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Bromide-Mediated C−H Bond Functionalization: Intermolecular Annulation of Phenylethanone Derivatives with Alkynes for the Synthesis of 1-Naphthols

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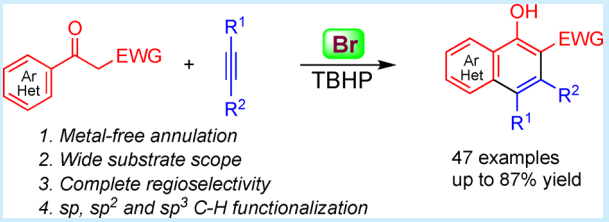
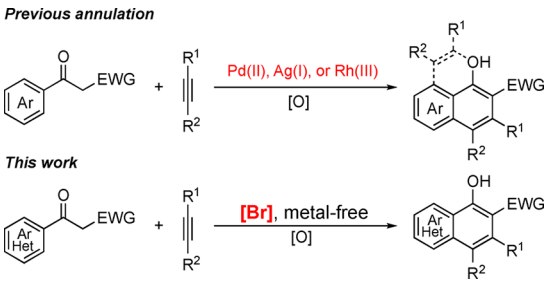
Supporting Information

ABSTRACT: Bromide-mediated intermolecular annulation of phenylethanone derivatives with alkynes has been developed, which allows for the regioselective formation of polysubstituted 1-naphthols. The usage of readily available bromine catalyst, broad substrate scope, and mild conditions make this protocol very practical. Mechanistic investigations reveal that the bromination of phenylethanone derivatives occurs to yield bromo-substituted intermediates, which react *in situ* with alkynes to furnish the desired 1-naphthols.



The synthesis of polycyclic compounds has always been of continued strong interest to organic chemists for their widespread application. In this context, the intermolecular annulation reactions of alkynes with arenes or heteroarenes via transition-metal-catalyzed C−H activation, which showed their atom- and step-economy without prefunctionalizing starting materials,[1] have attracted considerable attention. A variety of transition-metals, such as Rh,[2] Ru,[3] Pd,[4] Ni,[5] Cu,[6] Au,[7] Fe,[8] and Co,[9] were revealed to catalyze the annulations by constructing a C−N, C−O, or C−C bond to produce varying target molecules such as naphthanol, isoquinolines, indole, pyrroles, and so on. While these methods have recently emerged as reliable tools in generating diverse polycyclic compounds, they require the participation of metals, and certain reactions proceed at high temperatures. Because the terminal alkynes are prone to homocoupling under transition-metal-catalyzed conditions, most annulations of alkyne with arene are mainly limited to the use of internal alkynes.[1c] Moreover, one of the main problems encountered is the regioselectivity during the annulation of unsymmetrical alkynes, and this often results in the formation of the mixture of isomers. Therefore, development of metal-free, efficient, regioselective cyclization methods based on direct C−H bond functionalization is highly desirable. To our knowledge, the metal-free direct intermolecular annulation of arenes with alkynes is rare.[10] Early studies by Spyroudis and co-workers on the use of phenyliodonium ylides of 1,3-dicarbonyl compounds and terminal arynes for cyclizations revealed the limitations of this transformation due to the very high reactivity of iodonium ylides and low yields.[10a] Recently, Wei developed an oxidative benzannulation of enamines with alkynes for the synthesis of 1-amino-2-naphthalenecarboxylic acid derivatives by use of stoichiometric amounts of iodosylbenzene.[10b] Antonchick reported an elegant iodobenzene-catalyzed regioselective annulation of *N*-alkoxybenzamide derivatives with alkynes to synthesize isoquinolones.[10c] A similar hypervalent iodine(III)-promoted synthesis of isoquinolones was described by Zheng and co-workers.[10d] Although hypervalent iodines,[11] molecular iodine,[12] and even simple iodide salts[12,13] have been extensively investigated as the useful alternatives to transition-metal catalysts in the direct C−H functionalization, the catalytic utilization of bromine reagents in such transformations has received far less attention.[14] Here, we report a metal-free bromide-mediated oxidative annulation of phenylethanone derivatives with alkynes to furnish polysubstituted 1-naphthols under mild conditions. Highly substituted 1-naphthol is prevalent in natural products and biologically active molecules.[15] More recently, polysubstituted 1-naphthol synthesis via the direct oxidative annulation of alkynes with various readily available acetophenone derivatives catalyzed by transition metal catalysts, such as Rh(III),[2c,16] Pd(II),[17] and Ag(I),[18] have been reported (Scheme 1). Our reaction represents the first example of bromide-mediated C−H bond functionalization of arenes with alkynes and features readily available bromine

Scheme 1. Annulation for Synthesis of 1-Naphthols



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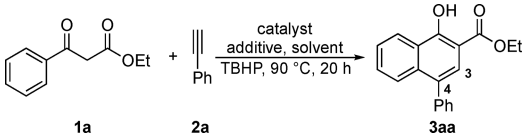
catalyst, metal-free intermolecular annulation, broad substrate scope, and complete regioselectivity. The annulation and aromatization readily proceeds with sp, sp^3, and unactivated sp^2 C−H bonds to form two C−C bonds simultaneously, providing a versatile, mild, and environmentally friendly alternative to existing protocols (Scheme 1).

At the outset of our investigation, the readily available ethyl benzoylacetate **1a** and phenylacetylene **2a** were employed as the model substrates, and various halides were examined using TBHP as oxidant. I_2 and iodide salts were inefficient as catalysts.[19] We next carried out the reaction using simple bromine reagents (Table 1). The expected annulation reaction took place, but gave

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3aa**

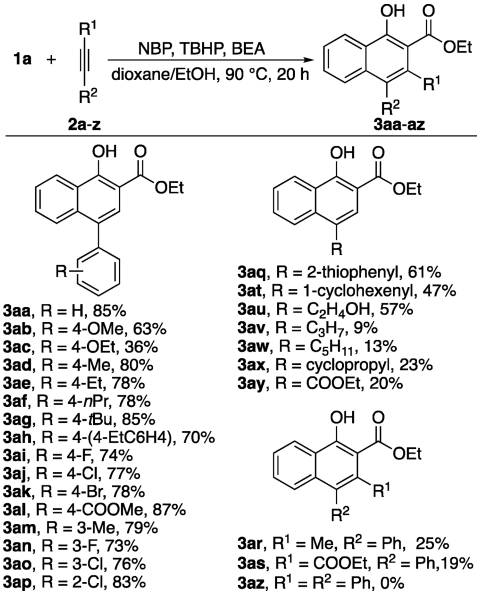
entry	catalyst	additive	solvent	yield (%)
1	Bu_4NBr		dioxane	6
2	LiBr		dioxane	11
3	NBS		dioxane	31
4	NBP		dioxane	25
5	NBP	PPh_3	dioxane	51
6	NBP	pyridine	dioxane	41
7	NBP	BEA	dioxane	61
8[b]	NBP	BEA	dioxane/EtOH	85
9[b]		BEA	dioxane/EtOH	49
10[b]	BEA	NBP	dioxane/EtOH	77
11[b]			dioxane/EtOH	0

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (20 mol %), additive (0.15 mmol), and TBHP (3.5 equiv, 70% aq) in 1,4-dioxane (2.0 mL) under air, isolated yield. [b]Compound **2a** (1.0 mmol), dioxane/EtOH (1:1, 4.0 mL).

very low yields of **3aa** with bromide salts (entries 1 and 2). To our delight, two *N*-bromoimides, *N*-bromosuccinimide (NBS) and *N*-bromophthalimide (NBP), increased the yield to 31% and 25%, respectively (entries 3 and 4). Although NBP gave a slight lower yield than NBS, we found that NBP-catalyzed annulation was almost free of side reaction. Based on the preliminary results, NBP was selected as the catalyst for further exploration. Gratifyingly, the yield of **3aa** could be significantly improved by the addition of 30 mol % of additives, such as PPh_3, pyridine, and 2-bromoethylamine hydrobromide (BEA) (entries 5−7). Especially BEA was the reaction additive that could afford the desired product **3aa** in 61% isolated yield (entry 7). When the amount of **2a** was raised to 200 mol %, higher yield of **3aa** was observed using a solvent combination of 1,4-dioxane and ethanol (entry 8). A control experiment showed that the yield was dramatically decreased in the absence of NBP (entry 9). Interestingly, when we used BEA as a catalyst and NBP as an additive, a good yield of **3aa** was also achieved (entry 10). It is worth noting that the present annulation cannot occur without bromine reagents (entry 11). Apart from the NMR spectroscopic analysis, the structure of **3aa** was further confirmed by single-crystal X-ray diffraction. Moreover, the annulation is completely regioselective since the phenyl group of phenylacetylene was installed at C4, without observing any of the C3 phenyl-substituted product.

With the best reaction conditions established, we applied this metal-free strategy to the cyclization of a wide range of alkynes. As illustrated in Scheme 2, both electron-donating and electron-

Scheme 2. Scope of the Alkynes[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), NBP (20 mol %), BEA (0.15 mmol), and TBHP (3.5 equiv, 70% aq) in dioxane/EtOH (1:1, 4.0 mL) under air, isolated yield.

withdrawing substituents were well tolerated on the phenyl fragment (**3aa-ap**). *Para*-, *meta*-, and *ortho*-substituted arylacetylenes participated smoothly in the annulation to generate **3aa−ap** as single regioisomers in 36−87% yields. We think that two electron-donating groups (−OMe and −OEt) might decrease the reactivity of alkynes, thus affording the product in slightly lower yields (**3ab** and **3ac**). It is noteworthy that aryl bromides, which are often unsuitable substrates for transition-metal-catalyzed C−H activation due to the competitive insertion of C−Br bond vs C−H bond, proved to be amenable to the current system (**3ak**). 2-Ethynylthiophene, which contained a heterocycle moiety, was compatible with the reaction conditions and provided product **3aq** in 61% yield. In the case of unsymmetrical disubstituted alkyne, they underwent exclusively regioselective annulation to afford the naphthols with the phenyl group being located at the C4-position (**3ar** and **3as**); however, only low yields were obtained, along with the recovered starting materials. The present metal-free oxidative conditions also allowed for additional functional groups on the alkyl moiety of alkyl terminal alkynes. It displayed a tolerance of sensitive alkenyl and hydroxyl groups, leading to the **3at** and **3au** in moderate yields. Unfortunately, other terminal alkynes with long alkyl chains, cyclopropyl, and ethyl carboxylate ester afforded the corresponding products in low yields (**3av−ay**). Diphenylacetylene was also subjected to the reaction conditions; however, none of the desired product was observed (**3az**). After investigation of the scope of alkynes, different aryl and heteroaryl ethanones were tested in annulation with alkynes **2a**, **2c**, and **2k** (Scheme 3). A range of ethyl benzoylacetates with different functional groups on the aryl moiety were compatible under the annulation conditions (**3ba-ka**). *Para*-substituted ethyl benzoylacetates bearing electron-donating and halide substituents afforded the corresponding 6-substituted naphthols **3ba**, **3ca**, and **3fa−ha** in good yields. 3,5-

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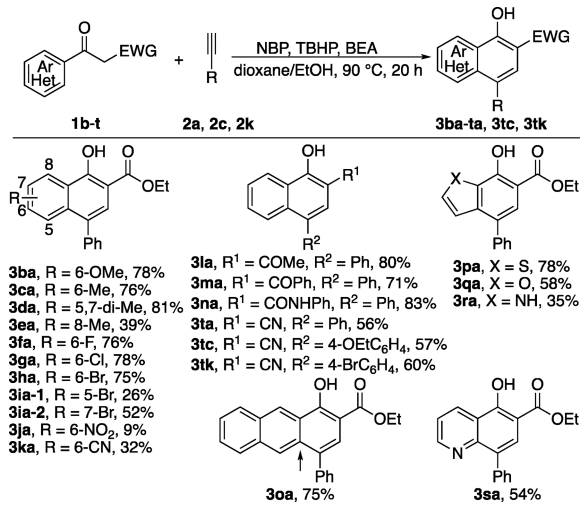
Scheme 3. Scope of the Aryl Ethanone[a]

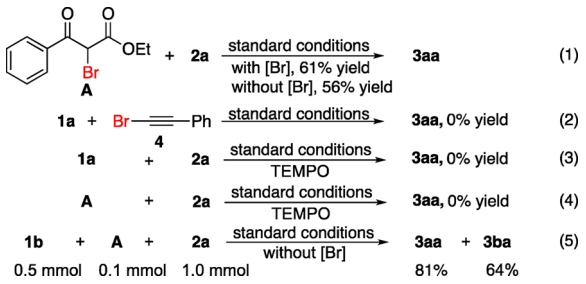


[a]Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), NBP (20 mol %), BEA (0.15 mmol), and TBHP (3.5 equiv, 70% aq) in dioxane/EtOH (1:1, 4.0 mL) under air, isolated yield.

Dimethyl substituted ethyl benzoylacetate produced desired product **3da** in high yield. However, in the case of *ortho*-methyl substituted ethyl benzoylacetate, a low yield of 39% was observed (**3ea**). Considering there are two possible annulation positions on the aryl moiety of the *meta*-substituted ethyl benzoylacetate, we conducted the reaction with *meta*-Br substrate to uncover the site-selectivity. Here, the annulation provided a 78% overall yield of two easily separable isomeric 1-naphthols **3ia−1** and **3ia−2** in 1:2 ratio in favor of the less sterically hindered isomer (**3ia−2**). The presence of electron-withdrawing substituents, such as NO_2 and CN, significantly decreases the yields of the products (**3ja** and **3ka**). In addition to the ethyl benzoylacetates, we were pleased to observe that the readily available benzoylacetone, dibenzoylmethane, and even 2-benzoylacetanilide are suitable substrates, providing the naphthols in high yields (**3la−na**). When ethyl 2-naphtholylacetate was employed, the annulation occurred regioselectively at the C3 position of the naphthyl ring to produce **3oa** as a single regioisomer in good yield. The unsaturated heterocycles, such as thiophene, furan, pyrrole, and pyridine may also serve as the aryl moiety, which coupled with **2a** at their C3 positions to furnish the valuable polysubstituted heterocycles (**3pa−sa**). We further applied the present annulation to the benzoylacetonitrile with different terminal alkynes, and the corresponding 2-nitrile substituted 1-naphthols were formed regioselectively in 56−60% yields (**3ta**, **3tc**, and **3tk**).

Having established the scope of the method, some investigations were carried out to study the reaction mechanism. During the reaction, in all cases, the formation of an unknown compound was observed, which gradually disappeared with the formation of products. In the model reaction, this compound was isolated from the crude reaction mixture and characterized by NMR and HRMS, and it was found to be ethyl 2-benzoyl-2-bromoacetate **A** (Scheme 4). Independently synthesized **A** was then subjected to reaction conditions. Regardless of whether Br mediators were used, the annulation proceeded smoothly to give the desired **3aa** in moderate yields (eq 1), thus suggesting that the present annulation is most likely to proceed through the intermediate **A**. Similar control experiments were carried out with phenylethynyl bromide **4**, which could be another possible

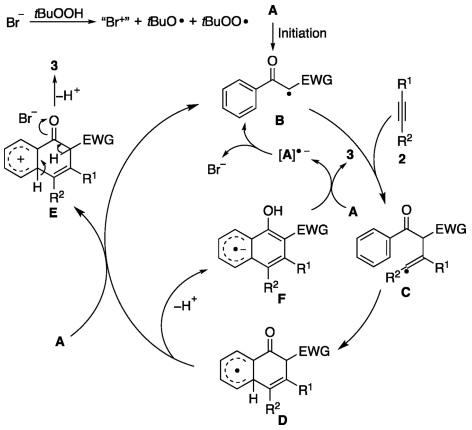
Scheme 4. Control Experiments



intermediate generated by bromination of alkynes. No conversion was observed when **4** was subjected to the reaction conditions (eq 2). The results exclude the possibility that **4** is involved as an intermediate in the annulation. The free radical inhibition study was then performed in the presence of TEMPO (3.5 equiv), and neither **3aa** nor intermediate **A** was detected (eq 3). Considering that the bromination of **1a** may involve a radical pathway, which can be blocked by TEMPO, bromide **A** was subsequently subjected to the reaction, and **3aa** was not observed either (eq 4). The experimental information indicates that the annulation of the resulting intermediate **A** with alkyne **2a** is in accordance with a free radical mechanism. Interestingly, when we treated **A** (20 mol %) with a mixture of **1b** and **2a** in the absence of Br mediators, the reaction produced **3aa** and **3ba** in 81% and 64% yield, respectively (eq 5). It indicates that the released bromine species from **A** perform the bromination with **1b**, which led to the subsequent cyclization with **2a**. Moreover, this result demonstrates that the bromine species is recycled in the reaction.

On the basis of the above observations and previous reports,[20] a plausible mechanism is proposed in Scheme 5. Initially, the

Scheme 5. Proposed Mechanism



oxidation of NBP and BEA generates the electrophilic active species "Br^+", which is believed to be a complex mixture of Br_2, BrO*t*Bu, BrOH, and $BrOH_2^+$.[21] The radicals *t*BuO• and *t*BuOO• are also generated from *t*BuOOH via a SET process. The resulting "Br^+" undergoes bromination with **1** to form intermediate **A**.[22] Subsequent homolytic cleavage of C−Br bond takes place to generate carbonyl alkyl radical **B**,[20a−c] which initiates a catalytic cycle.[23] Radical **B** couples with alkyne **2** to form vinyl radical **C**. We think that the stable arylvinyl radical **C** (R^2 = Ar) is formed preferentially in the cases of arylacetylenes, leading to naphthols with the complete regioselectivity. An intramolecular homolytic aromatic substitution (HAS) of **C** occurs to provide radical intermediate **D**.[20d,e] SET-oxidation of **D** by **A** generates a cationic

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intermediate **E**, which eventually yields naphthol **3** via deprotonation. Radical **B** and Br^- were regenerated through the oxidation (outside cycle).[23a,b] Alternatively, radical **D** can first be deprotonated to the corresponding radical anion **F**, which upon oxidation by **A** provides radical anion $[A]^{\bullet-}$ and final product **3**. Fragmentation of $[A]^{\bullet-}$ affords radical **B** and Br^- (inside cycle).[23a,b] In addition, the radical−radical coupling of **D** with more stabilized *t*BuOO$^\bullet$ followed by elimination of *t*BuOOH is also possible.[24]

In conclusion, employing simple and readily available bromine reagents, a mild and metal-free C−H bond functionalization for the synthesis of polysubstituted 1-naphthols with complete regioselectivity was developed. A comprehensive scope of this annulation reaction and tolerance of a wide range of functional groups were successfully demonstrated. Through the mechanistic study, the key reaction intermediate has been identified.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03186.

Detailed experimental procedures and spectral data (PDF)

Accession Codes

CCDC 912549 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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