<u>LETTERS</u>

lodine-Catalyzed Oxidative Functionalization of Azaarenes with Benzylic C(sp³)–H Bonds via N-Alkylation/Amidation Cascade: Two-Step Synthesis of Isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one

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(5) Supporting Information

ABSTRACT: An efficient and practical iodine-catalyzed oxidative functionalization of azaarenes with benzylic C–H bonds via an N-alkylation and amidation cascade is developed to provide isoquinolin-1(2H)-ones. This method utilizes readily available unfunctionalized azaarenes and methylarenes as starting materials and proceeds under metal-free conditions with good to excellent yields, avoiding the use of expensive noble metal catalysts and generation of halide and metal wastes.



The synthetic utility of this reaction is exemplified by the concise, two-step synthesis of isoindolo [2,1-b] isoquinolin-7(5H)-one.

soquinolin-1(2H)-ones are present in many natural products \mathbf{I} and pharmaceuticals.¹ For example, isoindolo[2,1-*b*]isoquinolin-7(5H)-one (1), rosettacin, and acuminatine maintain a remarkable activity against topoisomerase I (top 1) (Figure 1).² Certain derivatives of isoquinolin-1(2H)-ones feature antihypertensive activity;³ some others are useful NK3 antagonists,⁴ melatonin MT1 and MT2 receptor agonists,⁵ Rho-kinase inhibitors,⁶ JNK inhibitors,⁷ 5-HT3 antagonists, and thymidylate synthase (TS) inhibitors.⁸ The isoquinolin-1(2*H*)one pharmacophore is even found in drugs for treatment of stomach tumors and diseases of human brain cells.⁹ Therefore, the fascinating biological profiles of this group of compounds have stimulated researchers to develop various methods for the synthesis of isoquinolin-1(2H)-ones and their structural analogues.¹⁰ However, most of these transformations over-relied on expensive noble metal catalysts and elaborate designed substrates, such as transition-metal-catalyzed coupling and cyclization of ortho-halogenated benzamides with alkynes or ketones¹¹ and directed ortho C-H activation and annulation of N-substituted benzamides with alkynes.¹²

For the *N*-benzylisoquinolin-1(2H)-ones, to the best of our knowledge, there is only one report adopting a two-step procedure,¹³ which included the formation of a quaternary ammonium salt from the reaction of isoquinoline and benzyl



Figure 1. Examples of isoquinolin-1(2H)-one-fused natural products and pharmaceutics.

Scheme 1. Various Pathways for the Construction of N-Substituted Isoquinolin-1(2H)-ones



bromide followed by the alkaline ferricyanide oxidation using a large excess of $K_3Fe(CN)_6$, which not only resulted in low yields (around 30%) but also produced large amounts of KBr and K_4 Fe(CN)₆ as waste (Scheme 1a). On the contrary, the use of molecular iodine or iodide anion as a catalyst is a promising strategy and has attracted increasing attention.¹⁴ As part of our ongoing interest on benzylic $C(sp^3)$ -H bond functionalization,¹⁵ we recently reported the iodine-catalyzed oxidative benzylic C-H bond amination of azaarenes to afford 2heteroaryl quinazolinones, in which an benzylic C-H bond was converted to the benzylic iodide intermediate.^{15e} Inspired by this discovery, we conceived the possible construction of Nbenzylisoquinolin-1(2H)-ones from isoquinones and an unfunctionalized benzylic $C(sp^3)$ -H bond. Herein, we present an unprecedented oxidative functionalization of azaarenes with benzylic C(sp³)-H bonds via N-alkylation and amidation cascade (Scheme 1b), which was further applied to the concise, two-step synthesis of isoindolo[2,1-b]isoquinolin-7(5H)-one (1).

With our previous studies on iodine-catalyzed oxidative benzylic C–H bond amination in mind, 15e we first attempted

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(→→ + H	[I] (10 mol %)		
	2a	3a	<mark>0</mark> 4a	
entry	[I] (mol %)	[O] (equiv)	temp (°C)	yield ^{b} (%)
1	$I_{2}(5)$	DTBP(2)	130	<2
2	$I_{2}(5)$	TBHP (2)	130	23
3	$I_{2}(5)$	$H_{2}O_{2}(2)$	130	0
4	$I_{2}(5)$	TBHP (3)	130	72
5	$I_{2}(5)$	TBHP (3.5)	130	77
6	$I_{2}(5)$	TBHP (4)	130	78
7	CuI (5)	TBHP (3)	130	52
8	KI (10)	TBHP (3)	130	71
9	NIS(10)	TBHP (3)	130	68
10	$I_2(2.5)$	TBHP (3.5)	130	68
11	$I_2(10)$	TBHP (3.5)	130	58
12	$I_2(20)$	TBHP (3.5)	130	39
13	$I_{2}(5)$	TBHP (3.5)	120	84
14	$I_{2}(5)$	TBHP (3.5)	110	71
15	$I_{2}(5)$	TBHP (3.5)	100	43
16 ^c	$I_{2}(5)$	TBHP (3.5)	120	49
17 ^d	$I_{2}(5)$	TBHP (3.5)	120	44
18 ^e	$I_{2}(5)$	TBHP (3.5)	120	33
19 ^f	$I_{2}(5)$	TBHP (3.5)	120	46

^{*a*}Conditions: **2a** (0.4 mmol), catalyst (mol %), oxidant, in toluene (**3a**, 1.0 mL), reacted for 6 h under air atmosphere unless otherwise noted. ^{*b*}Isolated yields. ^{*c*}PhCl as solvent. ^{*d*}o-C₆H₄Cl₂ as solvent. ^{*e*}CH₃CN as solvent. ^{*f*}Dioxane as solvent.

Scheme 2. Influence of Alkylarenes on Iodine-Catalyzed Oxidative Functionalization of Isoquinoline



the reaction of isoquinoline (2a) and toluene (3a) with di-*tert*butyl peroxide (DTBP) as the oxidant in the presence of 5 mol % of molecular iodine as catalyst (Table 1, entry 1). The target *N*benzylisoquinolinone (4a) was detected by GC, although the yield was very low. The subsequent optimization revealed that the yield was critically affected by the oxidant used. The yield increased up to 23% by switching to *tert*-butyl hydroperoxide (TBHP, 5.5 M in dodecane) as the oxidant, but no desired Letter

Scheme 3. Influence of Azaarenes on the Iodine-Catalyzed Oxidative N-Alkylation and Amidation Cascade Reaction



Scheme 4. Mechanistic Experiments



Scheme 5. Plausible Mechanism for the Iodine-Catalyzed Oxidative Functionalization of Isoquinoline



product could be detected when hydroperoxide was used (entries 2 and 3). By increasing the amount of TBHP to 3.0 and 4.0 equiv, the yields of isoquinolinone (4a) were improved drastically to 72 and 78%, respectively (entries 4–6; aqueous TBHP was also applicable, although it resulted in slightly lower yields; see the SI for details). Next, other anionic iodine sources such as CuI and KI and cationic iodine such as NIS (*N*-iodosuccinimide) as catalyst were examined, all of which resulted in lower yields (entries 7–9). Later, the catalyst loading and reaction temperature were carefully optimized to provide the

Scheme 6. Different Approaches for the Synthesis of Topoisomerase I Inhibitor (1)



highest yield of 84% (entries 10-15). It is worth noting that this reaction can also be conducted in other solvents such as chlorobenzene, *o*-dichlorobenzene, acetonitrile, and dioxane, with 5 equiv of toluene added as reactant, but leading to decreased yields (entries 16-19).

The generality of this iodine-catalyzed oxidative functionalization of isoquinoline with benzylic C–H bonds was subsequently investigated. The substrate scope for the methylarene moiety is listed in Scheme 2. Methylarenes bearing electron-donating or -withdrawing substituents were successfully transformed into the desired isoquinolinone products via N-alkylation and amidation cascade in high yields, such as methoxy (**3b**), methyl (**3c**,**j**), halo (**3d**-**f**), and methoxycarbonyl (**3g**) groups. To our delight, both *m*-xylene (**3h**) and *o*-xylene (**3i**) reacted with isoquinoline readily, and good yields were realized, which revealed that there was no obvious steric hindrance effect for this cascade reaction. In addition to methylazaarenes, ethylbenzene (**31**) was also reactive, producing the corresponding N-alkylation and amidation products (**41**) in medium yields.

Encouraged by the exciting results obtained between the nucleophilic additions of isoquinoline with different alkylarenes, application of this iodine-catalyzed cascade reaction to other azaarenes was investigated next (Scheme 3). Substituted isoquinolines (2b-g) turned out to be suitable substrates for this transformation. To our delight, besides isoquinolines, the optimized reaction conditions can also be applied to the oxidative N-alkylation and amidation cascade reaction of quinazoline (2h), phthalazine (2i), and quinoline (2j) with toluene, although with quinoline (2a), perhaps due to the lower nucleophilicity of nitrogen.

During the substrate scope test (Scheme 2), the corresponding arylmethyl iodides were detected by GC–MS and ¹H NMR, which implies that this transformation might occur through a quaternary ammonium salt intermediate, similar to the reported two-step procedure.¹³ This assumption was further supported by the following mechanistic experiments. First, the quaternary ammonium salt **6** was synthesized by the reaction of isoquinoline (**2a**) and benzyl bromide in benzene. In the absence of iodine catalyst, the purified quaternary ammonium salt **6** can be readily transformed into the *N*-benzylisoquinolinone (**4a**) in 34% yield (in chlorobenzene), accompanied by the generation of *N*-benzyl-4-bromoisoquinolinone (7), which can be attributed to the further nucleophilic substitution of the enamide unit of product **4a** (Scheme 4a, see the Supporting Information for details). Alternatively, the quaternary ammonium salt **6** can also be generated in situ, which afforded the same products **4a** and 7, although the total yield was lower (Scheme 4b). Since the control experiments with benzyl bromide produced the amidation product smoothly in the absence of iodine, the function of iodine as the catalyst is confined to transforming benzylic C–H bond into benzyl iodide, and the amidation step does not require iodine. Next, *N*-benzyltetrahydroisoquinoline (**8**) was subjected to the standard conditions, and the oxidative amidation reaction proceeded smoothly to produce **4a** and **4a'** in 81% total yield (Scheme 4c). Unexpectedly, the addition of H₂O¹⁸ (2 equiv) did not yield the corresponding O¹⁸-enriched product **4a-O¹⁸** (Scheme 4d), which implied that the oxygen atom came from TBHP, not water.

On the basis of the mechanistic experiments described above and literature reports, ¹⁶ a plausible mechanism for this iodinecatalyzed oxidative functionalization of azaarenes with benzylic $C(sp^3)$ —H bonds is proposed in Scheme 5, with the reaction of isoquinoline (2a) and toluene (3a) shown as an example. First, the initial reaction of TBHP with molecular iodine would lead to the formation of ^tBuOI and HOI. The benzylic $C(sp^3)$ —H bond iodination reaction proceeds via a homolytic attack involving ^tBuOI or HOI to generate benzyl iodide, which reacted with isoquinoline readily to generate quaternary ammonium salt intermediate **A**. Subsequently, the nucleophilic addition of TBHP provides hemiaminal-type peroxide **B**,^{14a} which undergoes O–O bond cleavage to afford isoquinolinone product (4a). The molecular iodine as the catalyst can be regenerated by the oxidation of hydrogen iodide with TBHP.^{14b,c}

With this concise and efficient route to N-benzyl isoquinolinones in hand, we next turned our attention to the synthetic utility of these compounds. Isoindolo [2,1-b] isoquinolin-7(5H)one (1) was the representative compound identified as a topoisomerase 1 (top 1) inhibitor,² however, as far as we know, only three syntheses have been reported. The first synthesis of 1 was realized by Godfry in 1959 from the diammonium salt of 2,2'-dicarboxydesoxybenzoin, which was heated at 240 °C with diphenylamine as heat-transfer agent, followed by reduction by tin and hydrochloric acid in refluxing acetic acid (Scheme 6a).^{17a} The second one employed a lithiated toluamide-benzonitrile cycloaddition strategy, which included the deprotonation of N,N-diethyl-o-toluamide with n-butyllithium to give the anion, and then treated with substituted benzonitrile at -78 °C in THF to afford the 3-arylisoquinoline-1(2H)-one. Further deprotection and cyclization would provide the desired product 1 (Cho,

Scheme 6b).^{17b} The third synthesis based on the N-acyliminium chemistry starting from available anhydride or corresponding carboxylic acid, which was developed by Daich et al. (Scheme 6c).^{2c} While these three precedents utilized harsh conditions (240 or -78 °C) or multistep operations, we now show a concise two-step synthesis by integrating our N-alkylation/amidation cascade reaction with radical cyclization. Thus, the cascade reaction of isoquinoline (**2a**) and *o*-bromotoluene (**3m**) afforded *N*-benzylisoquinolinone **4m** (Scheme 6d),¹⁸ which was readily converted to isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (1) and its dihydro analogue (1') in 30 and 23% yield, respectively, by repeating the radical cyclization developed by Daich. It is worth noting that many other analogues of isoindolo[2,1-*b*]-isoquinolin-7(5*H*)-ones could be rapidly assembled by this new two-step procedure using readily available starting materials.

In conclusion, we have developed an efficient and practical iodine-catalyzed oxidative functionalization of azaarenes with benzylic C–H bonds via an N-alkylation and amidation cascade, which was integrated into the concise, two-step synthesis isoindolo[2,1-b] isoquinolin-7(5H)-one (1). This method utilizes unfunctionalized azaarenes and methylarenes as starting materials and proceeds under metal-free conditions with good to excellent yields, avoiding the use of expensive noble metal catalysts and generation of halide and metal wastes; thus, it is a "green" pathway for the construction of isoquinolinone. Further application of this strategy to other functionalizations of azaarenes is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00646.

General information, experimental procedures, detailed optimization, mechanistic experiments, compound characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Under the standard conditions, the reaction of isoquinoline (2a) and *o*-bromotoluene (3m) resulted in a much lower yield of 48% due to the debromination side reaction of product 4m to form 4a; thus, shorter reaction time and higher temperature were applied.