RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2024, **14**, 38146

Iridium-catalyzed reductive sulfonamidation of alkoxy aryl alkynes†

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Received 23rd October 2024
Accepted 19th November 2024

DOI: 10.1039/d4ra07579j

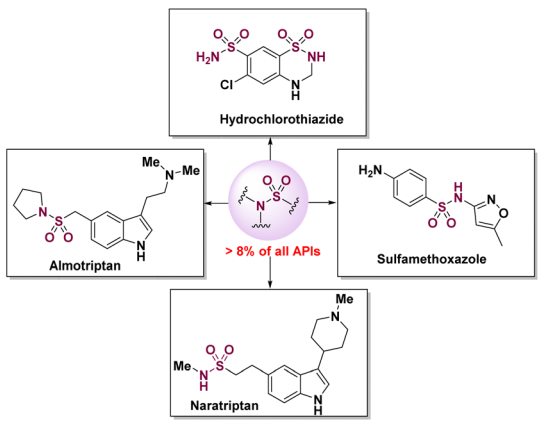
rsc.li/rsc-advances

Sulfonamides are valuable structural building blocks, bioactives, and pharmaceuticals. While there have been great achievements in the sulfonamidation of alkyl and alkenyl carbon, the sulfonamidation of alkynyl carbon has not been studied. Herein, we report the synthesis of *N*-benzylated sulfonamides from alkoxy aryl alkynes and sulfonamides enabled by Ir-catalyzed reductive sulfonamidation using HCO_2H as a hydrogen donor. This process was performed under mild conditions, resulting in the transformation of a variety of substituted benzene, heteroaromatic, and aliphatic sulfonamides. Particularly, the structural diversification of valdecoxib and zonisamide showcased the utility of this protocol.

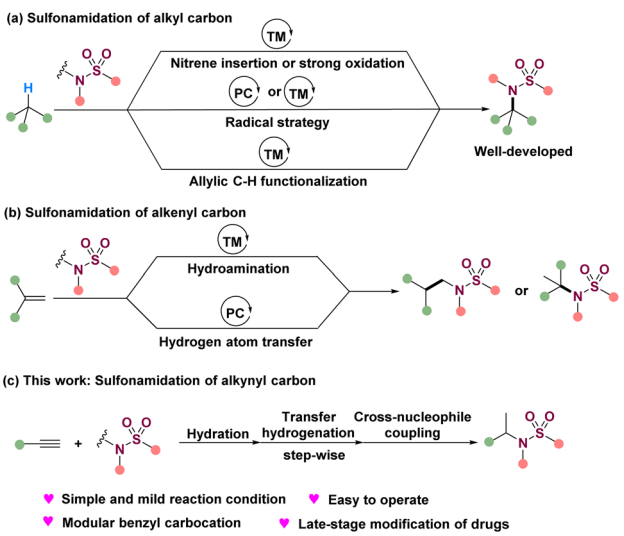
Introduction

Sulfonamides are not only valuable structural building blocks in synthetic intermediates, but are also commonly found in biological and pharmaceutical fields.[1] For instance, sulfonamides of almotriptan,[2] sulfamethoxazol,[3] hydrochlorothiazide,[4] and naratriptan[5] have found applications in the treatments of heavy migraine headache, urinary tract infections, and high blood pressure, respectively (Scheme 1). The latest statistics show that over 8% active pharmaceutical ingredients (APIs) contain sulfonamide skeletons, which have special physicochemical properties of metabolic stability.[6] Therefore, the extensive application of sulphonamides in medicinal chemistry has attracted the attention of chemists in the synthesis and functionalization of sulfonamides in recent decades.[7]

Reactions of primary sulfonamides with aliphatic halides,[8] alcohols,[9] and carbonyls[10] present classical strategies for the synthesis of sulfonamides, in which the organic,[11] inorganic,[12] Ir,[13] Ru,[14] Rh,[15] and other metal[16] catalysts are employed. Coupling of primary sulfonamides with aryl halides,[17] boronic acids,[18] and diaryliodonium triflate[19] constitutes another efficient approach to sulphonamide synthesis, where Cu,[20] Pd,[21] and Ni[22] metals are commonly utilized as catalysts. Direct sulfonamidation of alkyl carbon provides an atom- and step economy strategy for sulfonamide synthesis, with commendable substrate scope and efficiency (Scheme 2a).[23] However, the inevitable use of hypervalent iodine reagents or strong oxidation,[24] excessive equivalents of oxidants,[25] and poor



Scheme 1 Drugs containing sulfonamide motifs.



Scheme 2 Sulfonamidation of differential hybridized carbons.

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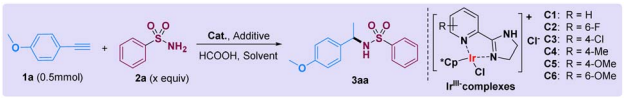
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ra07579j

regioselectivity[26] limit the application of this strategy. Approaches to sulfonamide synthesis based on the sulfonamidation of alkenyl carbon *via* classical hydroamination or hydrogen atom transfer of alkenes are attractive alternatives (Scheme 2b).[27] Notably, asymmetric sulfonamidation of alkenyl carbon for the synthesis of enantioenriched sulfonamides *via* hydrogen atom transfer has also be established.[28] While there have been great achievements with regards to sulfonamidation of alkyl and alkenyl carbon, the sulfonamidation of alkynyl carbon has not been studied.

With our continuous research on transfer hydrogenation with Cp*Ir complexes,[29] *N*-alkylation[30] or *para*-Friedel–Crafts alkylation[31] were achieved from alkynes *via* hydration and transfer hydrogenation. In a previous work, a relatively stable benzyl carbocation was generated from alkynes *via* a hydration, transfer hydrogenation, and successive dehydroxylation process, which might be captured by primary or secondary sulfonamides to deliver a variety of *N*-benzylated sulfonamides. Using alkynes as substrates comes with various challenges: (a) although hydration of alkynes had been developed in our

Table 1 Optimization of the synthesis of sulfonamide **3aa**[a]



Entry	Cat.	Additive (equiv.)	**2a** (*x* equiv.)	Solvent	Yield **3aa**[b] (%)
1	**C3**	TsOH (0.6)	1.0	H_2O	38
2	**C3**	TsOH (0.6)	1.0	DMF	N.D.
3	**C3**	TsOH (0.6)	1.0	TFEA	N.D.
4	**C3**	TsOH (0.6)	1.0	MeCN	N.D.
5	**C3**	TsOH (0.6)	1.0	*p*-Xylene	N.D.
6	**C3**	TsOH (0.6)	1.0	Dioxane	N.D.
7	**C3**	TsOH (0.6)	1.0	TFEA/H_2O[c]	36
8	**C3**	TsOH (0.6)	1.0	TFEA/H_2O[d]	42
9	**C3**	TsOH (0.6)	1.0	TFEA/H_2O[e]	22
10	**C3**	TsOH (0.6)	1.0	TFEA/H_2O[f]	Trace
11	**C3**	TsOH (0.6)	1.0	*p*-Xylene/H_2O[d]	30
12	—	TsOH (0.6)	1.0	TFEA/H_2O[d]	N.D.
13	**C1**	TsOH (0.6)	1.0	TFEA/H_2O[d]	40
14	**C2**	TsOH (0.6)	1.0	TFEA/H_2O[d]	37
15	**C4**	TsOH (0.6)	1.0	TFEA/H_2O[d]	37
16	**C5**	TsOH (0.6)	1.0	TFEA/H_2O[d]	45
17	**C6**	TsOH (0.6)	1.0	TFEA/H_2O[d]	41
18	**C5**	TsOH (0.6)	1.2	TFEA/H_2O[d]	45
19	**C5**	TsOH (0.6)	1.4	TFEA/H_2O[d]	46
20	**C5**	TsOH (0.6)	1.6	TFEA/H_2O[d]	46
21	**C5**	TsOH (0.6)	1.8	TFEA/H_2O[d]	48
22	**C5**	TsOH (0.6)	2.0	TFEA/H_2O[d]	77
23	**C5**	TsOH (0.6)	2.5	TFEA/H_2O[d]	70
24	**C5**	TsOH (0.6)	3.0	TFEA/H_2O[d]	76
25	**C5**	—	2.0	TFEA/H_2O[d]	N.D.
26	**C5**	$PhSO_3H$ (0.6)	2.0	TFEA/H_2O[d]	52
27	**C5**	R^1SO_3H (0.6)[g]	2.0	TFEA/H_2O[d]	44
28	**C5**	MSA (0.6)	2.0	TFEA/H_2O[d]	59
29	**C5**	R^2SO_3H (0.6)[g]	2.0	TFEA/H_2O[d]	35
30	**C5**	**TsOH (0.2)**	**2.0**	**TFEA/H_2O[d]**	**81 (79)**
31	**C5**	TsOH (0.4)	2.0	TFEA/H_2O[d]	80
32	**C5**	TsOH (0.8)	2.0	TFEA/H_2O[d]	46
33	**C5**	TsOH (1.0)	2.0	TFEA/H_2O[d]	43
34	**C5**	TsOH (1.5)	2.0	TFEA/H_2O[d]	29
35	**C5**	TsOH (2.0)	2.0	TFEA/H_2O[d]	18
36[h]	**C5**	TsOH (0.2)	2.0	TFEA/H_2O[d]	63
37[i]	**C5**	TsOH (0.2)	2.0	TFEA/H_2O[d]	42
38[j]	**C5**	TsOH (0.2)	2.0	TFEA/H_2O[d]	N.D.

[a] Reaction conditions: **1a** (0.5 mmol), Cat. (1.0 mol%), HCO_2H (10.0 equiv.), and solvent (1.5 mL) for 12 hours at 80 °C (under air). [b] Yield was determined by NMR with dimethyl terephthalate as the internal standard. [c] The ratio of the mixed solvent was 1 : 8 (v/v). [d] The ratio of the mixed solvent was 1 : 4 (v/v). [e] The ratio of the mixed solvent was 1 : 2 (v/v). [f] The ratio of the mixed solvent was 1 : 1 (v/v). [g] R_1 = 4-Cl-Ph; R_2 = 2-naphthyl. [h] 60 °C. [i] 100 °C. [j] Without HCO_2H.

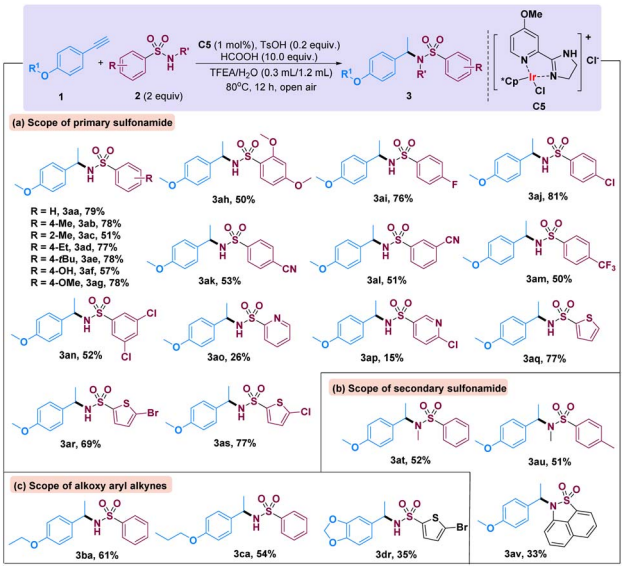
previous work,[31] there is a risk of deactivation of hydration using primary or secondary sulfonamides as nucleophilic reagents; (b) a similar outcome of poisoning subsequent transfer hydrogenation is possible under these reaction conditions; (c) a weaker nucleophilic property is noted while using nitrogen atoms as a nucleophilic reagent under acidic conditions, and using sulfonamides as nucleophilic agents will likely have similar related issues, hindering the final cross nucleophilic coupling process. Despite these difficulties, through protracted and unremitting efforts, herein, we realized the reductive sulfonamidation of alkynes with primary and secondary sulfonamides using metal catalysis, which provides inspiration for the synthesis of diversified sulfonamides (Scheme 2c).

Results and discussion

We initially examined the reductive sulfonamidation of alkynes by employing 4-ethynylanisole **1a** and benzene sulfonamide **2a** as model substrates, Cp*Ir complexes as catalyst,[32] and HCO_2H as a hydrogen donor (Table 1). Interestingly, the desired product **3aa** was produced at a 38% yield using H_2O as a solvent and TsOH as an additive (Table 1, entry 1). Screening of further reaction parameters indicated that the H_2O and Cp*Ir catalyst were essential for successful reductive sulfonamidation (Table 1, entries 2–11). Increasing the ratio of TFEA would decrease the yield of **3aa** (Table 1, entries 7–10). For instance, the yield of **3aa** was reduced to trace even though the ratio of TFEA and H_2O was loaded over 1 : 1 (Table 1, entry 10). Additionally, catalyst optimization (Table 1, entries 12–17) showed that the Cp*Ir complex **C5** could slightly enhance the sulfonamidation process leading to a 45% yield of the product **3aa** (Table 1, entry 16). Satisfyingly, increasing the loading of **2a** would sharply improve the yield of **3aa** (Table 1, entries 18–24). Of note, the control experiment demonstrated that a Lewis acid was crucial for this reductive sulfonamidation process (Table 1, entries 25–35) and decreasing the loading of TsOH to 0.2 equiv. resulted in the best yield of **3aa** (Table 1, entry 30). However, decreasing or increasing the reaction temperature was harmful to the production of **3aa** (Table 1, entries 36 and 37). Control experiment showed that HCO_2H was the essential hydrogen donor in this transformation, indicating that H_2O only act as a reaction media (Table 1, entry 38).

With the successfully optimized conditions, the substrate scope with respect to aryl alkynes and aryl sulfonamides was investigated (Table 2). As anticipated, aryl sulfonamides with electron-donating groups at differential positions were well tolerated, including methyl, ethyl, *tert*-butyl, hydroxyl, and methoxy, delivering the corresponding products (**3ab–3ag**) in good to excellent yields. Additionally, di-substituted aryl sulfonamide (**2h**) also performed well in this system. Aryl sulfonamides with electron-withdrawing groups, such as fluorine (**2i**), chlorine (**2j**, **2n**), nitrile (**2k**, **2l**), and trifluoromethyl (**2m**), were also efficient substrates to afford similar yields of the desired products (**3ai–3an**). However, significantly different

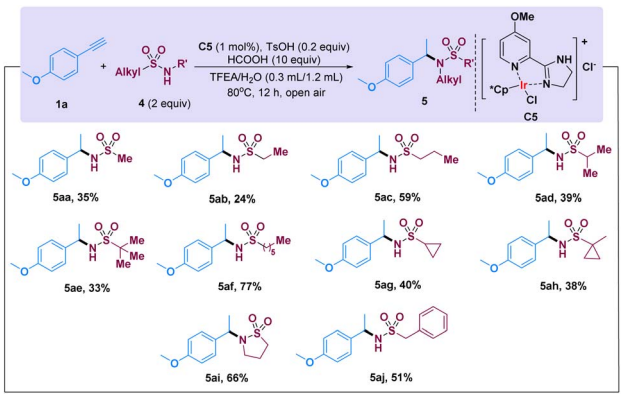
Table 2 Substrate scope of aromatic sulfonamides and alkoxy aryl alkynes[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), **C5** (1.0 mol%), HCO_2H (10.0 equiv.), and TFEA (0.3 mL), H_2O (1.2 mL) for 12 hours at 80 °C, and isolated yield.

yields were achieved with heteroaromatic sulfonamides (**2o–2s**) as substrates. For instance, low yield (15–26%) of corresponding products **3ao**, **3ap** were obtained using pyridine sulfonamides as substrates, while 2-thiophene-sulfonamides delivered the desired products **3aq–3as** in good yields (69–77%). This difference could be attributed to the difference in the density of π electrons. Interestingly, switching the primary aryl sulfonamides to secondary aryl sulfonamides also allowed the formation of the desired products (**3at–3av**) in moderate yields. Furthermore, other alkoxy-substituted aryl alkynes (**2b–2d**) were

Table 3 Substrate scope of alkyl sulfonamides[a]



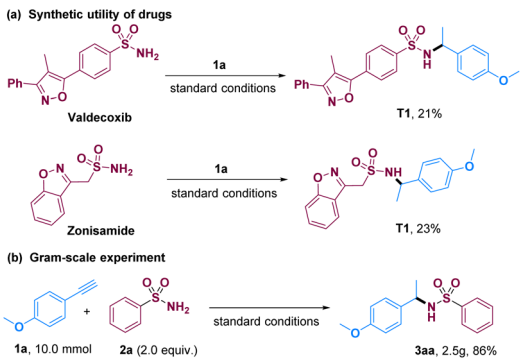
[a] Reaction conditions: **1a** (0.5 mmol), **4** (1.0 mmol), **C5** (1.0 mol%), HCO_2H (10.0 equiv.), and TFEA (0.3 mL), H_2O (1.2 mL) for 12 hours at 80 °C, and isolated yield.

also good substrates in the iridium catalyzed reductive sulfonamidation process.

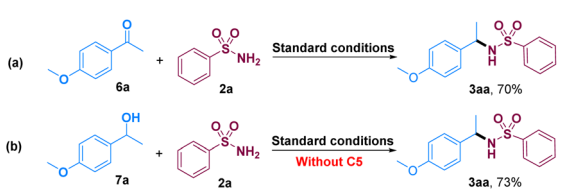
Having established the conversion of aromatic sulfonamides into diversified sulfonamides, this method was extended to employ alkyl sulfonamides as substrates (Table 3). In comparison with aryl sulfonamides, the corresponding products (**5aa**–**5ah**, **5aj**) were delivered in relatively lower yields using differential primary alkyl sulfonamides as substrates. Surprisingly, a better yield (66%) of sulfonamide **5ai** was delivered by using secondary cyclic aliphatic sulfonamide of 1,3-propanesultam as a substrate.

Following success in developing a broad range of sulfonamides, we then explored the synthetic applications of this method. First, we investigated the derivatization of drugs containing the sulfonamide scaffold, which are of interest in medicinal chemistry. As shown in Scheme 3a, valdecoxib (COX-2 inhibitor)[33] and zonisamide (used as an adjunctive therapy in adults with partial-onset of seizures)[34] could be easily converted into *N*-benzyl sulfonamides. Moreover, the model reaction was scaled to a 10.0 mmol reaction and it delivered 2.5 g of the sulfonamide **3aa** in 86% yield, which exhibited potential synthetic application in the organic chemistry industry (Scheme 3b).

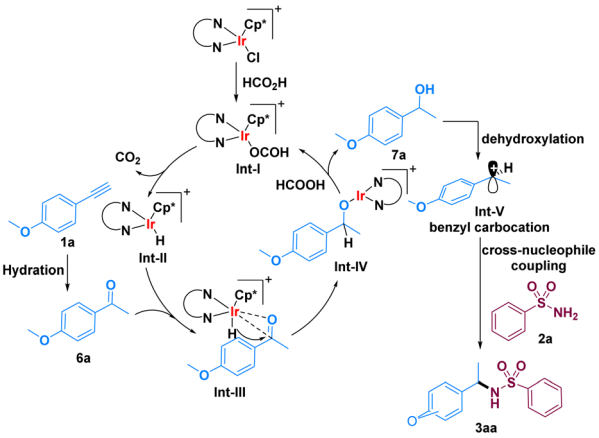
To gain more insights into the reaction mechanism, control experiments were performed. According to our previous work,[35] hydration of alkynes proceeded smoothly under acidic conditions to generate ketone and alcohol intermediates. Therefore, the ketone **6a** and sulfonamide **2a** were employed as substrates under standard conditions, resulting in a 70% yield of **3aa** (Scheme 4a). Moreover, subjecting alcohol **7a** and sulfonamide **2a** to the standard conditions in the absence of **C5** resulted in a 73% yield of **3aa** (Scheme 4b).



Scheme 3 Derivatization of drugs and gram-scale experiment.



Scheme 4 Control experiments.



Scheme 5 Proposed mechanism.

Based on the reaction result and control experiments (Scheme 4), a possible mechanism was proposed (Scheme 5). The mechanism is characterized by a catalytic cycle that includes hydration and a transfer hydrogenation process that was completed to generate the intermediate alcohol **7a**. Subsequently, carbocation occurred by dehydroxylation of **7a** under acidic conditions, which was followed by cross-nucleophile coupling with sulfonamide to produce the desired product **3aa**.

Conclusions

In conclusion, we have shown the sulfonamidation of alkoxy aryl alkynes with viable sulfonamides for the synthesis of diverse *N*-benzylated sulfonamides. This modular Cp*Ir complex-catalyzed reductive sulfonamidation synthesis was achieved under mild conditions. The reaction can be conducted at gram scale in air. Sulfonamide drugs of valdecoxib and zonisamide could also be employed as substrates and converted into *N*-benzyl sulfonamides. The good substrate suitability, wide range of functional group tolerance, scale-up performance, and mild reaction conditions provide evidence of the potential for the application of this reductive sulfonamidation transformation in rapid structural diversification of bioactive molecules.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Yuqiu Liang, Chengxiu Liu, and Penghao Wei: investigation, data curation, validation, visualization, manuscript, and ESI† writing and editing. Youchun Li and Lu Ouyang: conceptualization, funding acquisition, project administration, resources, supervision, visualization, revising the manuscript and the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Ganzhou Bureau of Science and Technology (2022-YB1402), the Fundamental Research Funds for Gannan Medical University (QD201810, QD202106, TD2021YX05, TD202310) for financial support.

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