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ARTICLE

AgOTf-Catalyzed Sequential Synthesis of 4-Isoquinolone via Oxidative Ring Opening of Aziridines and Aza-Michael Addition

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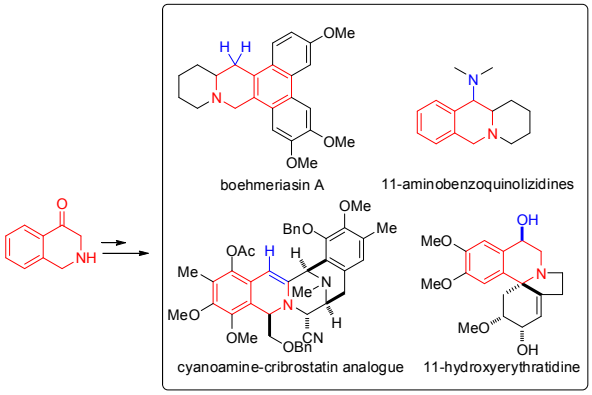
An efficient AgOTf-catalyzed sequential reaction involving oxidative ring-opening of aziridines by DMSO and aza-Michael addition has been developed. A series of 2,3-dihydro-4(1H)-isoquinolones were afforded in moderate to good yields by the formation of one new C=O bond and one new C-N bond. The features of this sequential reaction include high bonding efficiency, use of catalytic amount of catalysts, broad substrate scope and mild conditions. The methodology provide a good choice for constructing the libraries of 2,3-dihydro-4(1H)-isoquinolones.

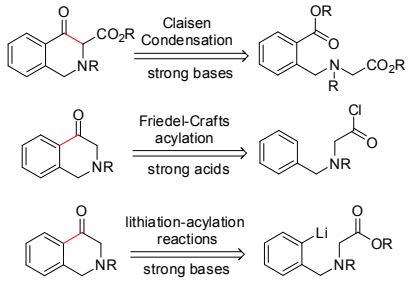
Introduction

2,3-Dihydro-4(1H)-isoquinolones[1] are an important class of nitrogen-containing cyclic compounds which are widely employed as organic synthetic intermediates of high significance in the synthesis of biologically active compounds containing the tetrahydroisoquinoline moieties. For example, they have been used to access several important biologically active compounds such as boehmeriasin A[2], 11-aminobenzoquinolizidine[3], cyanoamine-cribrostatin analogue[4] and 11-hydrooxyerythratidine[5] (Scheme 1). Besides, they are found in several biologically active compounds such as 11-saxicolaline A[6a] and 11-oxoerysodine[6b]. Typical strategies have been developed for the assembly of 2,3-dihydro-4(1H)-isoquinolones, including Claisen condensations[7], Friedel–Crafts acylations[8] and lithiation-acylation reactions[9] (Scheme 2). However, most of these existing strategies suffered from limited substrate scope, harsh reaction conditions or use of stoichiometric catalysts. Efficient and general approaches allowing more diversified syntheses of these valuable compounds are rare[10]. Consequently, a complementary method to the synthesis of 2,3-dihydro-4(1H)-isoquinolones are still in high demand.

Sequential reaction[11] has great advantages in the construction of complicated cyclic compounds from readily available materials due to their high efficiency in the formation of chemical bonds. Recently, we have described two examples



Scheme 1 Application examples of 2,3-dihydro-4(1H)-isoquinolones.



Scheme 2 Typical strategies for 2,3-dihydro-4(1H)-isoquinolones.

of sequential cyclization reactions based on ring opening of aziridines[12] and Michael addition of electron-deficient alkenes[13]. Under the catalysis of AgOTf, ring opening of aziridines with amines followed by aza-Michael addition led to tetrahydroisoquinolines and isoindolines in good yields with excellent *cis*-diastereoselectivities[14] (Scheme 3, eq 1 and eq 2). Under the catalysis of KOH, sequential Michael addition with malonic esters, ring opening of aziridines and lactamization afforded indane-fused pyrrolidin-2-ones in good yields with good diastereoselectivities[15] (Scheme 3, eq 3). In the process

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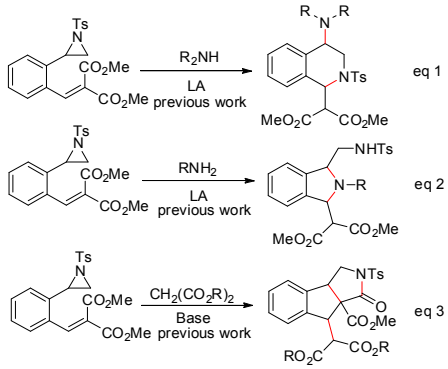
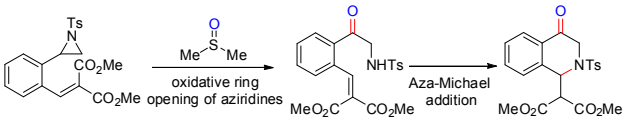


Scheme 3 Sequential reaction involving aziridines and electron-deficient alkenes.



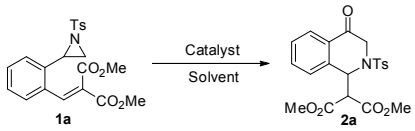
Scheme 4 Sequential reaction towards the 2,3-dihydro-4(1H)-isoquinolones.

of exploring these two sequential reactions, we found an interesting cyclization reaction involving sequential oxidative ring opening[16] of aziridines by the solvent DMSO and aza-Michael addition[17] (Scheme 4). In the presence of 20% mol AgOTf a series of 2,3-dihydro-4(1H)-isoquinolones were afforded in moderate to good yields in mild conditions by the formation of one new C=O bond and one new C-N bond. Undoubtedly this method provided a good choice for the rapid and efficient synthesis of 2,3-dihydro-4(1H)-isoquinolones. It was particularly well suited for the preparation of corresponding compound libraries. Herein, we hope to report the results of this sequential reaction.

Results and discussion

N-sulfonyl aziridine **1a** was selected as the model substrate to investigate the feasibility of this sequential reaction (Table 1). Initially, **1a** was treated with AgOTf (20 mol%) in dimethyl sulfoxide (DMSO) at 70 °C for 7 h, and to our delight cyclization product **2a** was successfully obtained in 67% yield (Table 1, entry 1). The structure of **2a** was unambiguously confirmed by X-ray crystal structure analysis[18] (Figure 1). Then a series of Lewis acids were screened to further improve the yield of this sequential reaction. Relatively lower yields were obtained when $BF_3{\cdot}OEt_2$, $SnCl_4$, $Yb(OTf)_3$ and $In(OTf)_3$ were used to catalyze the sequential reaction (Table 1, entries 2~5). Several bases such as DBU, NaH and *t*-BuOK were also selected to promote this sequential reaction, but no desired products were isolated (Table 1, entries 6~8). When we prolonged the reaction time to 18 h in the presence of AgOTf, the best result was obtained and **2a** was generated in 84% yield (Table 1, entry 9). In addition, the sequential reaction successfully afforded the product **2a** in a slightly decreased yield in *a* DMSO-DCE mixed solvent (Table 1, entry 10). We also tested the sequential reaction using 10 equiv of DMSO in DCE, but only a poor yield was observed (Table 1, entry 11).

Table 1 Optimization of the reaction conditions for the sequential reaction[a]



Entry	Catalyst	Solvent	T (h)	T (°C)	Yield[b] (%)
1	AgOTf	DMSO	7	70	67
2	$BF_3{\cdot}OEt_2$	DMSO	7	70	61
3	$SnCl_4$	DMSO	7	70	17
4	$In(OTf)_3$	DMSO	7	70	5
5	$Yb(OTf)_3$	DMSO	7	70	40
6	DBU	DMSO	7	70	0
7	NaH	DMSO	7	70	0
8	*t*-BuOK	DMSO	7	70	0
9	AgOTf	DMSO	18	70	84
10[c]	AgOTf	DMSO/DCE	18	70	64
11[d]	AgOTf	DCE	18	70	26

[a] Reaction conditions: **1a** (1 equiv., 0.05 mmol), the catalyst (20 mol%), the solvent (1 mL), in the open air. [b] Determined by ^{1}H NMR using 1-chloro-2,4-dinitrobenzene as the internal standard. [c] DMSO:DCE=1:1. [d] DMSO (10 equiv., 0.5 mmol) was used in DCE (1 mL).

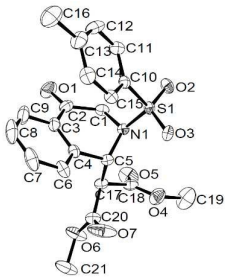


Figure 1 ORTEP drawing for the product **2a**.

With the optimized conditions established, we subsequently explored the generality of the sequential reaction by using a series of substrates **1** bearing electron-donating and electron-withdrawing on the aromatic ring. The results are given in Table 2. We found that various substituents residing at different positions (R^1~R^4) on the phenyl ring were compatible (entries 2~16). In general, the substrates with different electron-donating substituents like methyl (**1c** and **1f**), phenyl (**1h** and **1n**), *p*-methoxyphenyl (**1o**) and methoxyl (**1i**) successfully reacted with DMSO to afford the corresponding products **2** in good yields. The exception to this is that the electron-rich substrates **1g** and **1m** only led to products **2g** and **2m** in moderate yields. The electron-withdrawing substituents seemed to have a bad effect on the sequential reaction. The substrates **1b**, **1d**, **1e**, **1j, 1k** and **1p** with electron-withdrawing substituents gave slightly lower yields than those substrates with electron-donating substituents. It should be noted that the substrate **1h** with the nitro group reacted with DMSO to afford product **2h** in 20% yield. At last, the sequential reaction of the naphthalene-containing substrate **1q** with DMSO was

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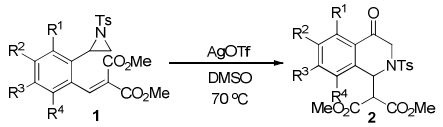
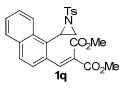
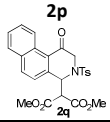
carried out under the optimized reaction conditions. Product **2q** was successfully obtained in a 50% yield (entry 17).

Table 2 Testing the electronic effects on the aromatic ring [a]



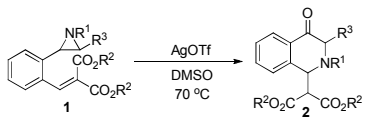
Entry	**1** $R^1/R^2/R^3/R^4$	Product	Yield[b] (%)
1	**1a** H/H/H/H	**2a**	84
2	**1b** F/H/H/H	**2b**	58
3	**1c** Me/H/H/H	**2c**	66
4	**1d** H/F/H/H	**2d**	60
5	**1e** H/Cl/H/H	**2e**	55
6	**1f** H/ Me/H/H	**2f**	82
7	**1g** H/*t*-Bu/H/H	**2g**	45
8	**1h** H/Ph/H/H	**2h**	87
9	**1i** H/OMe/H/H	**2i**	68
10	**1j** H/H/F/H	**2j**	63
11	**1k** H/H/Cl/H	**2k**	59
12	**1l** H/H/NO_2/H	**2l**	20
13	**1m** H/H/Me/H	**2m**	45
14	**1n** H/H/ Ph/H	**2n**	64
15	**1o** H/H/4-OMeC_6H_4/H	**2o**	68
16	**1p** H/H/H/F	**2p**	55
17			50

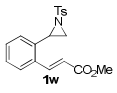
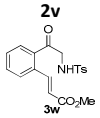
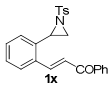
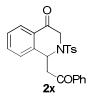
[a] Reaction conditions: **1** (1 equiv., 0.2 mmol), AgOTf (20 mol%, 0.04 mmol), 4 mL DMSO, 70 °C, 18 h, in the open air. [b] Isolated yields.

The substituent effect on the aziridines and the electron-deficient alkenes was also investigated to further extend the scope of this sequential reaction (Table 3). First, the influence of the protecting group of the N-atom of the aziridines for the sequential reaction was examined (entries 1 and 2). For the substrates **1r** and **1s**, the products **2r** and **2s** were successfully obtained in good yields. Then substrates **1t**~**1x** with different Michael acceptors were employed to react with DMSO under the optimized reaction conditions (entries 3~7). The diethyl ester substrate **1t**, the diisopropyl ester substrate **1u** and the dibenzyl ester substrate **1v** generated product **2t**, **2u** and **2v** in moderate to good yields**.** The treatment of the monomethyl ester substrate **1w** by DMSO only led to oxidative ring opening intermediate **3w** in 88% yield, instead of the desired product **2w**. When the monoketone substrate **1v** was subjected to the sequential reaction, a complex mixture was formed and the desired product was not isolated. Finally, the substrate **1y** with two neighboring substituent groups on the aziridine ring was used in the sequential reaction as well (entry 8). Under the optimized reaction conditions product **2y** was afforded in a moderate yield with a good diastereoselectivity (dr=5:1).

To understand the mechanism of the sequential reaction, several control experiments were investigated. In the absence

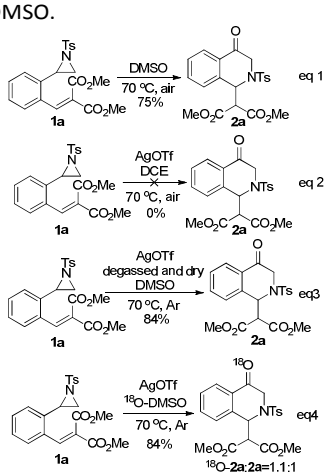
Table 3 Examining the substituent effect on the aziridines and the Michael acceptors[a]



Entry	**1** $R^1/R^2/R^3$	Product	Yield[b] (%)
1	**1r** Bs/Me/H	**2r**	78
2	**1s** Ns/Me/H	**2s**	93
3	**1t** Ts/Et/H	**2t**	60
4	**1u** Ts/*i*-Pr/H	**2u**	49
5	**1v** Ts/Bn/H	**2v**	62
6			88
7			0
8	**1y** Ts/Me/Me	**2y**	48[c]

[a] Reaction conditions: **1** (1 equiv., 0.2 mmol), AgOTf (20 mol%, 0.04 mmol), 4 mL DMSO, 70 °C, 18 h, in the open air. [b] Isolated yields. [c] dr=5:1.

of AgOTf, the reaction of **1a** with DMSO still led to product **2a** in 75% yield (Scheme 5, eq 1). However, when **1a** was treated with 20 mol % of AgOTf in the solvent DCE at 70 °C, no desired product **2a** was isolated (Scheme 5, eq 2).The two control experiments indicated that DMSO played a vital role in the formation of product **2a**. AgOTf was not necessary for the formation of product **2a**. But it was helpful for improving the yield of the sequential reaction. Moreover, there are two possible oxygen sources in the sequential reaction: molecular oxygen in air and DMSO. We first run the reaction of **1a** using degassed and dry DMSO in Ar (Scheme 5, eq 3). Similar with the reaction in air, product **2a** was afforded in 84% yield. Then the sequential reaction of **1a** was performed with ^{18}O-labeled DMSO (Scheme 5, eq 4). Product ^{18}O-**2a** and ^{16}O-**2a** was obtained in 84% yield with a ratio of 1.1:1 based on HRMS analysis (see Supporting Information). The two experiments suggested that the additional oxygen atom in product **2a** is original form DMSO.



Scheme 5 The controlled experiment of mechanistic studies

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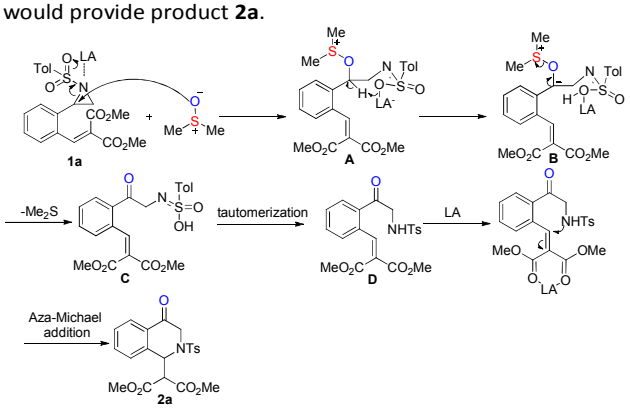
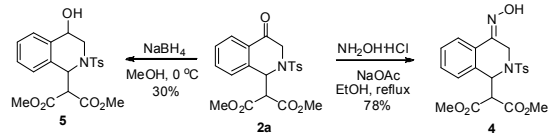
A possible mechanism was proposed for the present sequential reaction (Scheme 6). Regioselective nucleophilic ring-opening reaction of **1a** with DMSO was an initial starting point to drive this whole sequence of reactions. Then the ring-opening intermediate **A** underwent hydrogen migration in a six-membered transition state[16f, g] to afford the intermediate **B**. Further removal of Me_2S from the intermediate **B** followed by tautomerization led to the intermediate **D**. At last, conjugate addition between the newly generated nitrogen anion and highly activated Michael-type acceptor in intermediate **D** would provide product **2a**.



Scheme 6 A possible mechanism for the sequential reaction

Two one-step postfunctionalizations on the keto carbonyl group of **2a** were carried out (Scheme 7). **2a** reacted with hydroxylamine hydrochloride in EtOH to afford product **4** in 78% yield. The keto carbonyl group of **2a** was reduced by $NaBH_4$ to provide product **5** in 30% yield.



Scheme 7 Derivatization of **2a**

Conclusions

In conclusion, an efficient AgOTf-catalyzed reaction involving sequential oxidative ring opening of aziridines and aza-Michael addition has been developed. A series of 2,3-dihydro-4(1H)-isoquinolones with structural diversity were synthesized in moderate to good yields under mild conditions. Further investigations on this kind of sequential reaction based on ring opening of aziridines and Michael addition of electron-deficient alkenes are ongoing in our laboratory.

Experimental

General procedure for synthesis of compound 2.

In the open air, AgOTf (0.04 mmol, 20% cat.) was added to a solution of aziridine **1** (0.2 mmol) in dimethyl sulfoxide (4 mL) at room temperature. The reaction mixture was stirred at 70 ^{o}C for 18h. Then the reaction mixture was cooled to room temperature and poured into water (20 mL) and extracted with ethyl acetate (5 × 10 mL). The combined organic extract was washed with brine (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) to afford product **2**.

Acknowledgements

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18 CCDC 1555724 **2a** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.