography on silica gel using an eluent (petroleum ether–ethyl acetate, ethyl acetate–methanol, ethyl acetate–ethanol or diethyl ether) to provide the desired target product (**3a–h′**).

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