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Synthesis of sulfonylated benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones *via* I_2O_5-induced radical relay addition/cyclization of activated alkenes with sulfonylhydrazides

Yucai Tang [a,b,c,*], Meng Yang [a], Feifei Wang [a], Xia Hu [a], Gang Wang [a]

[a] College of Chemistry and Materials Engineering, Hunan Province Cooperative Innovation Center for the Construction & Development of Dongting Lake Ecological Economic Zone, Hunan University of Arts and Science, Changde 415000, PR China
[b] Hunan Provincial Key Laboratory of Water Treatment Functional Materials, Changde 415000, PR China
[c] Hunan Province Engineering Research Center of Electroplating Wastewater Reuse Technology, Changde 415000, PR China

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ABSTRACT

A facile I_2O_5 induced radical relay addition/cyclization of activated alkenes with sulfonylhydrazides has been successfully developed, leading to a broad range of sulfonylated benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones in moderate to good yields. The protocol has advantages of a metal-, base-, acid-, peroxide-free process, simple operation, and broad functional group tolerance.

Introduction

The fused-benzimidazo framework represents an important class of heterocycles owing to their potential biological activity, pharmaceutical significance and synthetic utility [1]. In particular, benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones skeleton are known as the core structures in many pharmaceutically active compounds and functional materials [2]. For example, compounds **A** and **B** are proved to display strong medicinal value, and compound **C** has been reported as a potential candidate for organic electronics (Fig. 1). As a consequence, the development of efficient approaches for the synthesis of structurally diverse benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones has attracted interest of chemists and pharmacologists.

In general, the traditional preparation of benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones relied on cyclization or condensation of *N*-(2-phenyl)ethylbenzimidazoles, *o*-halonitrobenzenes and tetrahydroisoquinolines (Scheme 1a) [3]. However, these methods often have one or more limitations in terms of the preprepared starting materials, harsh reaction conditions and limited functional group tolerability. In addition, Song and co-workers reported an elegant Cp*Rh(III)-catalyzed [4+2] annulation reaction to access benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones by applying commercial available 2-arylimidazoles and α-diazoketoesters as starting materials in 2018 (Scheme 1b) [4]. Despite important breakthroughs was achieved, potentially explosive diazo compounds and expensive $[Cp^*RhCl_2]_2$ catalyst were needed. In recent years, oxidative radical relay cascade reactions provide a powerful and versatile way to synthesize various heterocycle compounds [5]. In this context, *N*-acrylamide-substituted benzimidazoles have come to be used as radical acceptors and the groups of Yu [6], Reddy [7], Sun [8] and Lei [9] have independently developed radical cascade cyclization strategy for the synthesis of benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones by using RCOOH, $Ph_2P(O)H$, R_fI, PhCHO, TBPB, THF and $RB(OH)_2$ as the radical precursors, respectively (Scheme 1c). This series of methods provides a highly efficient route to construct benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-one motif with a wide substrate scope, however, these methods often require the use of metal catalysts, stoichiometric oxidant, acid/base reaction medium and high reaction temperatures, which might hinder its further synthetic applications. Thus, the development of a mild and environmentally friendly approach towards benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones is still highly desirable.

As an extremely valuable functional group, sulfone functionality is widely used in agrochemical, pharmaceuticals, and synthetic

* Corresponding author.
E-mail address: yctang1009@163.com (Y. Tang).

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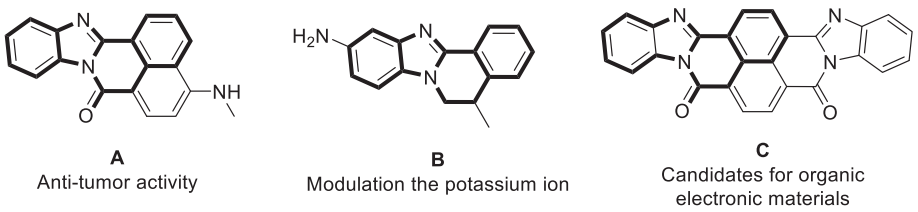
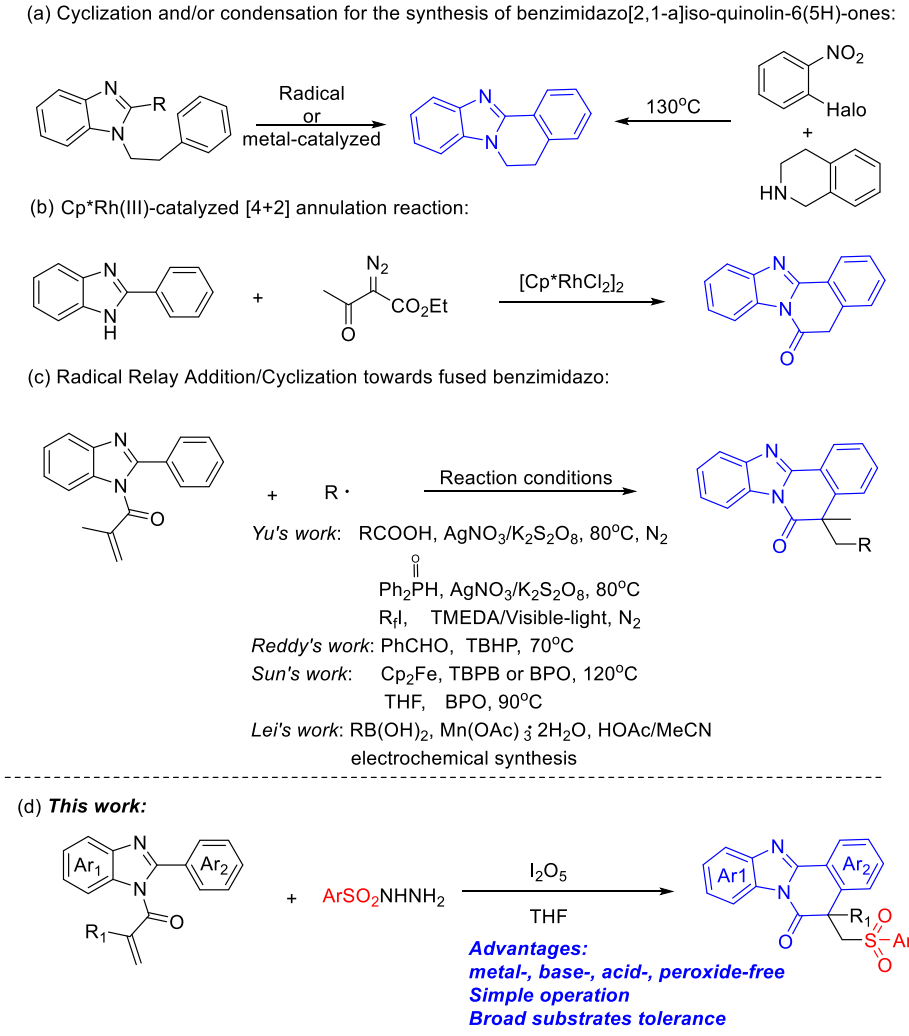


Fig. 1. Selected examples of benzimidazo-isoquinolin-6(*5H*)-ones.

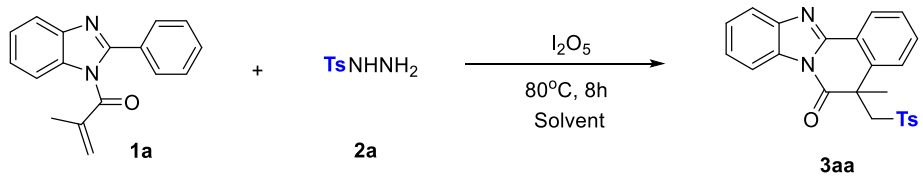


Scheme 1. Synthesis of benzimidazo[2,1-*a*]isoquinoline-6(*5H*)-ones.

precursors due to the unique biological and chemical properties of sulfone-containing molecules [10]. The development of novel, versatile strategies to construct different useful skeletons bearing sulfonyl groups would be highly significant. Among the various sulfonyl reagents, the incorporation of sulfonyl radicals, which generated *in situ* from sulfonylhydrazides, have been extensively researched and many successful alternative methods have been reported in the literature [11]. However, to the best of our knowledge, methods for the construction of molecules bearing both a sulfonyl group and a benzimidazo[2,1-*a*]isoquinolin-6(*5H*)-one motif have yet been reported. Based on the significance of the sulfonyl group and our ongoing interest in radical reactions [12], we herein report the first I_2O_5 induced radical relay addition/cyclization strategy for producing a variety of sulfonylated benzimidazo[2,1-*a*]isoquinolin-6(*5H*)-ones with sulfonylhydrazides as sulfonyl precursor (Scheme 1d). The present protocol has advantages of a metal-, base-, acid-, peroxide-free process, simple operation, and broad functional group tolerance.

We started the investigation by selecting the reaction of *N*-methacryloyl-2-phenylbenzoimidazole (**1a**) with *p*-toluenesulfonylhydrazide ($TsNHNH_2$) **2a** as the model reaction. To our delight, when the standard conditions established in our recently work were applied [12a], the reaction provided a 28% yield of the desired product **3aa** in MeCN at 80 °C for 8 h (Table 1, entry 1). Solvent screening experiments indicated that THF was the most suitable medium for the reaction, affording the desired benzimidazo

Table 1
Optimization of reaction conditions.[a]



1a 2a 3aa

Entry	Oxidant	Solvent	Yield(%)[b]
1	I_2O_5(2.0 eq.)	MeCN	28
2	I_2O_5(2.0 eq.)	1,4-Dioxane	54
3	I_2O_5(2.0 eq.)	Toluene	37
4	I_2O_5(2.0 eq.)	THF	72
5	I_2O_5(2.0 eq.)	DCE	46
6	I_2O_5(2.0 eq.)	MTBE	0
7	I_2O_5(2.0 eq.)	CPME	33
8	I_2O_5(2.0 eq.)	2-MeTHF	42
9	I_2O_5(2.0 eq.)	DMSO	Trace
10	I_2O_5(2.0 eq.)	DMF	Trace
11	I_2O_5(2.0 eq.)	THF	65[c]
12	I_2O_5(1.0 eq.)	THF	38
13	I_2O_5(3.0 eq.)	THF	67
14	I_2O_5(2.0 eq.)	THF	59[d]

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (2.0 eq., 0.5 mmol), I_2O_5 (2.0 equiv, 0.5 mmol) and solvent (2.0 mL) at 80 °C for 8 h. [b]Isolated yield based on **1a**. [c]1.5 eq. of $TsNHNH_2$. [d]60 °C.

[2,1-*a*]isoquinolin-6(*5H*)-ones **3aa** in 72% yield, and other solvents such as 1,4-dioxane, toluene, CPME (cyclopentyl methyl ether), 2-MeTHF and DCE gave low to moderate yields (Table 1, entries 2–8). By contrast, MTBE (methyl *tert*-butyl ether), DMF and DMSO were ineffective under the same conditions (Table 1, entries 6, 9–10). Further screening of the amount of *p*-toluenesulfonylhydrazide and oxidant revealed that either increasing or reducing the amount of $TsNHNH_2$ and I_2O_5 had no positive effect on the reaction efficiency (Table 1, entries 11–13). Finally, decreasing the reaction temperature also resulted in a lower yield of **3aa** (Table 1, entry 14).

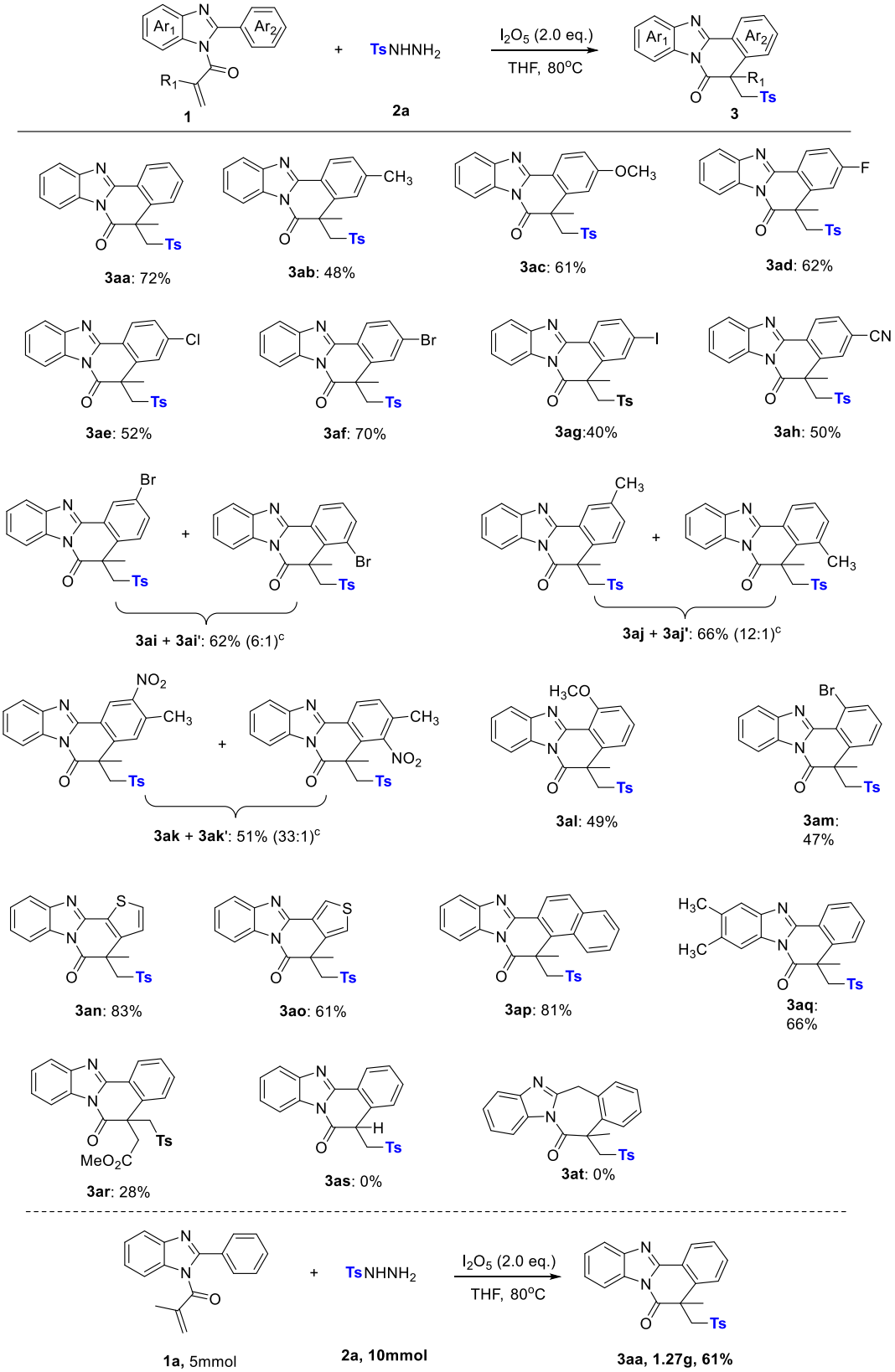
With the optimized conditions in hand, the substrate scope for this I_2O_5 induced addition/cyclization to access sulfonylated benzimidazo[2,1-*a*]isoquinolin-6(*5H*)-ones was investigated, as illustrated in Table 2. Initially, the suitability of various *N*-methacryloyl-2-phenylbenzoimidazole was studied under the standard conditions. It was found that various functional groups at the *para*-position of Ar_2, not only for the electron-donating groups (–Me, –OMe) but also for those electron-withdrawing substituents (–F, –Cl, –Br, –I, –CN), were tolerated well delivering the corresponding products **3ab**–**3ah** in moderate to good yields (40–70%). To investigate the regioselectivity of the transformation, the Ar_2 bearing a *meta*-bromo or *meta*-methyl substituent was treated with $TsNHNH_2$ under the optimized conditions, and a mixture of two regioisomers were generated in the ratio of 6:1 and 12:1, respectively (products **3ai**–**3aj**). When Ar_2 simultaneous bearing nitro and methyl substituents on the *meta*- and *para*-position, an obvious two regioisomers was generated in the ratio of 33:1 (product **3ak**). The reaction also proceeded smoothly with *ortho*-substituent on the Ar_2 affording the desired products **3al** and **3am** in moderate yields. In addition, heteroatom and naphthalene derived substrates **1** were also viable substrates to provide the corresponding benzimidazo[2,1-*a*]isoquinolin-6(*5H*)-ones **3an**–**3ap** in good yields. Moreover, Substrate **1** with multiple substituents on the Ar_1 occurred smoothly and gave the cyclization product in 66% yield (product **3aq**). The substituent effect at R_1 position was also evaluated. The CH_2CO_2Me substituent was compatible with the optimal conditions (product **3ar**), whereas monosubstituented olefin (R1 = H) did not undergo the cyclization (product **3as**). Attempts to construct seven-membered ring fused-benzimidazo framework by this radical relay reactions were fruitless, which might due to the ring strain (product **3at**). To further show the practical application of this method, *N*-methacryloyl-2-phenylbenzoimidazole (**1a**, 5 mmol) was employed in a gram-scale reaction and delivered **3aa** in 61% yield.

Next, a series of other sulfonylhydrazides with *N*-methacryloyl-2-phenylbenzoimidazole **1a** were investigated (Table 3). We were pleased to find that benzenesulfonyl hydrazide was able to furnish the desired product 5-methyl-5-((phenylsulfonyl)methyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(*5H*)-one (**3ba**) in 70% yield. Furthermore, benzenesulfonyl hydrazides **2**, bearing either electron-donating (–OMe) or electron-withdrawing (–F, –Cl, –Br, $–CF_3$) groups at the *ortho*- or *para*- positions of the aromatic ring were compatible with the optimized conditions, delivering the desired products in 45%~58% yields, respectively (products **3bb**–**3bg**). Finally, the reaction of naphthalene-2-sulfonohydrazide and thiophene-2-sulfonohydrazide with *N*-methacryloyl-2-phenylbenzoimidazole **1a** could also occurred smoothly and gave the cyclization products in good yield (products **3bh** ~ **3bi**).

To probe the mechanism of the reaction, we conducted several control experiments. Initially, we added 3.0 equiv of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine) or BHT (2,6-di-*tert*-butyl-4-methylphenol) in the reaction under standard conditions gave product **3aa** with trace amount and 10% yield, respectively (Scheme 2**,** eq 1). Whereafter, we researched whether sulfonyl radical produced in the reaction by adding 2.0 equiv 1,1-diphenylethylene and vinyl sulfone **4** was detected in 19% yield (Scheme 2**,** eq 2).

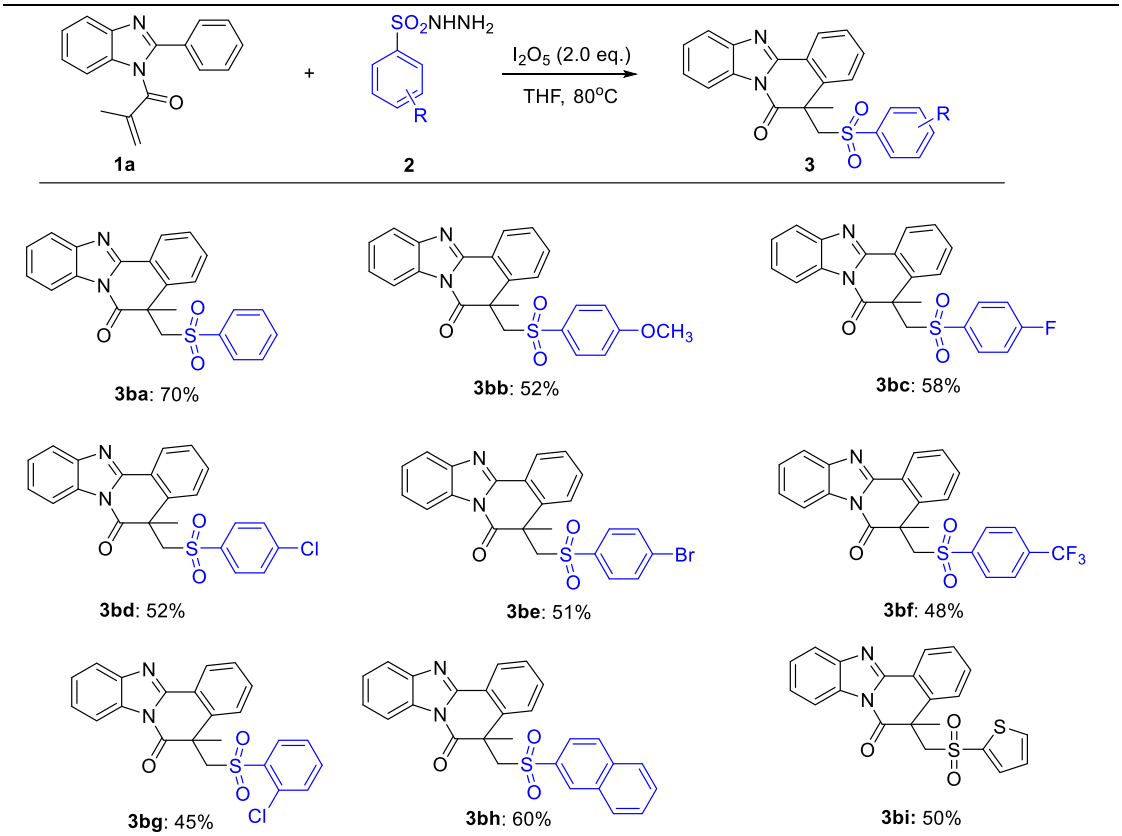
Based on the experimental results and previous reports [6–9,11,12a,13], a plausible mechanism for this transformation is proposed in Scheme 3. Initially, The single-electron oxidation of sulfonylhydrazide by I_2O_5 leads to the formation of sulfonyl radical **A**. Then, the addition of sulfonyl radicals to the C=C bond of **1** produce carbon radical intermediate **B**, which undergoes an intramolecular cyclization to deliver radical intermediate **C**. Following that, intermediate **C** was further oxidized *via* an

Table 2
Substrates scope of *N*-methacryloyl-2-phenylbenzoimidazoles.[a,b]

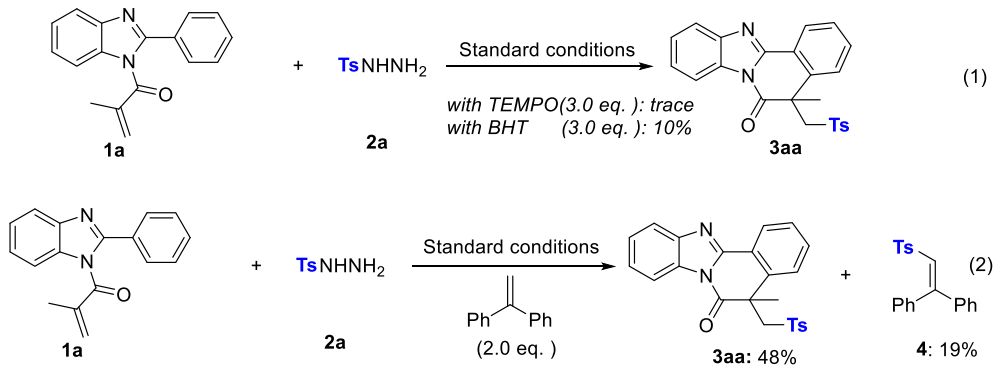


[a]Reaction conditions: Substrate **1** (0.25 mmol), **2a** (2.0 eq., 0.5 mmol), I_2O_5 (2.0 equiv, 0.5 mmol) and THF (2.0 mL) at 80 °C for 8 h. [b]Isolated yield based on **1a**. [c]The ratio of isomers was determined by ^1H NMR spectroscopy of the isolated products.

Table 3
Substrates scope of sulfonylhydrazides.[a,b]



[a]Reaction conditions: Substrate **1a** (0.25 mmol), **2** (2.0 eq., 0.5 mmol), I_2O_5 (2.0 equiv, 0.5 mmol) and THF (2.0 mL) at 80 °C for 8 h. [b]Isolated yield based on **1a**.



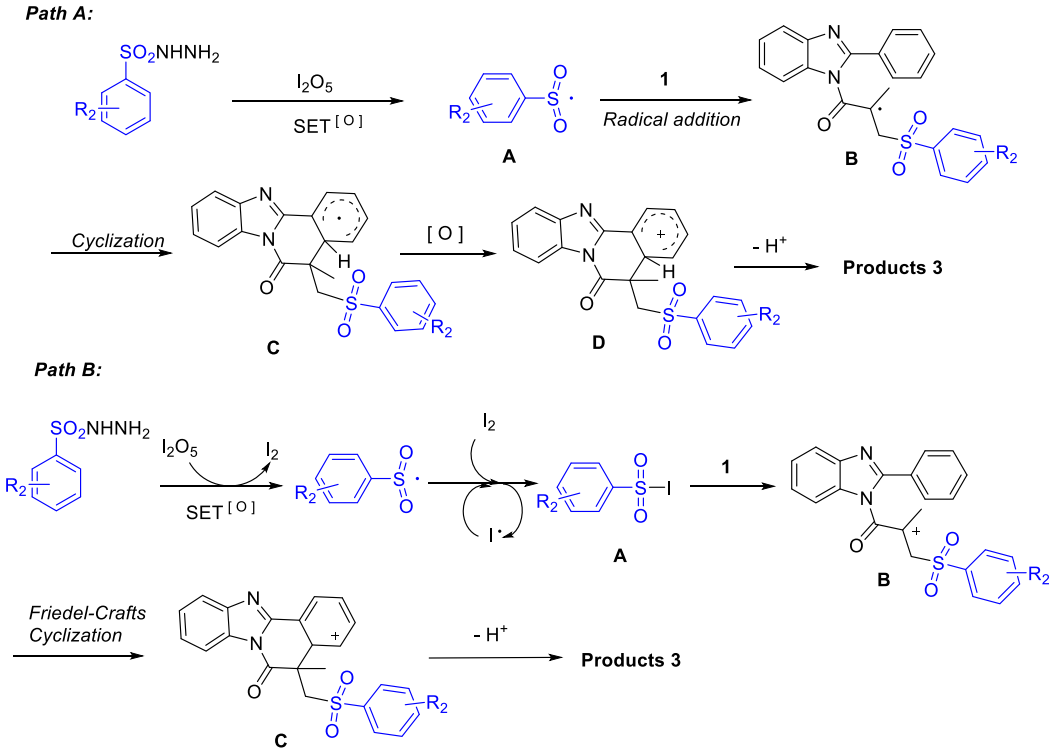
Scheme 2. Control experiments.

intermolecular single electron transfer (SET) process to form carbocation **D**. Finally, loss of a proton from **D** affords the desired products **3** (path A). It is also possible that products **3** is formed *via* the addition of arenesulphonyl iodides, which is generated from the reaction of sulfonyl radicals with I_2 or iodine free radicals, and then followed by a Friedel-Crafts reaction process (path B) [14].

In summary, we have disclosed a practical I_2O_5 induced radical relay addition/cyclization of activated alkenes with sulfonylhydrazides to synthesize various sulfonylated benzimidazo[2,1-*a*]isoquinolin-6(*5H*)-ones [15]. Compared with previous reports, the present protocol has competitive advantages as follows: (i) milder reaction conditions, such as metal-, base-, acid-, peroxide-free, thus makes this strategy more environmentally benign, practical and safe; (ii) the use of inexpensive and easily handled I_2O_5 as the oxidant and sulfonylhydrazides as radical precursor; (iii) simple operation; (iv) broad functional group tolerance and applicable to gram scale synthesis. Further applications involving this I_2O_5/-sulfonylhydrazides system are underway in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Scheme 3. Proposed mechanism.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152845.

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[15] **Typical Procedure for the Synthesis of 3.** An oven-dried reaction vessel was charged with substrate **1** (0.25 mmol), sulfonylhydrazide **2** (0.5 mmol) and I_2O_5 (167 mg, 0.5 mmol) in 2 mL THF. The vessel was sealed and heated to 80 °C for 8h. After completion the reaction, the reaction solution was cooled to room temperature and the volatiles were removed under vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 4:1) affording the desired product **3**. 5-***methyl-(tosylmethyl)benzo[4,]imidazo[2,1-a]isoquinolin-6(H)-one***(**3aa**): White Solid; mp 23–236 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.2 (d, *J* = 9.3 Hz, 1H), 8.34–8.20 (m, 1H), 7.91–7.79 (m, 1H), 7.2–7.3 (m, 4H), 7.29 (d, *J* = 8.3 Hz, 3H), 6.99 (d, *J* = 8.0 Hz, 2H), 4.7 (s, 1H), 4.00 (d, *J* = 14.7 Hz, 1H), 2.1 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.47, 149.21, 144.86, 143.62, 137.22, 136.11, 131.41, 127.90, 127.01, 126.26, 126.07, 12.76, 122.71, 21.33. HRMS (ESI) calcd for $C_{24}H_{21}N_2O_3S$ $(M+H)^+$ 417.1273, found 417.1270.