Copper(II) and 1,1'-Trimethylene-2,2'-biimidazole-promoted Arylation of Acetylacetone with Aryl Iodides

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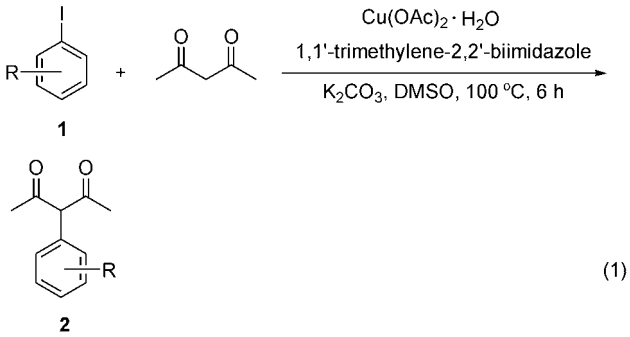
A new and efficient way was developed to carry out the reaction of acetylacetone with aryl iodides under the assistance of Cu(II) and 1,1'-trimethylene-2,2'-biimidazole at 100 ℃. 3-Aryl-2,4-pentanediones were obtained in excellent yields.

Keywords Cu(II)-promoted arylation reaction, 1,1'-trimethylene-2,2'-biimidazole, 3-aryl-2,4-pentanedione

Introduction

Reaction of aryl halides with carbon nucleophiles, such as anions of active methylene compounds, is a useful tool for the preparation of substituted aromatic compounds,[1-7] which are very important building blocks for synthesizing various heterocycles, amino alcohols and amino acids.[8-11] Among the methods available for the *α*-aryl carbonyl compounds, a great deal of recent attention has focused on the development of palladium-catalyzed arylation methodology.[12-15] Some exciting achievements have already appeared in the field. For instance, the coupling of diethyl malonate or ethyl cyanoacetate with aryl chloride could be carried out at 70 ℃ using certain phosphines as ligand.[14] However, high costs and toxicity of Pd reagents and the relative ligands limit their application in industrial employment. The arylation of activated methylene compounds mediated by copper(I) salts is a well-established process. Dating back to the development of the Hurtley reaction in 1929,[16] the reaction usually requires a stoichiometric amount of copper salt unless the halides are activated by an *o*-carboxylate group.[17-22] In 1993, Miura *et al.*[23] reported CuI-catalyzed arylation of acetylacetone with aryl iodides at 120 ℃. In recent years, research efforts in several laboratories have delivered a series of mild Ullmann type methodologies based on employing some specific ligands. For examples, in 2002, Buchwald and co-workers[24] reported CuI-catalyzed methods for arylation of diethyl malonate using suitable additives such as 2-phenylphenol. In 2005, Ma's group[25] and Jiang's[26] group discovered that *L*-proline was another type of effective ligands for CuI-catalyzed coupling reactions of aryl halides and activated methylene compounds.[25,26] Kwong *et al.*[27] found that in the presence of a catalytic amount of 2-picolinic acid and CuI, the coupling of aryl iodides and diethyl malonate was carried out smoothly even at room temperature. However, copper(II)-promoted arylation of acetylacetone with aryl iodides was seldom reported. In 2006, we[28] studied the 2,2'-biimidazole, Cu(II)-catalyzed coupling reaction of aryl iodides and phenols. As the catalytic system was applied to the arylation of acetylacetone, the desired products were not obtained, thus helped us to focus on a new catalytic system which had a higher activity than that. To our surprise, copper(II) and 1,1'-trimethylene-2,2'-biimidazole (**6**)-promoted arylation of acetylacetone with aryl iodides could be carried out at 100 ℃ in excellent yields (Eq. 1).



(1)

Experimental

In general, ^{1}H NMR (at 400 MHz) and ^{13}C NMR (at 100 MHz) spectra were recorded on Varian Inova-400 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. HRMS was recorded on a Micromass OA-TOF instrument. For preparative column chroma-

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Received November 3, 2009; revised March 29, 2010; accepted September 30, 2010.
Project supported by the National Natural Science Foundation of China (No. 20772088).

tography, silica gel H60 was used with the solvent system displayed in the text.

General procedure

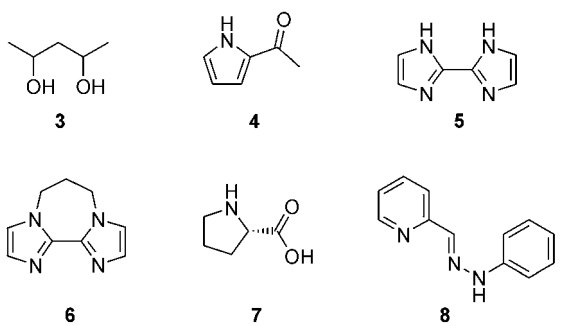
A mixture of 1 mmol of aryl halide, 2 mmol of acetylacetone, 4 mmol of K_2CO_3, 0.1 mmol of copper(II) salt, 0.2 mmol of 1,1'-trimethylene-2,2'-biimidazole and 1 mL of the solvent were heated at 100 ℃ for 6 h. After the reaction was completed as monitored by TLC, the cooled mixture was partitioned between ethyl acetate and saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual was loaded on a silica gel column and eluted with ethyl acetate/petroleum ether (*V*/*V*=1/20—30) to afford the product.

Results and discussion

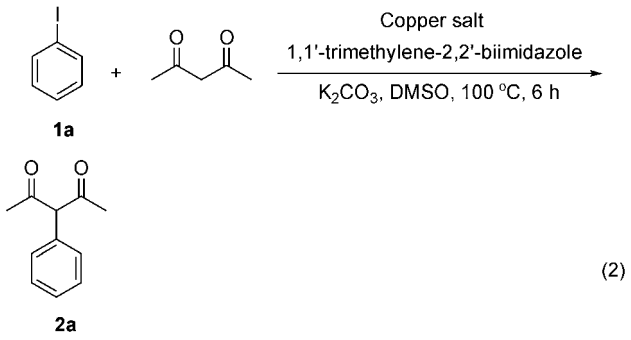
Effect of ligand and copper salt

In the first stage of the study, we tried to seek the optimal ligand from compounds **3**—**8** (Scheme 1) for the reaction of the model substrate acetylacetone with iodobenzene with $Cu(OAc)_2•H_2O$ as the catalyst. The reactions promoted by ligand **7** gave low yields, although **7** was often used as an excellent ligand for the C—C coupling,[25,26] ligands **3**, **4**, and **8** were also tested, and products were achieved. When the ligands were all replaced with 1,1'-trimethylene-2,2'-biimidazole (**6**), surprisingly the reaction provided 89% yield of 3-aryl-2,4-pentanediones. Finally, a control experiment without any ligand was carried out, and low yield was obtained under the similar condition. From the above descriptions, ligand **6** was chosen for further investigation. Thus, the reaction was carried out with different ratios of 1,1'-trimethylene-2,2'-biimidazole (**6**) and $Cu(OAc)_2•H_2O$. It was found that the combination of 20 mol% ligand and 10 mol% copper(II) was effective catalytic system.

Scheme 1



In order to find the best copper salt, the reaction of iodobenzene with acetylacetone was chosen as the model reaction (Eq. 2). According to the results in Table 1, $Cu(OAc)_2•H_2O$ was found to be the best copper salt.



(2)

Table 1 Reaction of acetylacetone with iodobenzene under the catalysis of copper salts and 1,1'-trimethylene-2,2'-biimidazole[a]

Entry	Copper salt	Isolated yield / %
1	$Cu(OAc)_2•H_2O$	89
2	$CuSO_4•5H_2O$	63
3	$CuCl_2•2H_2O$	58
4	CuI	42
5	$CuCl_2$	28
6	—	0[b]

[a] Reaction conditions: [Cu] (0.1 mmol), 1,1'-trimethylene-2,2'-biimidazole (0.2 mmol), acetylacetone (2 mmol), iodobenzene (1 mmol), K_2CO_3 (4 mmol), DMSO (1 mL), 100 ℃. [b] No copper salt and ligand.

As indicated in the Table 1, the yield of the reaction which was promoted by the copper salt with crystal water was much higher than that without water. It possibly proved that water participated in the reaction.

Effect of base

To find the suitable base, the reaction of acetylacetone with iodobenzene with different base was carried out at 100 ℃. Based on the results in Table 2, K_2CO_3 was found to be the suitable base.

Table 2 Reaction of acetylacetone with iodobenzene under the different base[a]

Entry	Base	Isolated yield/%
1	K_2CO_3	89
2	K_2CO_3	66[b]
3	Cs_2CO_3	75[c]
4	Na_2CO_3	35
5	K_3PO_4	41
6	NaOH	Trace
7	NEt_3	Trace

[a] Reaction conditions: $Cu(OAc)_2•H_2O$ (0.1 mmol), 1,1'-trimethylene-2,2'-biimidazole (0.2 mmol), acetylacetone (2 mmol), iodobenzene (1 mmol), base (4 mmol), DMSO (1 mL), 100 ℃. [b] 2 mmol of K_2CO_3. [c] 2 mmol of Cs_2CO_3.

Effect of solvent

In order to find the best solvent, the reaction of ace-

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tylacetone with iodobenzene was carried out in several kinds of normal solvent. According to the results in Table 3, DMSO was found to be the suitable reaction solvent.

Table 3 Reaction of acetylacetone with iodobenzene under the common organic solvent[a]

Entry	Solvent	Isolated yield/%
1	DMSO	89
2	DMF	Trace
3	THF	No reaction
4	Dioxane	21
5	Toluene	Trace

[a] Reaction conditions: $Cu(OAc)_2•H_2O$ (0.1 mmol), 1,1'-trimethylene-2,2'-biimidazole (0.2 mmol), acetylacetone (2 mmol), iodobenzene (1 mmol), K_2CO_3 (4 mmol), solvent (1 mL), 100 ℃.

Synthesis

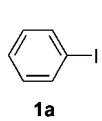
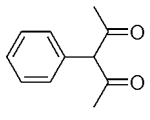
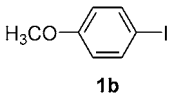
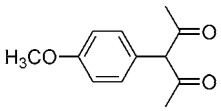
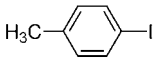
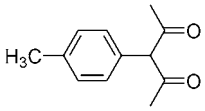
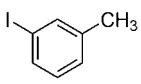
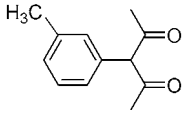
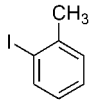
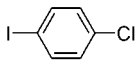
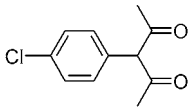
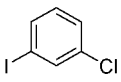
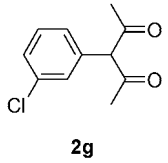
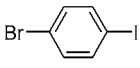
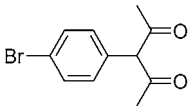
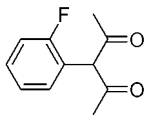
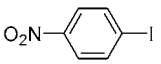
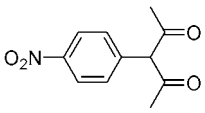
With optimized condition in hand, the reaction catalyzed by $Cu(OAc)_2•H_2O$ (10% mmol), 1,1'-trimethylene-2,2'-biimidazole (20% mmol) was tested with several different aryl iodides, and the results are summarized in Table 4.

The reaction was effective for a wide variety of aryl iodides in excellent yields. However, the protocol is not tolerant to the presence of a functional group at *ortho*-position of the aryl iodide as substrates (Table 4, Entry 5). It was also found that this system was not applied to the arylation of 1,3-diphenylpropane-1,3-dione, 1-phenyl-butane-1,3-dione, ethyl 3-oxobutanoate, diethyl malonate and ethyl 2-cyanoacetate.

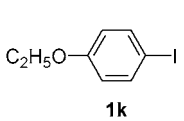
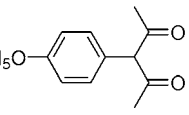
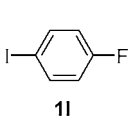
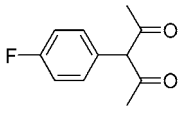
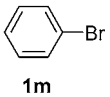
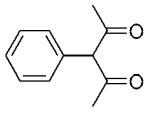
We turned our attention to insight into the mechanism of the reaction (Scheme 2). The solubility of copper acetate cooperated with 2,2'-biimidazole would be increased. Acetylacetone existed as the enolized anion in the conditon of base circumstance, and the acetoxylation of the methylene group seemed to proceed much more easily when intermediate **I** reacted with the enolized form of a 1,3-diketone to generate intermediate **II**. The intermediate **II** enhanced the enolized anion α-carbon nucleophilicity. The reaction of intermediate **II** with iodobenzene was greatly influenced by the substituent group R^1 and R^2. Definitely the S_NAr reaction was suppressed when R^2 was an aryl group and R^1 was an aryl group or an alkyl one due to the possible conjugation effect which stabilized the existed enolized anion. Apart from what presented above, the S_NAr reaction was also suppressed when R^2 was an aryl group and R^1 was an EtO group as a result of the electronic effect.

3-Phenylpentate-2,4-dione (2a)[28] Yield 89%, white solid, m.p. 38—40 ℃; ^{1}H NMR δ: 16.61 (s, 1H), 7.08—7.33 (m, 4H), 1.80 (s, 6H); ^{13}C NMR δ: 191.1, 137.1, 131.7, 129.0, 127.7, 115.4, 24.4; HRMS calcd for $C_{11}H_{11}O_2$ 176.0837, found 176.0838.

Table 4 Reaction of acetylacetone with different aryl iodides under the catalysis of $Cu(OAc)_2•H_2O$ and 1,1'-trimethylene-2,2'-biimidazole[a]

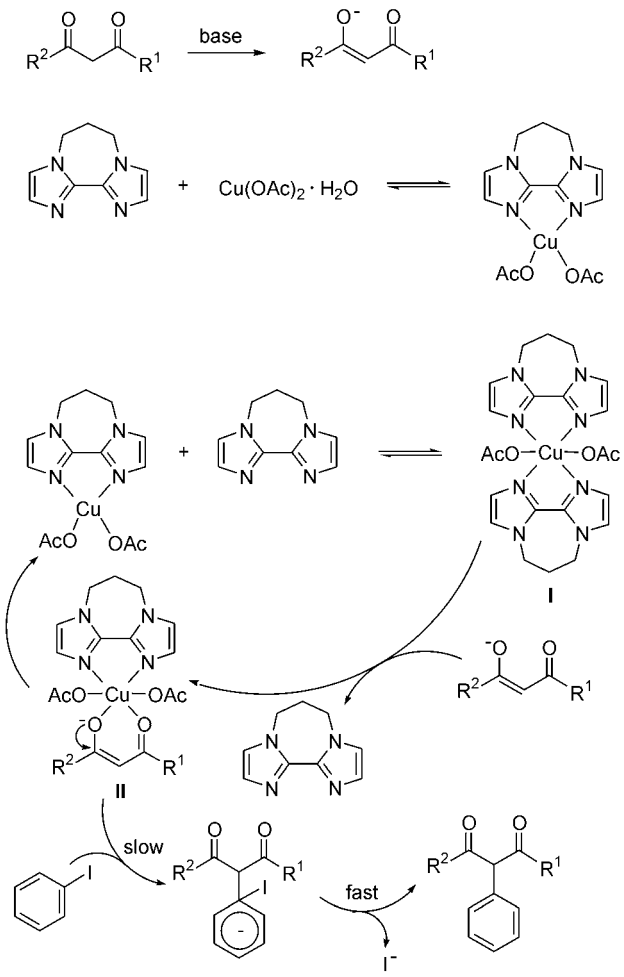
Entry	Aryl iodide	Product	Time/h	Yield[b]/%
1	 **1a**	 **2a**	6	89
2	 **1b**	 **2b**	6	85
3	 **1c**	 **2c**	3	87
4	 **1d**	 **2d**	6	83
5	 **1e**	—	6	0
6	 **1f**	 **2f**	6	81
7	 **1g**	 **2g**	6	73
8	 **1h**	 **2h**	6	83
9	 **1i**	 **2i**	6	65
10	 **1j**	 **2j**	6	76

Continued

Entry	Aryl iodide	Product	Time/h	Yield[b]/%
11	 1k	 2k	6	82
12	 1l	 2l	6	80
13	 1m	 2m	6	65

[a] Reaction conditions: $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), 1,1'-trimethylene-2,2'-biimidazole (0.2 mmol), acetylacetone (2 mmol), aryl aryl iodide (1 mmol), K_2CO_3 (4 mmol), DMSO (1 mL), 100 ℃. [b] Isolated yield.

Scheme 2



3-(4-Methoxyphenyl)pentane-2,4-dione[28] **(2b)** Yield 85%, white solid, m.p. 78—80 ℃; ^{1}H NMR δ: 16.64 (s, 1H), 7.07 (d, J=8.4 Hz, 2H), 6.91 (d, J=8.5 Hz, 2H), 3.83 (s, 3H), 1.88 (s, 6H); ^{13}C NMR δ: 191.4, 159.1, 138.4, 132.3, 129.2, 114.4, 55.4, 24.3; HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0944.

3-*p*-Tolylpentane-2,4-dione[28] **(2c)** Yield 87%, white solid, m.p. 66—68 ℃; ^{1}H NMR δ: 16.68 (s, 1H), 7.19 (d, J=7.8 Hz, 2H), 714 (d, J=7.7 Hz, 1H), 2.36 (s, 3H), 1.88 (s, 6H); ^{13}C NMR δ: 189.9, 136.1, 132.8, 129.8, 128.5, 113.9, 23.1, 20.1; HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0993.

3-*m*-Tolylpentane-2,4-dione (2d) Yield 83%, yellow solid, m.p. 36—38 ℃; ^{1}H NMR δ: 16.68 (s, 1H), 7.27 (t, J=7.5 Hz, 1H), 7.14 (d, J=7.7 Hz, 1H), 6.97 (t, J=7.7 Hz, 2H), 2.37 (s, 3H), 1.89 (s, 6H); ^{13}C NMR δ: 191.4, 138.8, 137.2, 132.2, 129.1, 128.6, 128.5, 110.2, 23.1, 20.1; HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0995.

3-(4-Chlorophenyl)pentane-2,4-dione[27] **(2f)** Yield 76%, yellow solid, m.p. 82—84 ℃; ^{1}H NMR δ: 16.69 (s, 1H), 7.37 (d, J=8.3 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 1.89 (s, 6H); ^{13}C NMR δ: 190.2, 134.7, 132.9, 131.8, 128.4, 113.4, 23.5; HRMS calcd for $C_{11}H_{11}ClO_2$ 210.0448, found 210.0448.

3-(3-Chlorophenyl)pentane-2,4-dione[27] **(2g)** Yield 81%, yellow solid, m.p. 52—54 ℃; ^{1}H NMR δ: 16.69 (s, 1H), 7.37 (d, J=8.3 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 1.89 (s, 6H); ^{13}C NMR δ: 190.8, 138.7, 134.5, 131.1, 130.1, 114.1, 24.2; HRMS calcd for $C_{11}H_{11}ClO_2$ 210.0448, found 210.0448.

3-(4-Bromophenyl)pentane-2,4-dione[29] **(2h)** Yield 83%, yellow solid, m.p. 76—78 ℃; ^{1}H NMR δ: 16.70 (s, 1H), 7.53 (d, J=8.4 Hz, 2H), 7.06 (d, J=8.4 Hz, 2H), 1.89 (s, 6H); ^{13}C NMR δ: 189.8, 134.8, 131.8, 131.0, 120.7, 113.0, 23.2; HRMS calcd for $C_{11}H_{11}BrO_2$ 253.9942, found 253.9942.

3-(2-Fluorophenyl)pentane-2,4-dione (2i) Yield 65%, yellow oil; ^{1}H NMR δ: 16.81 (s, 1H), 7.32—7.37 (m, 1H), 7.18 (d, J=8.4 Hz, 2H), 7.12 (t, J=8.7 Hz, 1H), 1.91 (s, 6H); ^{13}C NMR δ: 190.8, 161.3, 158.8, 132.8 (d, J=2.6 Hz), 129.6 (d, J=8.0 Hz), 124.0 (d, J=3.8 Hz), 115.5 (d, J=22.6 Hz), 107.7, 23.4; HRMS calcd for $C_{11}H_{11}FO_2$ 190.0743, found 190.0745.

3-(4-Nitrophenyl)pentane-2,4-dione[27] **(2j)** Yield 76%, yellow solid, m.p. 104—106 ℃; ^{1}H NMR δ: 16.78 (s, 1H), 8.27 (d, J=8.7 Hz, 2H), 7.39 (d, J=8.7 Hz, 2H), 1.91 (s, 6H); ^{13}C NMR δ: 190.9, 147.7, 144.5, 132.6, 124.5, 114.1, 24.7; HRMS calcd for $C_{11}H_{11}NO_4$ 221.0688, found 221.0688.

3-(4-Ethoxyphenyl)pentane-2,4-dione (2k) Yield 82%, white solid, m.p. 66—68 ℃; ^{1}H NMR δ: 16.66 (s, 1H), 7.06 (d, J=8.6 Hz, 2H), 6.90 (d, J=8.6 Hz, 2H), 4.04 (q, J=6.8 Hz, 2H), 1.91 (s, 6H), 1.45 (t, J=7.0 Hz); ^{13}C NMR δ: 191.7, 158.6, 132.5, 129.3, 115.0, 24.6, 15.3; HRMS calcd for $C_{13}H_{16}O_3$ 221.1099, found 221.1166.

3-(4-Fluorophenyl)pentane-2,4-dione (2l) Yield 80%, yellow oil; ^{1}H NMR δ: 16.69 (s, 1H), 7.06—7.18

(m, 4H), 1.89 (s, 6H); ^{13}C NMR δ: 191.3, 164.1, 160.8, 133.0, 132.9, 116.2, 115.9, 24.2; HRMS calcd for $C_{11}H_{11}FO_2$ 190.0743, found 190.0745.

Conclusion

In summary, a mild, simple and efficient way was developed to carry out the Ullmann α-aryl carbonyl compounds synthesis, which is applicable to a large variety of substrates with different functional groups. This simple and remarkably active catalytic system represents the first report of Ullmann-type C—C bond formation using $Cu(OAc)_2 \cdot H_2O$, which potentially offers an efficient protocol in accessing a variety of α-arylated dicarbonyl compounds.

Acknowledgements

We would like to thank good suggestions from Ma, Dawei of Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China.

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(E0911031 Li, L.; Fan, Y.)

