RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2018, **8**, 74

A new and facile approach to 1,2-dihydroisoquinolin-3(4*H*)-imines by the Cu(I)-catalyzed reaction of 2-ethynylbenzyl methanesulfonates, sulfonyl azides and amines†

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Received 14th November 2017
Accepted 11th December 2017

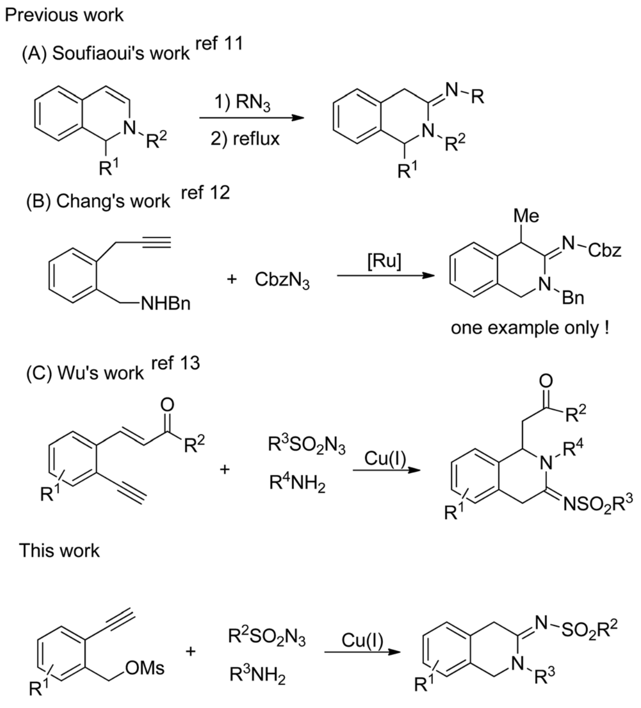
DOI: 10.1039/c7ra12412k

rsc.li/rsc-advances

A new, step-economical and operationally simple access to unsubstituted 1,2-dihydroisoquinolin-3(4*H*)-imines by Cu-catalyzed MCRs under mild conditions is described. In addition, selective hydrolysis of imines to the corresponding 1,2-dihydroisoquinolin-3(4*H*)-ones under refluxed conc. HCl has also been investigated.

Introduction

Heterocycle skeletons are popular scaffolds in various pharmaceuticals, biologically active compounds and functional materials.[1] Tetrahydroisoquinoline (THIQ), an important nitrogen-containing heterocycle skeleton, is also found frequently in naturally existing alkaloids which have been shown to have a wide range of interesting biological activities such as antimuor, antimicrobial activities, and other pharmacological properties.[2] Due to these advantages, great efforts have been made to develop various methodologies toward the synthesis of the THIQ skeleton and its derivatives. In general, traditional synthetic methods for the construction of this class of compounds are the Bischler–Napieralski cyclization/reduction,[3] the Pictet–Spengler reaction,[3a,4] the noble-transition metal-catalyzed asymmetric direct hydrogenation of isoquinoline or dihydroisoquinoline derivatives[5] and some other elegant reactions.[6] In recent years, in order to further expand the desirable molecular library of the THIQ alkaloids for the discovery of pharmaceutically active compounds, many excellent approaches by directly using THIQ precursors to their derivatives have also been developed. For example, currently, the most popular strategies to construct the THIQ skeleton-containing derivatives are the nucleophilic addition to the preformed $C{=}N^+$ bond of cyclic precursors offered from the substrate of tetrahydroisoquinoline *via* the oxidative cross-dehydrogenative coupling (CDC) reaction[7] or the redox-neutral reaction[8] and those associated with free radical intermediates.[9] Among the above-mentioned synthetic strategies, although all approaches can provide access to the THIQ skeleton and their derivatives, the synthetic pathways towards 1,2-dihydroisoquinolin-3(4*H*)-imines, which are a class of important members of THIQ family and have been wildly applied in material sciences and biological research,[10] are rarely reported in the literature. A more careful literature survey indicates that only Soufiaoui *et al.* in 1992 described their synthesis *via* the 1,3-dipolar cycloaddition of arylazides with 1,2-dihydroisoquinoline derivatives followed by splitting decomposition[11] under heating (Scheme 1A) and Chang's group



Scheme 1 Different strategies for the construction of 1,2-dihydroisoquinolin-3(4*H*)-imine.

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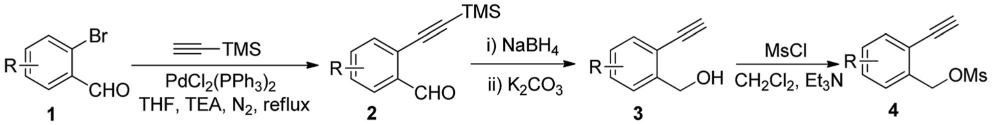
† Electronic supplementary information (ESI) available. CCDC 1574819. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra12412k

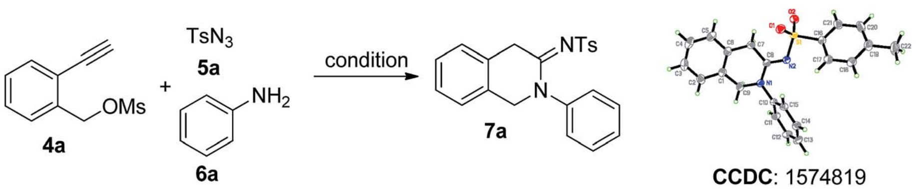


Scheme 2 Facile synthesis of 2-ethynylbenzyl methanesulfonates **4**.

in 2006 reported a catalytic one-pot approach to the title product using aminoalkyne and azide as substrate under mild condition[12] (Scheme 1B). However, these methods to synthesize 1,2-dihydroisoquinolin-3(4*H*)-imine suffered from some disadvantages including multiple reaction steps,[11] harsh reaction conditions,[11] few scope of substrate (one example only!)[12] and the use of noble metal.[12] Therefore, the search for a step-economical, more convenient and efficient catalytic system with attractive features such as easily accessible starting materials, mild reaction conditions, and nontoxic side products to generate structural diversity of 1,2-dihydroisoquinolin-3(4*H*)-imine is of great value.

As an ideal synthetic tool, multicomponent reactions (MCRs) involving a tandem reaction process with three or more reagents in a single process under mild conditions have emerged as a powerful and attractive strategy for the synthesis of structurally diverse organic molecules. Recently, the methodology is also applied in the synthesis of 1,2-dihydroisoquinolin-3(4*H*)-imines. For instance, Wu's group in 2011 presented one type of 1,2-dihydroisoquinolin-3(4*H*)-imines *via* MCRs using 2-ethynylphenyl-chalcones, sulfonyl azides and amines as substrates under Cu(I) catalyst (Scheme 1C),[13] in which the strategy may experience the reaction process with the active ketenimine intermediate investigated widely by the pioneers.[14] It is well known that the pharmacological and biological activity of molecule is shown to be dependent on the nature of substituents. However, most MCRs follow a single reaction route to afford only one substituted type of molecular skeleton and their derivatives. Therefore, development of novel MCRs for the selective formation of diverse substituted molecules containing the same molecular skeleton is a worthy and challenging goal. As a continuation of our interest in ketenimine chemistry and THIQ skeleton, we herein report a convenient and efficient synthetic strategy for the synthesis of 1,2-

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Base	Solvent	Temp. (°C)	Yield[b] (%)
1[c]	CuI	Et_3N	DCM	rt	40
2	Cu_2O	Et_3N	DCM	rt	nd
3	CuCl	Et_3N	DCM	rt	47
4	CuBr	Et_3N	DCM	rt	54
5	CuBr	Et_3N	DCM	40	57
6	CuBr	Et_3N	DCM	50	60
7	CuBr	Et_3N	DCM	60	77
8	CuBr	Et_3N	DCM	70	50
9	CuBr	Et_3N	$CHCl_3$	60	64
10	CuBr	Et_3N	MeCN	60	35
11	CuBr	Et_3N	THF	60	67
12	CuBr	Et_3N	Dioxane	60	50
13	CuBr	Et_3N	DMF	60	35
14	CuBr	K_2CO_3	DCM	60	Trace
15	CuBr	$(iPr_2)NEt$	DCM	60	70
16	CuBr	DBU	DCM	60	nd
17	CuBr	DABCO	DCM	60	37
18[d]	CuBr	Et_3N	DCM	60	82
19[e]	CuBr	Et_3N	DCM	60	80

[a] Reaction conditions: toluenesulfonyl azide (0.36 mmol), 2-ethynylbenzyl methanesulfonate (0.3 mmol), phenylamine (0.36 mmol), base (0.45 mmol), catalyst (0.03 mmol),solvent (1 mL). [b] Isolated yields. nd = not detected. [c] Reaction carried out for 12 h. [d] Reaction carried out for 0.5 h. [e] Reaction carried out for 1 h.

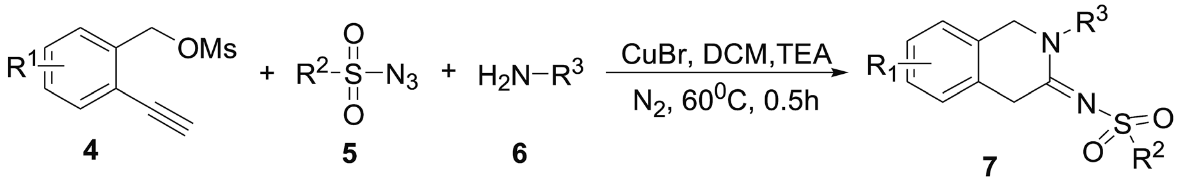
dihydroisoquinolin-3(4*H*)-imines *via* novel MCRs from 2-ethynylbenzyl methanesulfonates, sulfonyl azides and amines (Scheme 1, this work).

Results and discussion

Our studies started with the synthesis of variously substituted 2-ethynylbenzyl methanesulfonates **4** from substituted 2-bromobenzaldehyde **1** according to the literature procedures[15] as indicated in Scheme 2.

And then, under N_2 and sealed tube, we carried out a model MCRs of 2-ethynylbenzyl methanesulfonate **4a** with TsN_3 **5a** and phenylamine **6a** in dichloromethane at room temperature in the presence of CuI and Et_3N for 12 h (Table 1). To our delight, the desired product (entry 1), 2-dihydroisoquinolin-3(4*H*)-imine of **7a** was isolated in 40% yield, and its structure was further conformed by X-ray crystallographic analysis (showed in Table 1). Inspired by the result of reaction, we continue to optimize the reaction condition of model reaction to improve the yield of **7a** to the highest. The results for various optimization experiments are summarized in Table 1. Subsequently, other copper salt were then screened under the reaction condition just mentioned. The results indicated that, in comparison to the potential copper catalyst, only CuBr was proven to be more effective one (54%), whereas Cu_2O even can not lead to the formation of **7a** (entries 1–4). When the reaction temperature under CuBr as catalyst was gradually increased from rt to 60 °C, the yield of **7a** increases to 77%. However, it was found that further elevating the reaction temperature, in contrast, made the yield decrease (entries 5–8). We next examined the effect of solvent in the MCRs. The results revealed that dichloromethane (77%) was the most suitable solvent for the reaction (entry 7,

Table 2 Substrate scope of MCRs for the formation of **7**[a]



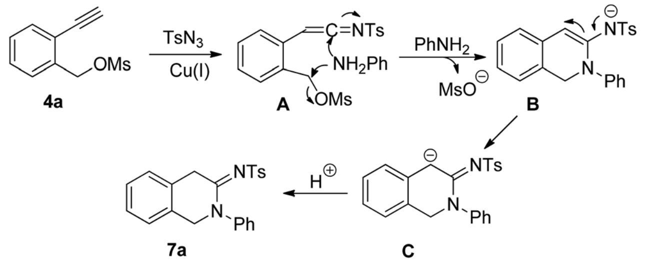
Entry	R^1	R^2	R^3	Product	Yield[b] [%]
1	H(**4a**)	4-$CH_3C_6H_4$(**5a**)	C_6H_5(**6a**)	**7a**	82
2	**4a**	**5a**	4-$CH_3C_6H_4$(**6b**)	**7b**	78
3	**4a**	**5a**	4-FC_6H_4(**6c**)	**7c**	84
4	**4a**	**5a**	4-ClC_6H_4(**6d**)	**7d**	77
5	**4a**	**5a**	2-$CH_3OC_6H_4$(**6e**)	**7e**	68
6	**4a**	**5a**	2-FC_6H_4(**6f**)	**7f**	76
7	**4a**	**5a**	2,6-EtC_6H_3(**6g**)	**7g**	65
8	**4a**	**5a**	2,4,6-$CH_3C_6H_2$(**6h**)	**7h**	74
9	**4a**	**5a**	Bn(**6i**)	**7i**	35
10	**4a**	**5a**	^{t}Bu(**6j**)	**7j**	0
11	**4a**	C_6H_5(**5b**)	**6a**	**7k**	80
12	**4a**	**5b**	**6e**	**7l**	78
13	**4a**	**5b**	**6h**	**7m**	74
14	**4a**	2,4,6-$CH_3C_6H_2$(**5c**)	**6a**	**7n**	85
15	**4a**	**5c**	**6c**	**7o**	84
16	4-F(**4b**)	**5a**	**6a**	**7p**	51
17	**4b**	**5a**	**6c**	**7q**	83
18	5-F(**4c**)	**5a**	**6a**	**7r**	89
19	**4c**	**5a**	**6b**	**7s**	77
20	**4c**	**5a**	**6c**	**7t**	84
21	**4c**	**5b**	**6c**	**7u**	81
22	**4c**	**5c**	**6a**	**7v**	80
23	6-F(**4d**)	**5a**	**6a**	**7w**	75
24	**4d**	**5a**	**6c**	**7x**	88
25	**4d**	**5b**	**6a**	**7y**	71
26	4-Cl(**4e**)	**5a**	**6a**	**7z**	77
27	**4e**	**5a**	**6c**	**7aa**	87
28	**4e**	**5b**	**6c**	**7ab**	72
29	4-CH_3(**4f**)	**5a**	**6a**	**7ac**	77
30	**4f**	**5a**	**6b**	**7ad**	73
31	**4f**	**5a**	**6c**	**7ae**	51

[a] Optimal reaction conditions: **4** (0.2 mmol), CuBr (0.02 mmol), Et_3N (0.3 mmol) in DCM (1 mL), sealed and then heated at 60 °C for 0.5 h under N_2.
[b] Isolated yields are given.

entries 9–13). As showed in Table 1, different base also affected the final desired outcome. The reaction was carried out efficiently when triethylamine acted as the base, furnishing the desired product in 77% yield, and the corresponding product was not almost afforded in the presence of K_2CO_3 or DBU (entry 7, entries 14–17). Additionally, it should be noted that the reaction time also played the important role in improving the yield of target product. The experimental results indicated the shorter reaction time would be beneficial to the formation of **7a** (entry 7, entries 18–19). Hence, after screening the reaction condition of MCRs, the optimized conditions to selectively obtain the desired product **7a**, under N_2 and sealed tube, are identified as the employment of Et_3N as base and CuBr as catalyst in dichloromethane for 0.5 h at 60 °C.

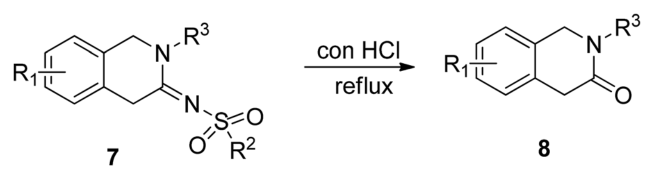
With the optimized reaction conditions secured, we subsequently applied the optimized conditions for the formation of **7a** to explore the scope and generality of the MCRs. The results in this section, as summarized in Table 2, demonstrated that the present method is generally applicable in the formation of target products depending on the employment of the corresponding starting materials. It was found that all aromatic substrates bearing various substutution such as electron donating and withdrawing group underwent smoothly this transformation generating the corresponding products 7 with moderate to excellent yields. However, we also found that in addition to the substrates with withdrawing group such as F at the *para* position of phenyl ring giving the lower yields (51% in both) (entries 16, 31), the property of other substituents on phenyl ring showed no obvious impact on the yield of corresponding products. Intriguingly, when the substrates are aliphatic amines, the methodology only furnish either the low corresponding yield (entry 9, 35%) or no desired product (entry 10, 0%). The result may be caused by the fact that in contrast to aromatic amines, aliphatic amines with stronger nucleophilic have higher activity and lower selectivity. Therefore, when aliphatic amines reacted with other substrates, the product in a low or no yield will be achieved.

Based on the above results and the chemistry related to ketenimine, a plausible mechanism of this MCRs is proposed and shown in Scheme 3. Taking the formation of **7a** as an example, first, the ketenimine intermediate **A** is formed *via* the reaction of 2-ethynylbenzyl methanesulfonate (**4a**) with TsN_3 under the optimized conditions. Subsequently, when the anilines added into the reaction, the double nucleophilic addition would happen to afford the intermediate **B**. And then, intermediate **B** will tautomerize into the intermediate **C**. Finally, the intermediate **C**, which undergo sequential proton transfer, will transform into the desired product **7a**.



Scheme 3 Possible reaction mechanism for the formation of **7a**.

Table 3 Hydrolysis of imines **7** to 1,2-dihydroisoquinolin-3(4*H*)-ones **8**[a]



Entry	R^1	R^2	R^3	Product	Yield[b] [%]
1	H(a)	4-$CH_3C_6H_4$(b)	C_6H_5	**8a**	66
2	a	b	4-$CH_3C_6H_4$	**8b**	74
3	a	b	4-FC_6H_4	**8c**	59
4	a	b	4-ClC_6H_4	**8d**	69

[a] Reaction conditions: 7 (0.5 mmol), conc HCl (10 mL), reactions refluxed for 12 h. [b] Isolated yields.

Subsequently, to further take advantage of the synthetic application of this methodology, we then explored the synthesis of 1,2-dihydroisoquinolin-3(4*H*)-ones **8** by hydrolysis of the resulting products **7**. To the best of our knowledge, **8** were considered as important building block in organic synthesis[16] and have good physiological activities in medicinal chemistry. For example, more recently, the researchers found that the compounds containing the skeleton of 1,2-dihydroisoquinolin-3(4*H*)-one were acetylcholinesterase and β-secretase dual inhibitors in treatment with alzheimer's disease.[17] Therefore, we proceeded to treat the dihydroisoquinolin-3(4*H*)-imines **7** with concentrated HCl under reflux for 12 h. To our delight, the corresponding title products **8** were achieved in good yields (Table 3). The results indicate that **7** can be considered as a class of important precursor of 1,2-dihydroisoquinolin-3(4*H*)-ones **8**.

In summary, a new and facile MCRs for the formation of unsubstituted 1,2-dihydroisoquinolin-3(4*H*)-imines in good yields has been developed under mild condition. The experimental results indicated that various aromatic substrates could be well tolerated in this reaction. Meanwhile, selective hydrolysis of imines to the corresponding 1,2-dihydroisoquinolin-3(4*H*)-ones has also been investigated under refluxed conc. HCl. In addition, some 2-ethynylbenzyl methanesulfonates that had not previously been reported were also synthesized and characterized. The methodology provides a step-economical and operationally simple access to functionalized desired product and can further enrich the compound library of 1,2-dihydroisoquinolin-3(4*H*)-imine.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support by the Science Foundation of Shanghai Institute of Technology (grant number YJ2013-61).

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