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Facile synthesis of 1-naphthols through a copper-catalyzed arylation of methyl ketones with *o*-bromoacetophenones

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ABSTRACT

The coupling reactions of simple methyl ketones with *o*-bromoacetophenones and subsquential cyclization reactions were realized to produce a range of 1-naphthols. These cascade reactions were initiated by a rare Cu-catalyzed arylation reaction of methyl ketones with aromatic bromides.

1. Introduction

Cu-catalyzed arylation reactions are very practical and efficient to transfer aromatic halides into more valuable aromatic compounds [1]. Although a large variety of hetero-atomed (N, O and S) nucleophiles are generally applied as the partner of aromatic halides in these reaction [2–4], C-nucleophiles are limited to highly activated carbonyl compounds such as keto-esters, malonic acid derivatives, or diketones [5]. Very recently, the first example of Cu-catalyzed α-arylation of benzyl phenyl ketones with aromatic iodides was also realized [6]. The Cu-catalyzed arylation of simple ketones (such as methyl ketones) is very attractive but remains a big challenge [7]. On the other hand, only aromatic iodides (other than bromides and chlorides) gave satisfactory results in most Cu-catalyzed arylation reactions.

As one part of our ongoing project on synthesizing cyclic compounds with copper catalysts [8], recently, we reported a specific example that Cu-catalyzed arylation reaction of simple methyl ketones with *o*-iodoacetophenones was realized under very mild conditions and a tandem cyclization followed to give useful 1-naphthol derivatives [9]. After great effort, the reaction was found to be applicable to *o*-bromoacetophenones, which was initiated by a rare Cu-catalyzed arylation reaction of methyl ketones with aromatic bromides (Scheme 1)! Since substituted *o*-bromoacetophenones are more economical, readily available but less reactive than corresponding *o*-iodoacetophenones, it is worth reporting that the Cu-catalyzed arylation reactions of simple methyl ketones with *o*-bromoacetophenones and subsquential cyclization reactions to 1-naphthols [10].

2. Experimental

All the reactions were carried out in a pre-dried screwcapped tube with a Teflon-lined septum under N_2 atmosphere. Bromo acetophenone derivatives except bromoacetophenone **1a** were prepared according to the literatures. All of the solvents were freshly distilled. Column chromatography was performed on silica gel (particle size 10–40 μm, Ocean Chemical Factory of Qingdao, China). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL AL-300 MHz or AL-400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent. Chemical shifts (δ) were given in ppm, referenced to the residual proton resonance of $CDCl_3$ (7.26), to the carbon resonance of $CDCl_3$ (77.16). Coupling constants (J) were given in Hertz (Hz). The term m, dq, q, t, d, s referred to multiplet, doublet quartet, quartet, triplet, doublet, singlet. Mass spectra were obtained using Bruker Esquire ion trap mass spectrometer in positive mode. The reaction progress was monitored by GC-MS if applicable, using *n*-dodecane as internal standard.

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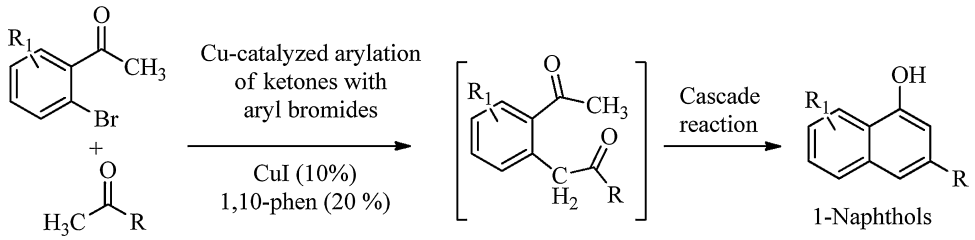


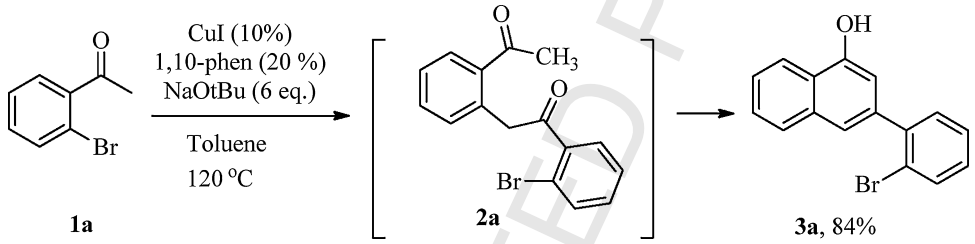
Scheme 1. Facile synthesis of 1-naphthols through a copper-catalyzed arylation of methyl ketones with *o*-bromoacetophenones.

2.1. General procedure for the preparation of desired compound ***3a-l***

A sealed tube was charged with the mixture of CuI (0.1 mmol, 19.0 mg), 1,10-phenanthroline (0.2 mmol, 36.0 mg), NaO^{t}Bu (6 mmol, 0.576 g) and bromo acetophenone derivatives **1** (1.0 mmol). The tube was evacuated and recharged with N_2 for 3 times. Before toluene (2.0 mL) was added, the tube was sealed and the mixture was allowed to stir at 120 °C for 4 h. After completion, the mixture was cooled to room temperature, then 2 mol/L HCl aq. (1–2 mL) was added and the mixture was extracted with Et_2O (5 mL × 3), dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel (petroleum ether/diethyl ether: 25/1 to 10/1) provided the corresponding product **3a-l** as a solid or yellow oil.

2.2. General procedure for the preparation of desired compound ***3m-q***

A sealed tube was charged with the mixture of CuI (0.1 mmol, 19.0 mg), 1,10-phenanthroline (0.2 mmol, 36.0 mg), NaO^{t}Bu (6 mmol, 0.576 g) and *o*-bromoacetophenone **1a** (1.0 mmol). The



Scheme 2. The best condition for the formation of **3a**.

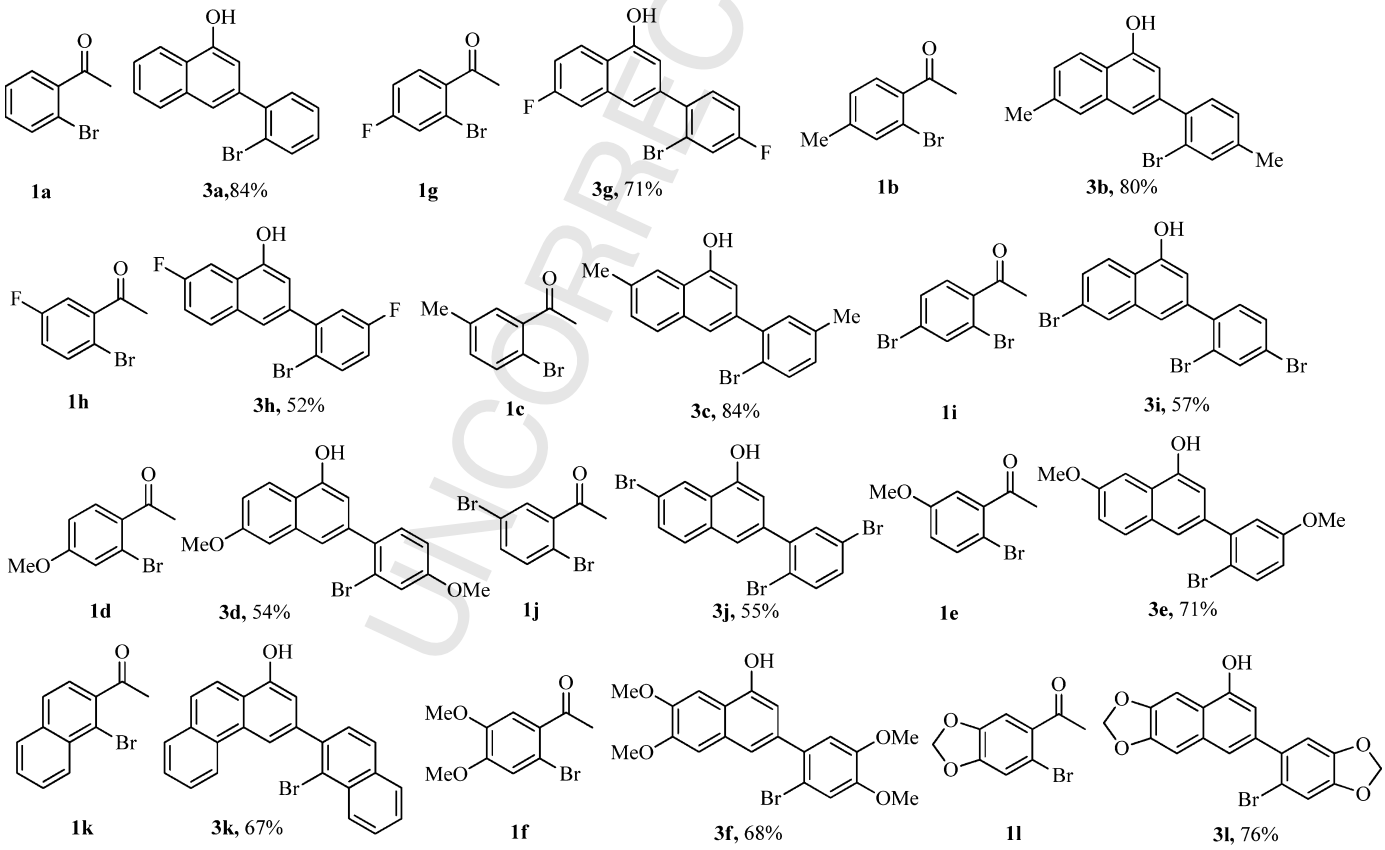


Fig. 1. 1-Naphthols **3** formed by the dimerization of **1**.

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tube was evacuated and recharged with N_2 for 3 times. After toluene (2.0 mL) was added, ketone **1m-q** (3 equiv., 3 mmol) was added to the tube slowly. Then the tube was sealed and the mixture was allowed to stir at 120 °C for 4 hours. After completion, the mixture was cooled to room temperature, then 2 mol/L HCl aq. (1–2 mL) was added and the mixture was extracted with Et_2O (5 mL × 3), dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel (petroleum ether/diethyl ether: 25/1 to 10/1) provided the corresponding product **3m-q** as a solid.

3. Results and discussion

The beginning study stemmed from the synthesis 1-naphthols *via* dimerization of *o*-bromoacetophenones **1a**. We attempted to carry out the reaction under the same reaction as used in the case of *o*-iodoacetophenones but failed to get any product **2a** [9]. Considering the lower reactivity of *o*-bromoacetophenones, the reaction temperature was raised to 80 °C with THF as the solvent. Excitingly, the expected product **2a** was formed in 20% yield. It is worth noting that NaO^{t}Bu was found as the best base for this reaction and the amount of NaO^{t}Bu was crucial: **2a** was formed in 58% yield with 5 equiv. of NaO^{t}Bu, and in 70% yield with 6 equiv. of NaO^{t}Bu (See Table S1 in Supporting information). When the reaction was carried out in toluene at 120 °C, **3a** was isolated in 84% yield after normal work-up (Scheme 2) (For the details of optimization, see Supporting information).

Inspired by the above result, a series of substituted *o*-bromoacetophenones **1** were homo-dimerized to give functionalized 1-naphthols **3**, and the results were listed in Fig. 1. Generally, *o*-bromoacetophenones **1** with a range of substitutents such as methyl, methoxide, fluoro, and bromo groups (**1b-1j**) could perform the reactions well to give substituted phenyl-1-naphthols (**3b-3j**). Excitedly, when polycyclic substrates (**1k-1l**) were used, ring-fused 1-naphthols were obtained (**3k-3l**). The structure of **3l** was unequivocally confirmed with X-ray diffraction (Fig. 2).

Encouraged by the successful synthesis of 1-naphthols *via* the homo-dimerization of *o*-bromoacetophenones **1**, we attempted to realize the cross-cyclization of *o*-bromoacetophenone **1a** with other simple ketones. Apparently, this reaction is more challenging since the homo-dimerization of *o*-bromoacetophenones should be avoided. To our delight, as shown in Table 1, it was found when simple ketones **1m-1q** were used much excess to *o*-bromoacetophenone **1a**, only cross-cyclization products were isolated. Interestingly, when asymmetric ketone, 2-butanone **1n** was employed, only 2-ethyl-1-naphthol **3n** was isolated, which indicated CH_3 group was more reactive than CH_2 group in this reaction. Propiophenone **1q** was also fit for this reaction to produce 3,4-disubstituted 1-naphthol **3q**, albeit in a lower yield.

We also attempted the reaction of *o*-iodine acetophenone with **1o-1q** according to the condition in Table 1. Unfortunately, under this condition, the reaction gave messy products due to the strong reactivity of *o*-iodine acetophenone.

It is worth noting that those synthesized 1-naphthols **3a-3l** with one bromo-atom were able to be further modified. For example, compound **3a** was reduced to give **3o** by the treatment with $HCOONH_4$ solution in the presence of Pd/C (10%) (Scheme 3) [11]. Under a standard Suzuki-coupling condition with phenylboronic acid, compound **3a** was successfully converted to **3r** in 75% yield (Scheme 4) [12]. Moreover, the modification of compound **3a** was sometimes able to be done in one pot during its formation from **1a** (Scheme 5). When **1a** was reacted with trifluoroethanol in the standard condition [13], product **3s** was isolated in 78% yield.

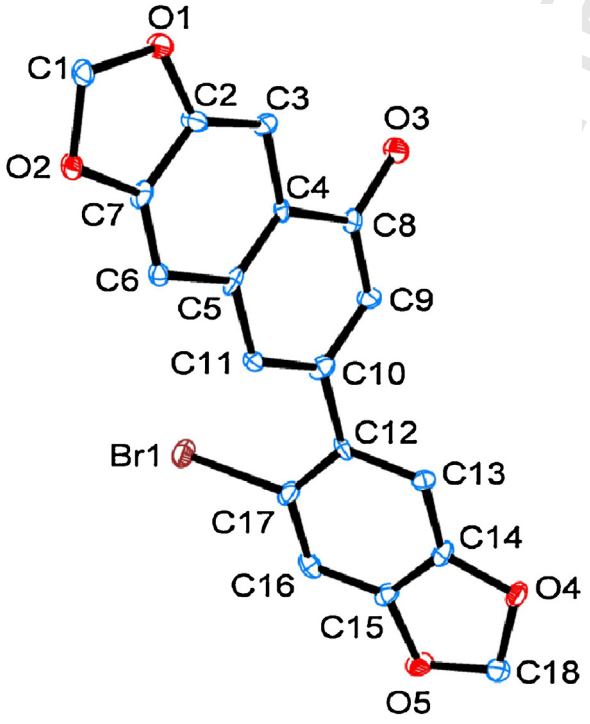
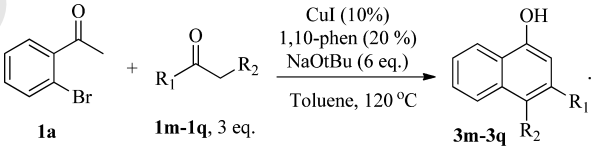
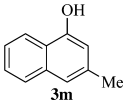
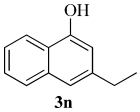
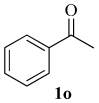
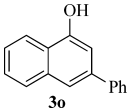
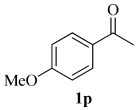
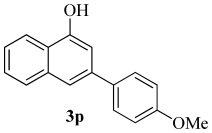
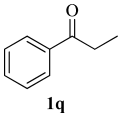
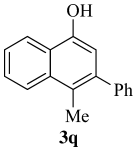


Fig. 2. Crystal structure of **3l** (CCDC number: 935169). Hydrogen atoms are omitted for clarity.

Table 1
1-Naphthols **3m-3q** formed by the reaction of **1a** with methyl ketones.



1m-1q	3m-3q	Yield (%)
 1m	 3m	58
 1n	 3n	43
 1o	 3o	64
 1p	 3p	63
 1q	 3q	45

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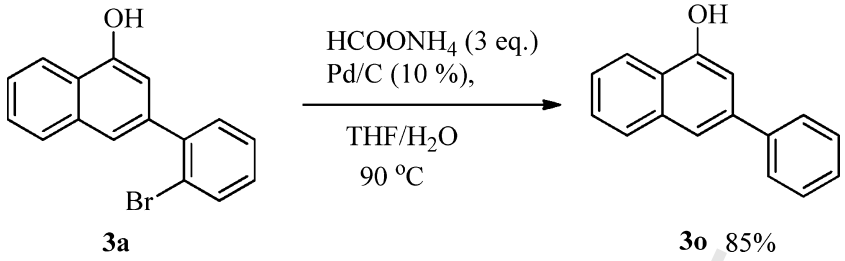
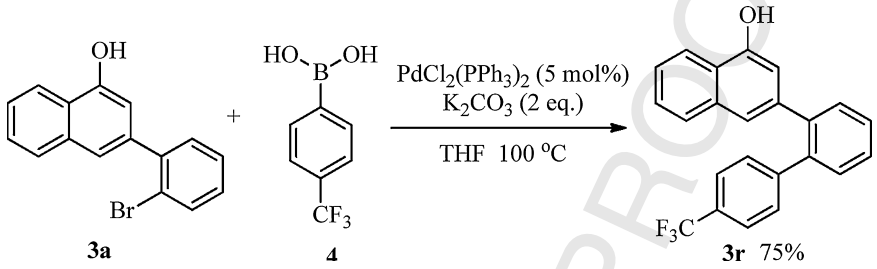
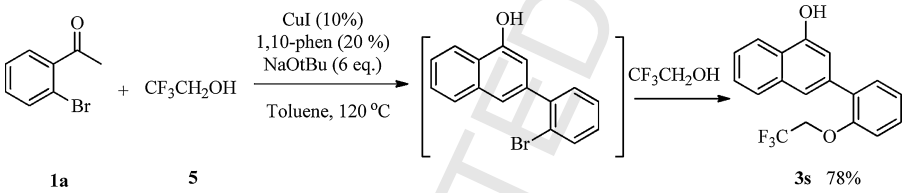


Scheme 3. The reductive of 1-naphthol **3a** in the presence of Pd/C.



Scheme 4. Suzuki-coupling of 1-naphthol **3a** and phenylboronic acid.



Scheme 5. Synthesis of compound **3s** in one pot from 1-naphthol **3a**.

4. Conclusion

In conclusion, we have developed Cu-catalyzed cyclization reaction for the synthesis of 1-naphthols by the dimerization of *o*-bromoacetophenones **1** or cross-cyclization of *o*-bromoacetophenones **1** with simple ketones **1m-1q**. The process was initiated by a rare Cu-catalyzed arylation of simple methyl ketones with aromatic bromides. The cascade strategy with simple substrates and catalyst marks a significant departure from known approaches. Therefore, we believe this method will be very useful in organic chemistry and medicinal chemistry.

Acknowledgment

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