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Cu/Ag-Catalyzed Reaction of Azirines with Anthranils: Synthesis of (Quinazolin-2-yl)methanone Derivatives

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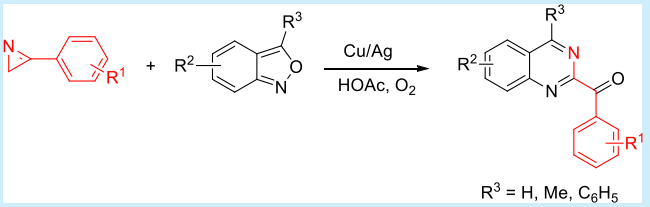
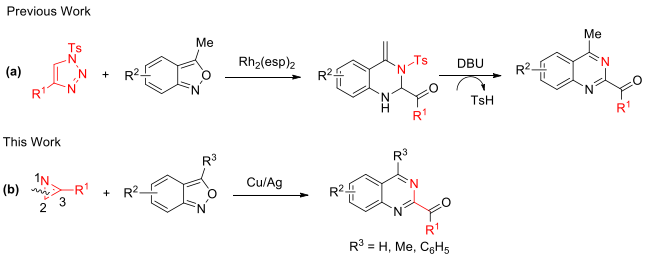
ABSTRACT: A Cu/Ag-catalyzed annulation of 3-aryl-2*H*-azirines with anthranils has been developed to expedite syntheses of (quinazolin2-yl)methanone derivatives. The transformation represents an unprecedented approach which employs a copper catalysis to cleave both a N−C^2 azirine bond and N−O anthranil bond. Subsequently, an unexplored 1,3-hydroxyl migration and *β*-N elimination are likely the key to access (quinazolin-2-yl)methanone derivatives.



Nitrogen-containing heterocyclic scaffolds are significant synthetic targets that widely exist in bioactive products and functional materials.[1] With the advent of new transition-metal-catalyzed reactions and the recognition that versatile synthetic intermediates can open up new vistas of reactivity, the development of novel methods to quickly access important heterocycles will be of long-standing interest of synthetic chemists. Quinazoline is a well-known strutural motif which has a broad spectrum of biological activity[2] such as sedative, anticonvulsant, anticancer, antitussive, antidiabetic properties. Nowadays, the effective molecular targeted drugs for lung cancer such as gefitunib and erlotinib are all quinazoline-related scaffolds.[3] Over the past decades, numerous protocols had been established to synthesize these particular heterocyles. For example, reactions utilizing 2-aminobenzylamine with either aldehydes, nitriles, amines, alcohols, or acids in the presence of various oxidants are the classical methods to achieve 2-substituted quinazolines.[4] However, methods for synthesis of quinazolin-2-yl-methanone derivatives with potential activities have rarely been investigated. Recently, the Tang group disclosed a Rh(II)-catalyzed synthesis of (4-methylquinazolin-2-yl)(phenyl)methanone derivatives through transannulation of *N*-sulfonyl-1,2,3-triazoles with 2,1-benzisoxazoles (Scheme 1a).[5] However, this protocol requires expensive transition metals, and the atom economy of using *N*-sulfonyl-1,2,3-triazoles as cycloaddition component is unsatisfactory. In view of the importance of heterocycles in drug reseach and our ongoing research interest in developing new synthetic methods derived from the cheap, earth abundant metal catalysis, we became interested in exploring novel approaches to produce (quinazolin-2-yl)methanones.

2*H*-Azirines have been extensively used as precursors in the synthesis of 4−7-membered nitrogen-containing heterocycles.[6] Although UV irradiation causes the cleavage of the C−C bond of the three-membered ring, the majority of annulation reactions occur through the ring-opening of C−N bonds of azirines under conditions such as heating or the attack of various nucleophiles, carbenes, carbenoids, and transition metals. In contrast, various transition metals like Cu(II), Fe(II), Rh(II), Ni(II), or Pd(II) are known to catalyze the ring opening mainly via a N−C^2 bond cleavage to give 4−6-membered heterocycles.[7] Anthranils are also a class of versatile synthetic intermediates owing to their significant coordinating property and cleavable N−O bonds. In various metal such as Rh-, Cu-, Au-, and Pd-catalyzed reactions, anthranils have been used as nucleophiles or aryl nitrene intermediates, and the breakage of N−O bonds leads to a skeleton which normally contains an electrophilic formyl group.[8] Although the dual functionalities of anthranils are extradinarily useful for constructing organic *π*-conjugated molecules containing nitrogen atoms, to the best of our knowledge, the cleavage of C−N bonds of 2*H*-azirines attacked by anthranils as nucleophiles or

Scheme 1. Transition-Metal-Catalyzed Synthesis of (Quinazolin-2-yl)methanones



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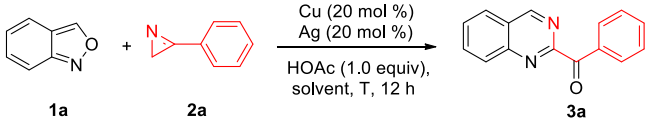
nitrenes is unprecedented, probably because 2*H*-azirines can also act as the nucleophile to cleave the N−O bond of anthranils. It is rarely seen that either of the coupling components can coordinate with metal and further have ring-opening through formation of a nitrene complex. Since the mechanistically interesting reaction has never been explored, we report a Cu/Ag-catalyzed annulation of anthranils with 3-aryl-2*H*-azirines to construct (quinazolin-2-yl)-methanones derivatives with specific selectivity and good functional group tolerance (Scheme 1b).

First, we conducted a reaction of anthranil **1a** (0.2 mmol), 3-phenyl-2*H*-azirine **2a** (0.4 mmol), copper(I) acetate (20 mol %), and HOAc (1 equiv) in DCE. After stirring at 80 °C for 12 h under a nitrogen atmosphere, no product was detected. Different copper catalysts such as CuCl, CuBr, and CuI were also tried, none of them were effective to induce the reaction. Fortunately, when $AgSbF_6$ (20 mol %) was employed, the reaction proceeded smoothly to produce phenyl(quinazolin-2-yl)methanone **3a**,[4a,9] albeit in moderate isolated yield (Table 1, entry 1). Then, the effects of silver additives such as $AgNTf_2$, AgOTf, AgOAc, and $AgBF_4$ were studied, but only $AgNTf_2$ gave the desired product in 38% yield (Table 1, entries 4−7). Increasing the reaction temperature from 80 to 100 °C furnished a slightly higher yield of **3a** (entry 8). Further improvement was achieved by screening different copper salts at 100 °C (entries 9−12). Although the reaction can undergo dehydrogenation spontaneously, oxidants such as TBHP, PIDA, and oxygen were added in order to improve the reaction efficacy (Table 1, entries 13−15). To our delight, the presence of oxygen accelerated the reaction rate and **3a** was obtained in 59% yield (Table 1, entry 15). Several solvents have also been tested for the model reaction and found that DMF, THF, toluene, and acetonitrile all led to poor results (Table 1, entries 16−19). Finally, up to 71% yield of **3a** was gained by reducing the quantity of $Cu(OAc)_2$ from 20 to 12 mol % (Table 1, entry 20).

Table 1. Optimization of Reaction Conditions[a]



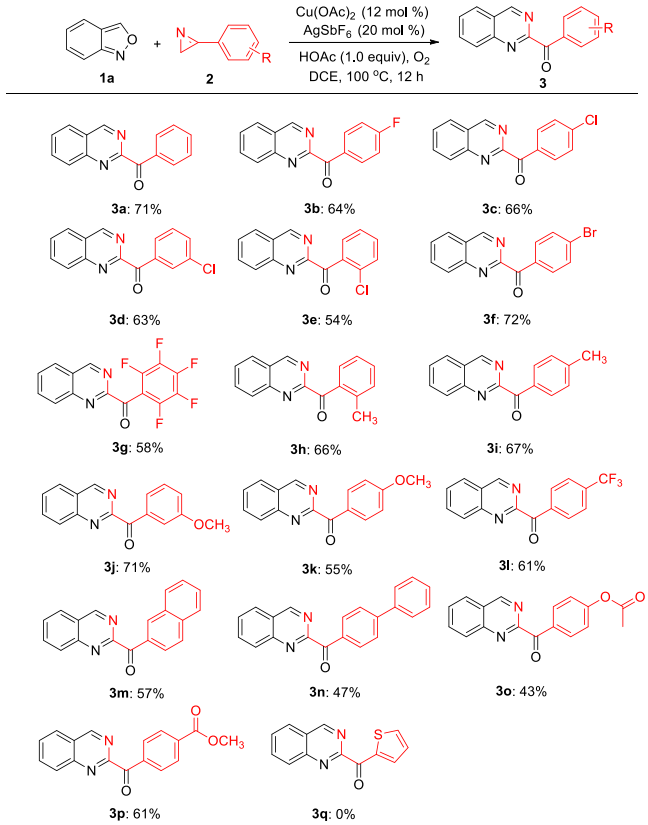
1a 2a 3a

entry	Cu	Ag	solvent	temp (°C)	yield[b] (%)
1	CuOAc	$AgSbF_6$	DCE	80	40
2[c]	CuOAc	$AgSbF_6$	DCE	80	ND
3[d]	CuOAc	$AgSbF_6$	DCE	80	10
4	CuOAc	$AgNTf_2$	DCE	80	38
5	CuOAc	AgOTf	DCE	80	trace
6	CuOAc	AgOAc	DCE	80	trace
7	CuOAc	$AgBF_4$	DCE	80	trace
8	CuOAc	$AgSbF_6$	DCE	100	42
9	$Cu(OAc)_2$	$AgSbF_6$	DCE	100	48
10	CuCl	$AgSbF_6$	DCE	100	45
11	CuBr	$AgSbF_6$	DCE	100	40
12	CuI	$AgSbF_6$	DCE	100	40
13[e]	$Cu(OAc)_2$	$AgSbF_6$	DCE	100	48
14[f]	$Cu(OAc)_2$	$AgSbF_6$	DCE	100	32
15[g]	$Cu(OAc)_2$	$AgSbF_6$	DCE	100	59
16[g]	$Cu(OAc)_2$	$AgSbF_6$	MeCN	100	ND
17[g]	$Cu(OAc)_2$	$AgSbF_6$	THF	100	ND
18[g]	$Cu(OAc)_2$	$AgSbF_6$	toluene	100	31
19[g]	$Cu(OAc)_2$	$AgSbF_6$	DMF	100	42
20[g,h]	$Cu(OAc)_2$	$AgSbF_6$	DCE	100	71
21[h]	**None**	**$AgSbF_6$**	**DCE**	**100**	**ND**

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Cu (20 mol %), Ag (20 mol %) and HOAc (1.0 equiv) were stirred in a solvent (2.0 mL) under N_2 for 12 h. [b]Isolated yield after chromatography. [c]HOAc was not used. [d]**1a** (0.4 mmol), **2a** (0.2 mmol) were used. [e]TBHP (0.2 mmol) was used. [f]PIDA (0.2 mmol) was added. [g]under O_2. [h]Cu (12 mol %) was used.

With the optimized conditions in hand, we sought to study the reaction scope with respect to the azirine substrates (Scheme 2). Gratifyingly, a variety of azirines with electronically and sterically variable functional groups at different positions were accommodated well. As depicted in Scheme 2, the steric hindrance did not influence the reaction efficiency significantly where a Cl and methyl at the *ortho*-positions gave good yields (**3e** and **3h**). Monohalogen (F, Cl, Br) or pentafluoro substituents and electron-donating groups (OMe or Me) at the *meta*- or *para*-positions were well tolerated, and the (quinazolin-2-yl)methanones products were isolated in 54−72% yield (**3a**−**3k**). Notably, azirines bearing electron-withdrawing groups such as CF_3, OAc, and COOMe at the *para*-position also reacted smoothly. Moreover, the reaction condition was compatible with the substrate bearing other aromatic rings (**3m**). However, when 3-(thiophene-2-yl)-2*H*-azirine was subjected to the current conditions, no desired product (**3q**) was obtained.

Scheme 2. Substrate Scope of 2*H*-Azirines of Synthesis of (Quinazolin-2-yl)methanones[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Cu (12 mol %), Ag (20 mol %), and HOAc (1.0 equiv) were stirred in DCE (2.0 mL) under O_2 for 12 h. [b]Isolated yield after chromatography.

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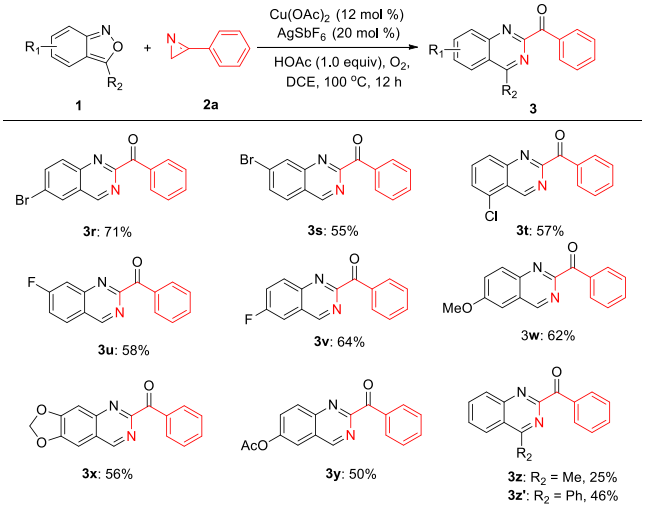
Org. Lett. XXXX, XXX, XXX−XXX

We next explored the scope of the anthranil coupling reagents (Scheme 3). The reactions of 3-phenyl-2*H*-azirine

Scheme 3. Substrate Scope of Anthranils of Synthesis of (Quinazolin-2-yl)methanones[a,b]

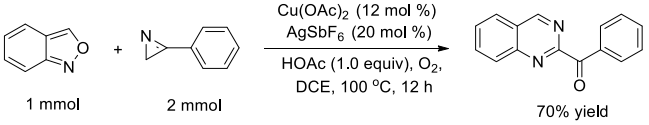


[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Cu (12 mol %), Ag (20 mol %), and HOAc (1.0 equiv) were stirred in DCE (2.0 mL) under O_2 for 12 h. [b]Isolated yield after chromatography.

with anthranils bearing halogen (F, Cl, Br) at different positions all furnished products in good yields (55−71%) (**3r**−**3v**). Both electron-donating groups such as OMe or alkoxy (**3w** and **3x**) and weak electron-withdrawing group OAc (**3y**) performed well in the reaction leading to the desired products in 50−62% yields. The annulation reaction was also extended to anthranils with an alkyl or phenyl group at the C-3 position and gave slightly lower yields of the corresponding 4-substituted-quinazolin-2-yl)(phenyl)methanones, as shown by the cases of **3z** and **3z′**.

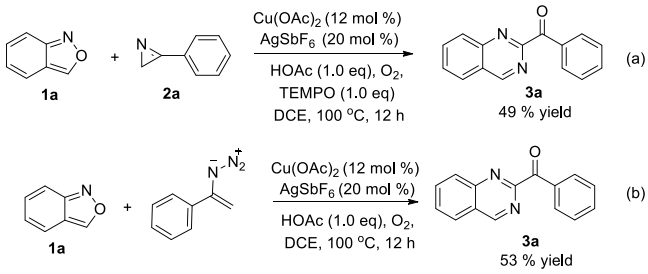
To illustrate the utility of this protocol in organic synthesis, a scale-up reaction of **1a** with **2a** under the standard reaction conditions was conducted. The reaction proceeded well to deliver the product **3a** in 70% yield, which is comparable to those in the smaller scale reaction (Scheme 4).

Scheme 4. Scale-up Reaction



To gain more mechanistic insights of this new methodology, we also conducted the control experiments. First, 1 equiv of a known radical quencher TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was subjected to the standard reaction to identify if there was any free-radical intermediate involved (Scheme 5a). The reaction works albeit in a slightly lower yield of (quinazolin-2-yl)methanones **3a**, which indicates that a radical mechanism is unlikely. It is well-known that both azirines and vinyl azides can convert into vinyl nitrenes upon heating.[10] Treatment of anthranil **1a** with (1-azidovinyl)benzene under optimized reaction condition gave 53% yield of product **3a** (Scheme 5b), revealing that the reaction probably occurs through vinyl nitrene metal complex formation. Notably, while

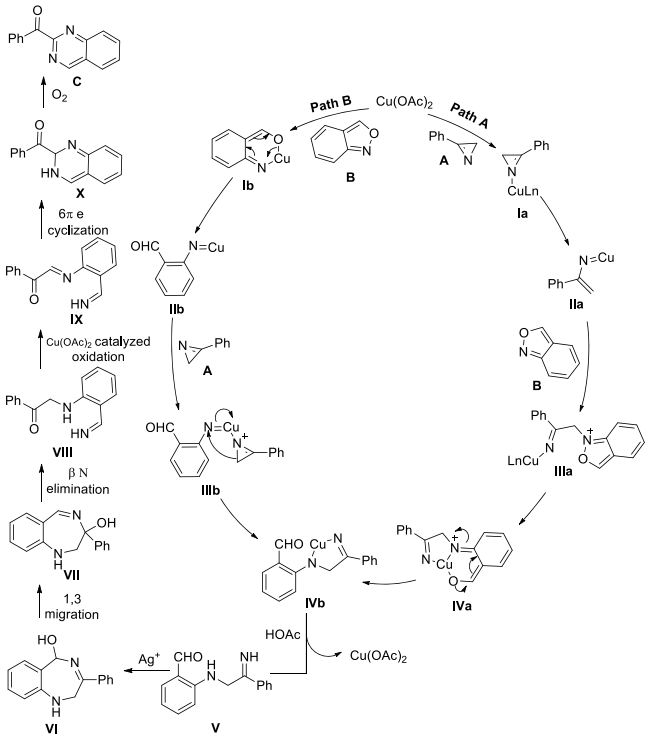
Scheme 5. Control Reactions



anthranils can also form aryl nitrene intermediate, azirines engage in the reaction through an imine annulation could not be completely excluded.

A proposed mechanism to account for the formation of quinazolin-2-yl-(phenyl)methanones is depicted in Scheme 6.

Scheme 6. Plausible Catalytic Cycle



Azirine **A** coordinates with the copper catalyst producing azirine complex **Ia**, which is further transformed into the nitrene copper complex **IIa** through a reversible N−C^2 bond cleavage.[7a,b] **IIa** is then attacked by anthranil to form intermediate **IIIa**. In **IIIa** Cu gets insertion into the adjacent N−O bond to generate intermediate **IVa**, which quickly isomerizes to produce the complex **IVb** (path A). Alternatively, Cu salt can insert into the cleavable N−O bond of anthranil **B** and lead to formation of the copper nitrenoid species **IIb**, which further coordinates with 2*H*-azirine **A** to provide intermediate **IIIb**. Subsequent migratory insertion of nitrenoid into the N−C^2 bond in **IIIb** affords the complex **IVb** (path B). Protonation of **IVb** by HOAc delivers the intermediate **V** and copper(II) acetate is regenerated to finish the whole catalytic cycle. $AgSbF_6$ promoted cyclization of **V** generates the intermediate **VI**.[11] 1,3 migration of hydroxy group and *β*-N elimination are followed to produce *α*-aminocarbonyl inter-

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Org. Lett. XXXX, XXX, XXX−XXX

mediate **VIII**, which can be coordinated with copper(II) and oxidized to form intermediate **IX**.[12] It further evolves into the 1,2-dihydroquinazoline product **X** via 6π electrocyclization. Finally, autoxidation of **X** affords the quinazoline derivative **C**.

In summary, a novel, short, and atom-economical synthesis of quinazoline derivatives through Cu/Ag-catalyzed annulation of 3-aryl-2*H*-azirines with anthranils was developed. This synthetic strategy has first utilized two building blocks, either of which can coordinate with copper and further have ring opening through formation of a nitrene complex. A possible mechanism involving the formation of copper nitrenoid, 1,3-hydroxy migration, and β-N elimination is postulated to clarify the generation of (quinazolin-2-yl)methanones. Further investigations of the reaction mechanism and the synthetic utility involving 2*H*-azirines or anthranils are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02222.

Experimental details and chemical compound information (PDF)

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Notes

The authors declare no competing financial interest.

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