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Synthesis of *N*-(Isoquinolin-1-yl)sulfonamides via Ag_2O-Catalyzed Tandem Reaction of *ortho*-Alkynylbenzaldoximes with Benchtop Stabilized Ketenimines

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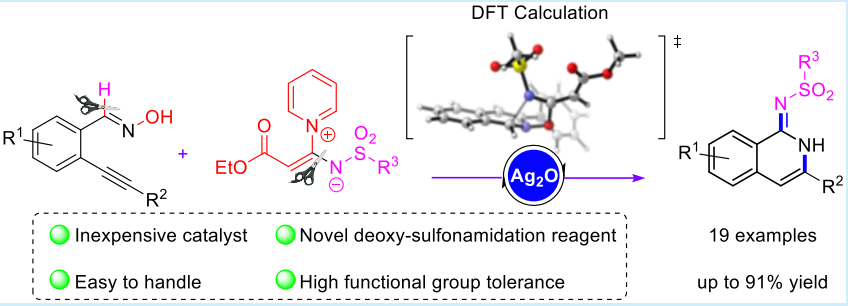

ABSTRACT: In this project, a moderately efficient approach to multisubstituted *N*-(isoquinolin-1-yl)sulfonamide derivatives was illustrated, utilizing *ortho*-alkynylbenzaldoximes and zwitterionic ketenimine salts in a tandem reaction catalyzed by silver oxide. The oxophilicity of Ag_2O, along with its nature as Lewis acid, pave the way for a smooth [3 + 2] cycloaddition between isoquinoline *N*-oxides and ketenimine species, which is a key step in this reaction. DFT calculation suggests that 1,3-dipolar cycloaddition of nitrone and ketenimine proceeds through a selective stepwise mechanism.

Sulfonamide-containing isoquinolines are frequently defined as of the most privileged *N*-heterocyclic frameworks in numerous biologically active compounds.[1] Among this family, there has not been much dedication toward developing a simple yet efficient synthetic method for delivering *N*-(isoquinolin-1-yl)sulfonamides. In this regard, sulfonylation of 1-amino-substituted isoquinolines as inaccessible starting materials with arylsulfonyl chlorides is one of the most common methods.[1a] In order to find available precursors, there are also a few multistep routes for synthesizing *N*-(isoquinolin-1-yl)sulfonamide scaffolds via aza-Wittig type reactions and copper-catalyzed *N*-heteroarylations.[1b,2] In addition to multistep methods, promoting a new one-step procedure is in high demand. Cao and co-workers reported that *N*-(isoquinolin-1-yl)sulfonamides could be generated through a palladium-catalyzed *N*-arylation of aryl chlorides with eligible sulfonamides.[3] In the context of direct C−H functionalization, Wu's group presented a Ni-catalyzed amidation reaction employing *N*-fluorobenzenesulfonamides as a $PhSO_2N$- moiety transferor, which was uncooperative in giving isoquinoline derivatives, resulting in meager yields.[4] A breakthrough in metal-free synthesize of *N*-arylsulfonamides including *N*-(quinolin-2-yl)sulfonamides and *N*-(isoquinolin-1-yl)sulfonamides was demonstrated by Bao and co-workers via a [3 + 3] cycloaddition of quinoline and isoquinoline *N*-oxides with sulfonamides in the presence of excess amounts of $PhI(OAc)_2$ and PPh_3 (Scheme 1).[5]

The reported methods suffer from some drawbacks, such as the requirement of a multistep procedure, excessive formation of waste, carrying out the reaction under microwave radiation, high temperature, use of organic halides, and formidable challenge in the introduction of substituents on the aromatic ring. Hence, continuous efforts are still needed to find a more efficient and general approach to *N*-(isoquinolin-1-yl)-sulfonamide scaffolds from readily available starting materials.

In the last few decades, *ortho*-alkynylbenzaldoximes have attracted intense attention as a powerful synthetic tool for the preparation of isoquinoline derivatives.[6] In this context, the reactivity of this well-known precursor has been studied with various dipolarophiles such as alkynes,[6b−g] alkene,[6d] and heteroallenes.[6c] Recently, our group reported the silver(I)-catalyzed reaction of *o*-alkynylbenzaldoximes with propargylic

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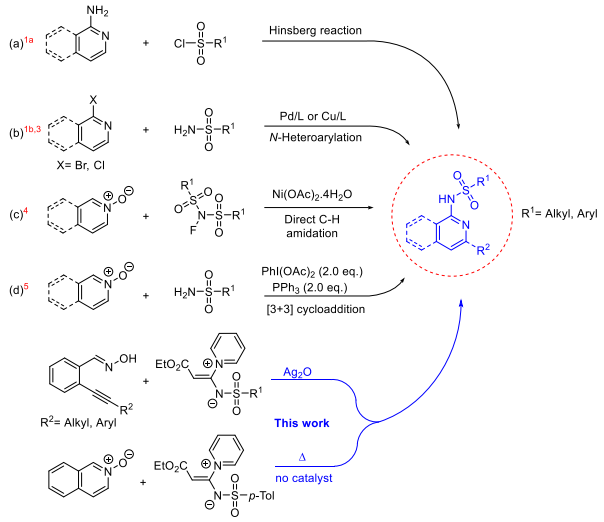
Scheme 1. General Approach for the Synthesis of *N*-(Isoquinolin-1-yl)sulfonamides

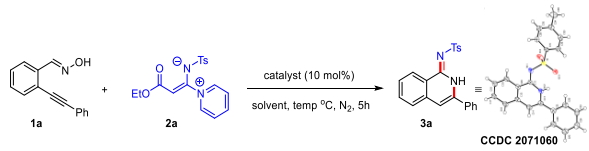


alcohols as an efficient path for the synthesis of 2-(isoquinolin-1-yl) prop-2-en-1-ones via a novel tandem reaction.[6g] After careful examination of all these reports, we envisioned that *o*-alkynylbenzaldoximes could be the key to solve the puzzle of synthesizing *N*-(isoquinolin-1-yl)sulfonamides.

Aware that cycloaddition reactions of ketenimine species as a reactive heterocumulene with compatible 1,3-dipoles[7] and 2- or 4-atom synthons[8] have been addressed on the synthesis of myriad heterocyclic compounds,[9] we have anticipated that ketenimine may be a suitable reaction partner for *ortho*-alkynylbenzaldoximes. Herein, we disclose the development of a novel method for the synthesis of valuable *N*-(isoquinolin-1-yl)sulfonamide derivatives through a tandem reaction of *ortho*-alkynylbenzaldoximes and pyridine-stabilized ketenimine salts in the presence of silver oxide as a catalyst.

To test the feasibility of our hypothesis, we first tried to investigate the reaction of 2-(phenylethynyl)benzaldehyde oxime **1a** as the isoquinoline *N*-oxide precursor with phenylacetylene and tosyl azide as a common in situ generated ketenimine[10] in the presence of a base and catalytic amount of copper(I) bromide and silver triflate (see the Supporting Information for more details). This targeted strategy was inspired by Wu's work for the synthesis of 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines.[11] This proposed route could not fulfill our purpose since 3-phenylisoquinoline was obtained as the product in 55% yield. Thus, we shifted our focus on newly discovered pyridine-stabilized ketenimines,[12] and zwitterionic salt **2a** was selected as a model substrate to react with 2-(phenylethynyl)benzaldehyde oxime **1a**. At the outset, when the reaction was carried out in the presence of 10 mol % silver triflate in dichloroethane at room temperature under a N_2 atmosphere, unexpected (*Z*)-4-methyl-*N*-(3-phenylisoquinolin-1(2*H*)-ylidene)benzenesulfonamide **3a** was obtained in 40% yield (Table 1, entry 1). X-ray structure shows that, due to intramolecular hydrogen bonding, the iminoisoquinoline tautomeric form of *N*-(isoquinolin-1-yl)sulfonamides is more stable (Table 1). Encouraged by this result, we attempted to optimize the reaction by raising the temperature (Table 1, entries 1−3). Gratifyingly, the yield considerably increased to 66% at 50 °C (Table 1, entry 3). We then screened a variety of several silver catalysts. Switching the catalyst to $AgNO_3$, compound **3a** could be generated in only 45% yield, and no

Table 1. Optimization of the Reaction Conditions



entry[a]	catalyst	solvent	temp (°C)	yield (%)[b]
1	Ag(OTf)	DCE	25	40
2	Ag(OTf)	DCE	30	44
3	Ag(OTf)	DCE	50	66
4	$AgNO_3$	DCE	50	45
5	AgCl	DCE	50	NR[c]
6	$Ag(CF_3CO_2)$	DCE	50	73
7	**Ag_2O**	**DCE**	**50**	**91**
8	Ag_2O	DMF	50	60
9	Ag_2O	toluene	50	56
10	Ag_2O	THF	50	66
11	Ag_2O	MeCN	50	64
12	Ag_2O	MeOH	50	37
13	Ag_2O[d]	DCE	50	48
14	Ag_2O[e]	DCE	50	55

[a]Reaction Conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), catalyst (10 mol %), solvent (1.5 mL), under N_2 atmosphere, temp °C, 5 h. [b]Isolated yield. [c]No reaction observed. [d]Catalyst (5 mol %). [e]Catalyst (20 mol %).

product detected in the presence of AgCl (Table 1, entries 4 and 5). Further exploration revealed that (*Z*)-4-methyl-*N*-(3-phenylisoquinolin-1(2*H*)-ylidene)benzenesulfonamide **3a** could be formed in 73% and 91% yields when $Ag(CF_3CO_2)$ and Ag_2O are employed as the reaction catalyst, respectively (Table 1, entries 6 and 7). We also inspected a series of solvents (Table 1, entries 8−12), but no better results were obtained, and dichloroethane was found to be the most favorable in terms of yields. Also, performing of reaction under ambient air condition was only accompanied by an increase in byproducts, showing that an inert atmosphere is necessary for the best results. Lower yields came about when the reaction was carried out with the lesser and higher amounts of catalyst (Table 1, entries 13 and 14), which might respectively be related to the turnover number of Ag_2O and the likely increase of side reactions.

Following these optimization studies, a wide range of substituted *ortho*-alkynylbenzaldoximes was tested to establish the scope and generality of this Ag_2O-catalyzed tandem sequence (Scheme 2). In the majority of cases, the anticipated reaction proceeded smoothly, leading to corresponding *N*-(isoquinolin-1-yl)sulfonamides **3** in moderate to good yields. *ortho*-Alkynylbenzaldoxime derivatives that bear electron-donating groups (R = C_6H_5, Me, OMe, OCH_2O) on phenyl ring at both R^1 and R^2 positions were quite compatible, furnishing the targeted products (**3b−3d**, **3f−3h**) in 70−83% yields. In contrast, chloro-substituted *ortho*-alkynylbenzaldoxime at R^1 position could give the desired product **3e** in only 51% yield, and no desired product was detected in case of using a stronger electron-withdrawing group (**3l**, **3m**). This finding may be linked to the descending HOMO energy level of isoquinoline *N*-oxide and eventuated stability in the existence of electron-withdrawing groups. It appears that the nature of substituents R^2 attached to the triple bond could have a large impact on the reaction efficiency since aryl groups (**3a−3i**) have demonstrated better results than alkyls (**3j**, **3k**,

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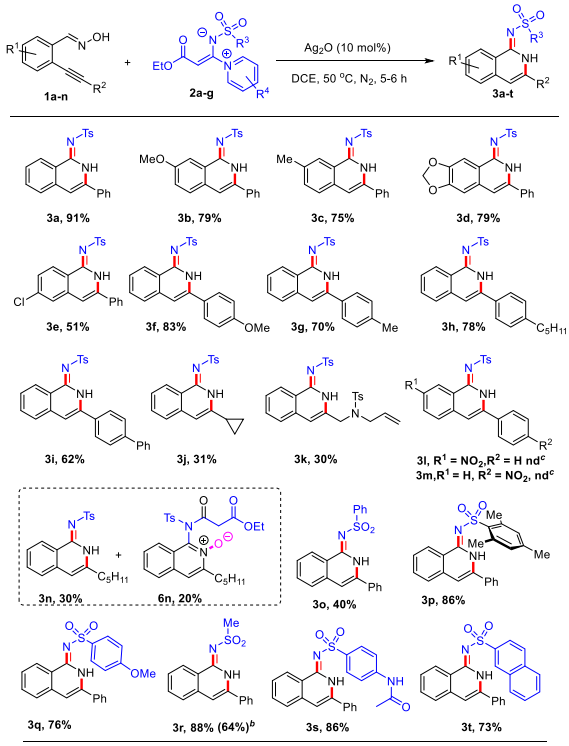
Scheme 2. Substrate Scope[a]



[a]Reactions were performed with **1** (0.3 mmol), **2** (1.0 equiv), Ag_2O (10 mol %) in DCE (1.5 mL) heated at 50 °C in an oil bath under N_2 atmosphere. [b]1.0 mmol scale. [c]nd = not detected.

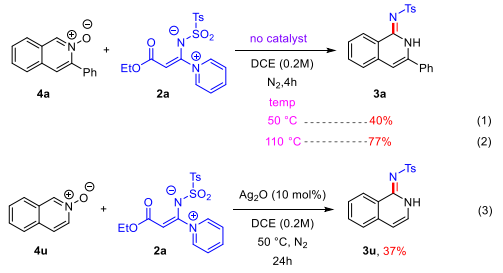
3n). Moreover, chemoselectivity in this tandem reaction can be inferred from the untouched double bond of the allyl group moiety in derivative **3k**.

In addition to the desired product **3n**, byproduct **6n** has been generated in a very low yield (Scheme 2) using **1n** as starting material. Neither performing of reaction under an oxygen atmosphere nor changing the silver catalyst source to $Ag(CF_3CO_2)$ could give us different results. Although we currently have no logical explanation for this oxidation, the confirmed structure of byproduct **6n** by spectral analysis (see Supporting Information) could help provide a reasonable mechanism. Eventually, the scope with regard to ketenimine zwitterionic salts was examined (for detailed structures of ketenimine salts, including R^4, see Supporting Information) (Scheme 2). To our delight, ketenimine salts with both aliphatic and aromatic groups at their R^3 position were well tolerated, rendering the expected *N*-(isoquinolin-1-yl)-sulfonamides (**3p**−**3t**) in 73−88% yields; however, compound **3o** with no substituent on its phenyl ring at the R^3 position was obtained in low yield. It is noteworthy that the presence of the hindered 2-mesitylenesulfonyl group had no significant effect on the reaction yield, and the corresponding product **3p** was formed in high yield.

In order to investigate whether silver oxide had a role in the following steps after the known formation of *N*-oxide **4a**, a control experiment was performed between independently prepared isoquinoline *N*-oxide **4a** and ketenimine salt **2a** in the absence of reaction catalyst (Scheme 3, eq 1).

The dramatic drop in the yield suggests that besides π-acid activation of the triple bond by silver oxide in the formation of related nitrone (6-*endo* cyclization step), subsequent steps are probably affected via LUMO lowering ability of silver catalyst.

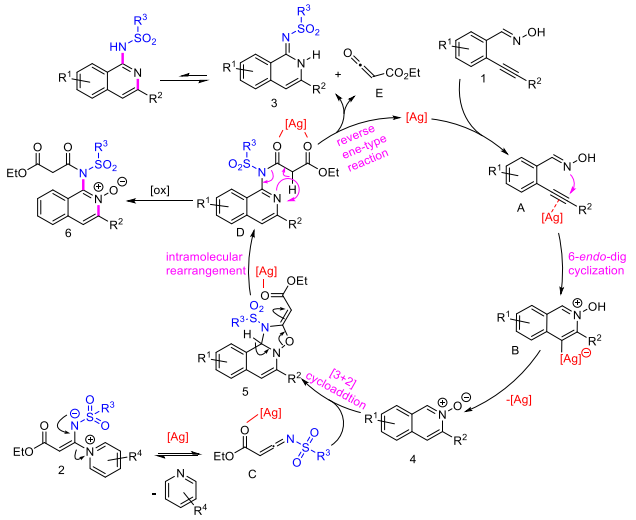
Scheme 3. Control Experiments



On the other hand, the exact experiment only in higher temperature gives rise to product **3a** in 77% yield, exposing that functionalization of isoquinoline *N*-oxides could also be feasible by using of ketenimine zwitterionic salts in a catalyst-free condition; however, good performance of the reaction in low temperatures depends on the significant help of Ag_2O catalyst (Scheme 3, eq 2). Furthermore, isoquinoline *N*-oxide without any alkyl or aryl group at its C-3 position could afford expected deoxy-sulfonamidation product **3u** in 37% yield, illustrating that simple isoquinoline *N*-oxides are also bearable under optimized conditions (Scheme 3, eq 3).

A plausible reaction mechanism for constructing functionalized *N*-(isoquinolin-1-yl)sulfonamides **3** is depicted in Scheme 4. We propose the tandem reaction initiated by the

Scheme 4. Proposed Mechanism for the Ag_2O-Catalyzed Tandem Reaction of *ortho*-Alkynylbenzaldoximes with Ketenimine Zwitterionic Salts



formation of isoquinoline *N*-oxide **4** through a silver(I)-catalyzed 6-*endo* cyclization of *ortho*-alkynylbenzaldoxime **1**. Meanwhile, the liberation of pyridine or 2,6-dimethylpyridine from zwitterionic salt **2** would afford electrophilic ketenimine **C**. Then, in situ generated ketenimine **C** undergoes a silver(I)-catalyzed 1,3-dipolar cycloaddition (1,3-DC) with isoquinoline *N*-oxide **4** to give [3 + 2] cycloadduct **5**.[13]

To shed light on the mechanism of 1,3-DC as the critical step of the reaction, we carried out a series of density functional theory (DFT) studies at the B3LYP/6-31G(d,p) level of theory using the Gaussian 09 package (see the Supporting Information for more details). 3-((Methylsulfonyl)imino)acrylate (**Ket**) and 3-phenylisoquinoline 2-oxide (**4a**) have been selected as the models for

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ketenimine and isoquinoline *N*-oxide, respectively. The HOMO−LUMO energy value analysis of optimized starting materials indicated that $HOMO_{dipole}$−$LUMO_{dipolarophile}$ interaction controls the 1,3-DC reaction in type I (Figure 1a).

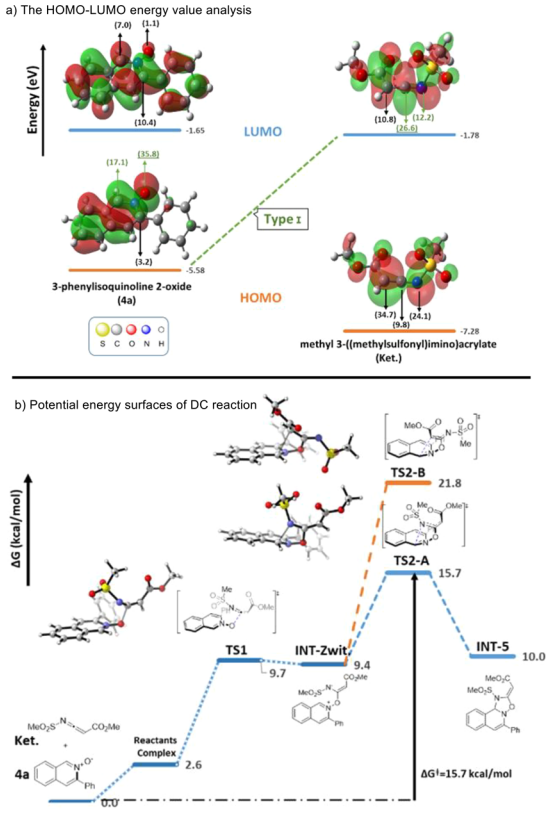

Figure 1. (a) The HOMO−LUMO energy value analysis (are in eV) and FMO-CA that are given in parentheses. (b) Potential energy surfaces of the stepwise cycloaddition of methyl 3-((methylsulfonyl)-imino) acrylate (**Ket**) and 3-phenylisoquinoline 2-oxide (**4a**) (all energies are in kcal/mol).

Frontier molecular orbital contribution analysis (FMO-CA)[14] predicts well the selectivity of the reaction; that is, the atoms with the highest HOMO-CA in **4a** react with the atoms with the highest LUMO-CA in the **Ket** (Figure 1a). To give further insight into the cycloaddition step, potential energy surface (PES), relative transition state (TS), and intermediates (INT) are shown in Figure 1b. The PES reveals that 1,3-DC proceeds via a stepwise-fashion through the zwitterionic intermediate **INT-Zwit**. Accordingly, the first step in the 1,3-DC is nucleophilic addition of isoquinoline *N*-oxide **4a** to the central carbon atom of ketenimine **Ket**, and the cyclization process could carry on from either the nitrogen or carbon atom in intermediate **INT-Zwit**. The obtained theoretical datum for barrier difference between two pathways for the chemoselectivity is 6.1 kcal/mol (**TS2-B**, relative to **TS2-A**) in favor of **TS2-A**.

Subsequent intramolecular rearrangement of cycloadduct **5** leads to compound **D**, and obtaining **6n** verifies the intermediacy of compound **D** in the discussed reaction, which further goes through a reverse ene-type reaction due to the high basicity of its amidinic functional group, resulting in *N*-(isoquinolin-1(2*H*)-ylidene) sulfonamide **3** (Scheme 4).

In conclusion, we have developed a novel Ag_2O-catalyzed tandem reaction for assembly of *N*-(isoquinolin-1-yl)-sulfonamides starting from readily accessible *ortho*-alkynylbenzaldoximes and benchtop stable ketenimines. The reaction proceeds smoothly under mild conditions via a cascade sequence, involving 6-*endo* cyclization, 1,3-DC, intramolecular rearrangement, and reverse ene-type reaction. DFT calculation proves 1,3-DC occurs via a stepwise-fashion. The second step selectively prefers to conduct the cyclization from nitrogen atom of ketenimine; these data are in agreement with experimental results. This methodology allows the simultaneous formation of two C−N bonds, delivering a broad scope of valuable and potentially bioactive scaffolds in moderate to excellent yields. This project has represented that ketenimine zwitterionic salts can also be utilized as mighty sulfonamidation reagents without the necessary assistance of any catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00937.

General experimental procedures, computational, characterization details, ^{1}H NMR, ^{13}C NMR, and MS spectra of all compounds (PDF)

Accession Codes

CCDC 2071060 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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