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Preparation of anthranils *via* chemoselective oxidative radical cyclization of 3-(2-azidoaryl) substituted propargyl alcohols†

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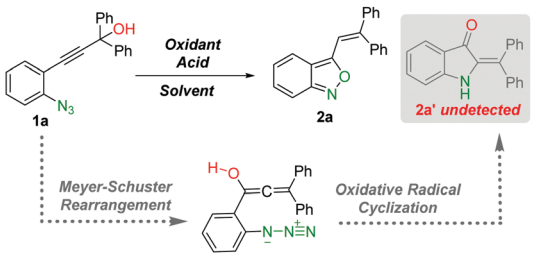
In the presence of $K_2S_2O_8$ and HOAc, 3-(2-azidoaryl) substituted propargyl alcohols can go through chemoselective oxidative radical cyclizations to give a pool of anthranils based on Meyer–Schuster rearrangement. It's proposed that the cyclizations were triggered exclusively by the direct attack of oxygen radicals on the azides. The weak N–O bonds in anthranils could be easily cleaved in the presence of transition metal catalysts and went through aminations with 2-oxo-2-phenylacetic acid and iodobenzene.

Recently, propargylic alcohols, which can be easily obtained from terminal alkynes and aldehydes or ketones, have extensively been applied as synthetic intermediates in modern organic synthesis.[1] Propargylic alcohols and its derivatives can go through highly efficient cascade reactions in the presence of acids based on Meyer–Schuster rearrangement,[2] and structurally versatile enones, carbocycles, and heterocycles have been obtained *via* this strategy.[3] What's more, allenols derived from propargylic alcohols *via* Meyer–Schuster rearrangement, could go through oxidative radical cyclizations in the presence of appropriate radical receptors.[4] Based on our interest in propargylic alcohols 3-(2-azidophenyl)-1,1-diphenylprop-2-yn-1-ol (**1a**) was synthesized in our laboratory. We imagined that in the presence of acid and oxidant, compound **2a′** would be obtained *via* cascade reactions of Meyer–Schuster rearrangement and oxidative radical cyclization. However, the designed product **2a′**, which is more thermodynamically stable, was not observed, and instead an unexpected product of 2,1-benzoisoxazole (**2a**) was obtained (Scheme 1).

The result thrilled us, as anthranils (2,1-benzoisoxazoles) are important fused heteroaromatic compounds, which can be employed as antimicrobial and anti-inflammatory agents, and antimalarial drugs.[5] Also, anthranils can be employed as inhibitors of the Protooncogene Pim-1 Kinase (Fig. 1).[6] More importantly, the weak N–O bonds in anthranils can be easily cleaved. Owing to their unique structure properties,[7] anthranil and its derivatives are very important synthetic intermediates.[8] Anthranils have been vastly employed in gold-catalyzed nitrene-transfer reactions of alkynes.[9] What's more, anthranils have often been used in C–H amidation reactions[10] and the synthesis of indole and quinoline derivatives and other N-contained heterocyclic compounds.[11] Although anthranil is an important unit core, relatively few strategies for its synthesis have been reported; this might be because these compounds contain weak N–O bonds, so they can easily go through a ring-opening process under transition-metal catalysis. In the reported references, the reductive heterocyclizations of 2-nitroacylbenzene derivatives were the most common approaches for preparing anthranil and its derivatives.[12] In addition, intramolecular cyclization of 2-azido aryl ketones could also afford 2,1-benzisoxazoles.[13] In view of its importance, more expedient synthetic strategies need to be explored.

Based on our interest in 2,1-benzisoxazoles, which can be employed as masked nitrogen nucleophiles and go through



Scheme 1 Cascade reaction of **1a**.

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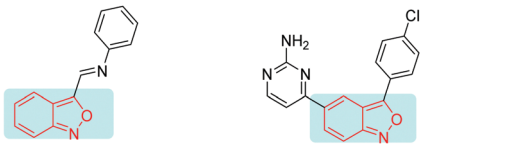
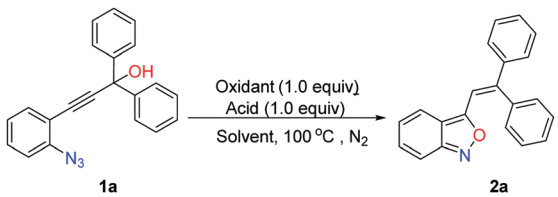


Fig. 1 Representative anthranil analogues with biological potential.

amination reactions with various carbon sources, and considering the importance of this core, we next optimized the reaction conditions (Table 1). Based on our initial try where treatment of **1a** with $(NH_4)_2S_2O_8$ in CH_3CN afforded **2a** in 20% isolated yield (Table 1, entry 1), several oxidants were tested (Table 1, entries 2–4). Among them, $Na_2S_2O_8$ was proven to be better and could improve the yield of **2a** to 40%. We were convinced that the cyclization was initiated by Meyer–Schuster rearrangement, thus several Brønsted acids and Lewis acids were then tested (Table 1, entries 5–9). To our delight, when 1.0 equivalent of HOAc was added to the reaction system, the yield of **2a** was improved to 50%. However, other acids afforded diminished yields (Table 1, entries 6–9). After that, the solvent was also screened (Table 1, entries 10–12). Luckily, when the reaction was carried out in toluene, the isolated yield of **2a** could be improved to 87% with exclusively chemoselectivity.

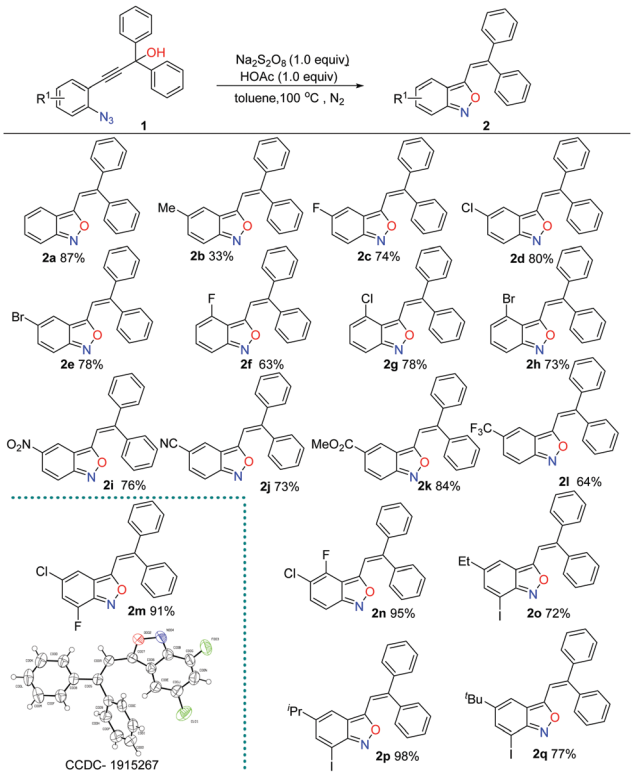
Under the optimized reaction conditions, various substitutions (R^1) that were attached at the 3-(2-azidophenyl) ring of compound **1** were examined (Scheme 2). Electronic characters of the substituents affect the reactions largely. It was found that an electron-donating group, for example methyl substituted compound (**1b**), afforded a low yield of **2b**. No desired product was obtained when methoxyl was attached at the 3-(2-azidophenyl) ring of compound **1**.[14] In contrast, when an electron-withdrawing group, such as fluro, chloro, bromo, nitro, cynao, ester, or trifluoromethyl groups were attached to the 3-(2-azidophenyl) ring, the yields of the desired products were good (**2c–2l**). The electronic effects of the substituents were even more obvious when two halogen atoms were attached to the 3-(2-azidophenyl) rings, as the isolated yields of the desired products **2m** and **2n** could be obtained as 91% and 95%, respectively. A frustrated yield was obtained when an alkyl group was attached to the 2-azide substituted phenyl ring (**2a**), and surprisingly when an iodo group co-exists with an alkyl group on the 3-(2-azidophenyl) rings, the desired products could be obtained in good to high yields (**2o–2q**).

Table 1 Optimization of the reaction conditions[a]



Entry	Oxidants	Acids	Solvent	Yield[b]
1	$(NH_4)_2S_2O_8$	—	CH_3CN	20
2	$Na_2S_2O_8$	—	CH_3CN	40
3	$K_2S_2O_8$	—	CH_3CN	20
4	DDQ	—	CH_3CN	Trace
5	$Na_2S_2O_8$	HOAc	CH_3CN	50
6	$Na_2S_2O_8$	TsOH	CH_3CN	—
7	$Na_2S_2O_8$	$Cu(OTf)_2$	CH_3CN	Trace
8	$Na_2S_2O_8$	$FeCl_3$	CH_3CN	Trace
9	$Na_2S_2O_8$	AgOTf	CH_3CN	45
10	$Na_2S_2O_8$	HOAc	EtOH	57
11	$Na_2S_2O_8$	HOAc	Dioxane	55
12	$Na_2S_2O_8$	HOAc	Toluene	87

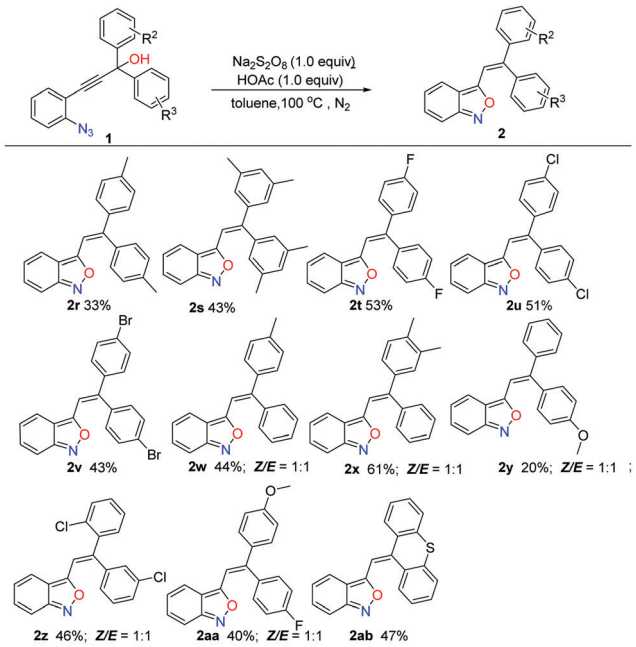
Reaction conditions: [a] **1a** (0.2 mmol), oxidants (1.0 equiv.), acids (1.0 equiv.) and solvent (2.0 mL) were stirred in a sealed tube at 100 °C for 12 h under N_2. [b] Isolated yields.



Scheme 2 Substrate scope study.[a]

Next, the effects of substituents of R^2 and R^3 were also examined under our optimal reaction conditions (Scheme 3). Neither alkyl nor halogen substituents were seemingly detrimental to the yields (**2r–2v**). Substrates with different substituents of R^2 and R^3 were also synthesized and examined (**2w–2aa**). No stereoselectivities were observed in the products, and the ratio of *Z*-/*E*-configuration was almost 1 : 1.[15] Interestingly, 9-((2-azidophenyl)ethynyl)-9*H*-thioxanthen-9-ol (**1ab**) reacted smoothly under our reaction conditions and afforded **2ab** in 47% yield.

Although anthranils have vastly been applied in organic synthesis, the 3-substituted substrate scope is very limited. A pool of anthranils have been synthesized under our reaction conditions, and then their applications in organic synthesis were tested and verified (Scheme 4).[16] The weak N–O bond in **2a** could be smoothly cleaved in the presence of CuI, and the ring

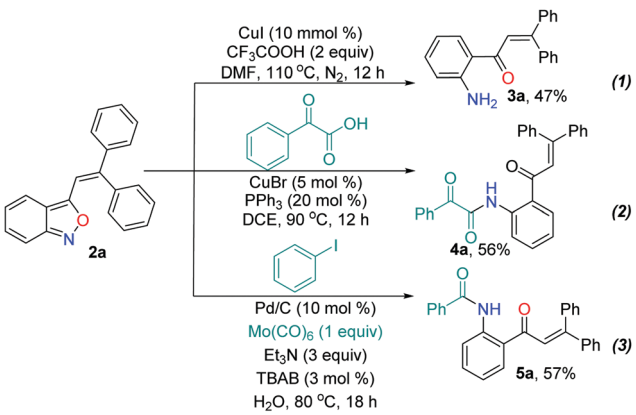


Reaction conditions: [a] **1** (0.2 mmol), $Na_2S_2O_8$ (1.0 equiv), HOAc (1.0 equiv) and Toluene (2.0 ml) were stirred in a sealed tube at 100 °C for 12 h under N_2; isolated yields.

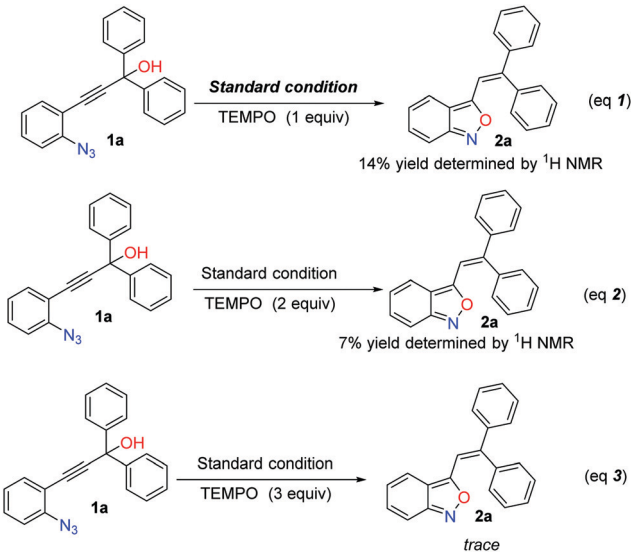
Scheme 3 Substrate scope study.[a]

opening product **3a** was obtained in 47% yield (eq 1).[17] What's more, **2a** could also be employed as a nitrogen nucleophile and could go through amination reactions in the presence of carbon sources. 2-Oxo-2-phenylacetic acid went through decarboxylation in the presence of CuBr, and then reacted with **2a** affording α-ketoamide **4a** (eq 2).[18] Iodobenzene together with $Mo(CO)_6$ as the solid CO source, could also go through a coupling reaction with **2a** smoothly and gave **5a** in 57% yield (eq 3).[19] Although the 3-position of benzoisoxazole was substituted with 1,1-diphenylvinyl, a very large group, the reactivities of **2a** were not affected.

To gain insight into the reaction mechanism, TEMPO was added to the reaction system under standard conditions (Scheme 5). It can be seen that when 1.0 equivalent of TEMPO was added, a sluggish yield of **2a** was obtained (eq 1). When the



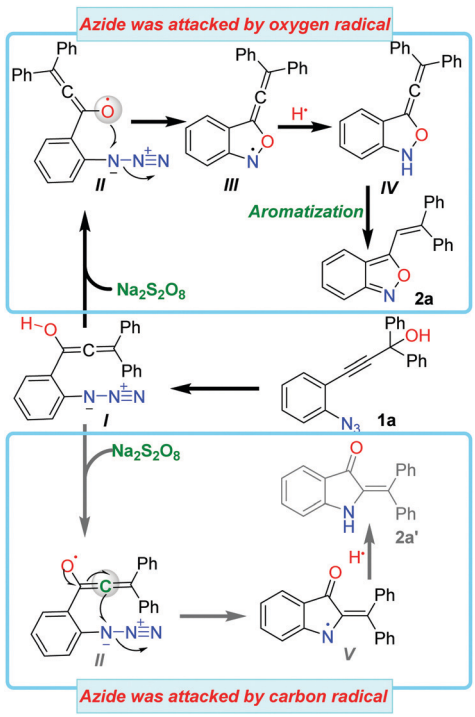
Scheme 4 Transformation of **2a**.[a]



Scheme 5 Control experiments under standard conditions.

amounts of TEMPO were increased to 2.0 equivalents, the yield of **2a** was reduced to 7% (eq 2). And when 3.0 equivalents of TEMPO were added, a trace amount of **2a** was detected (eq 3). The experiments suggested that the organic radical was involved in the cyclization process.

Based on previous reports and the experimental results, a plausible reaction mechanism is outlined in Scheme 6. It's imagined that **1a** would first go through Meyer–Schuster rearrangement to give an allenol intermediate (**I**), which was



Scheme 6 Plausible reaction mechanism.

immediately oxidized to form the allenol radical intermediate (**II**).

Next, the azide group was attacked directly by the oxygen radical to afford intermediate (**III**), which was then captured by a hydrogen radical to give intermediate (**VI**). Finally, the intermediate (**VI**) goes through an aromatization process to afford product **2a**. The initial designed process, that the azide group was attacked by a carbon radical to give intermediate **V**, was unrealized. Thus, product **2a′** was not observed. The whole reaction process showed excellent chemoselectivities.

In conclusion, a new strategy has been developed for the synthesis of anthranils under metal free conditions. Excellent chemoselectivity was seen in the product, as the azide group was attacked exclusively by oxygen radicals. The synthesized anthranils are important N-heterocycles, which can be employed as masked N-nucleophiles in various transformations. For example, the weak N–O bonds could be cleaved in the presence of Cu(I)-salts or Pd/C and go through aminations with 2-oxo-2-phenylacetic acid and iodobenzene.

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Conflicts of interest

There are no conflicts to declare.

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