Efficient and general synthesis of oxazino[4,3-*a*]indoles by cascade addition-cyclization reactions of (1*H*-indol-2-yl)methanols and vinyl sulfonium salts†

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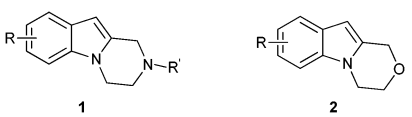
An efficient and general approach to oxazino[4,3-*a*]indole architectures is described. The addition-cyclization cascade of (1*H*-indol-2-yl)methanols with vinyl sulfonium salts affords oxazino[4,3-*a*]indole derivatives in high yields.

Fused indole moieties are widely present as important structural units in diverse naturally occurring alkaloids, pharmaceuticals and agrochemicals.[1] N-Fused indoles are particularly important because of their remarkable biological properties across a broad spectrum of pharmacological screens. For example, 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **1** have been shown to be powerful 5-HT_{2C} receptor ligands and 5-HT_4 receptor antagonists.[2] It has also been found that 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indoles **2** exhibit potent antidepressant activity,[3a] and notably antitumor activities (Scheme 1).[3b]

Despite their remarkable biological importance, the synthesis of this type of N-fused indole remains a significant challenge in organic chemistry.[1c,4] Methodology based on ring closure including intramolecular alkylations, radical cyclizations and trans-annulation reactions, has been the most prevalent over the past decades.[5] Recently, Bandini and Umani-Ronchi[6] have elegantly disclosed a novel catalytic strategy for the preparation of 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones by means of aza-Michael reactions of α,β-unsaturated esters. Akiyama and co-workers[7] have developed a direct catalytic C–H carbenoid insertion approach to generate various N-fused indoles with a range of cyclic amino sub-structures. However, in contrast to numerous publications concerning the synthesis of pyrazino[1,2-*a*]-indoles,[2,6] the development of efficient methods to construct oxazino[4,3-*a*] indoles has been the subject of relatively few investigations.[3,8] Conventional synthesis of oxazino[4,3-*a*]-indoles usually requires several synthetic steps, in moderate to low yields. Thus, it is necessary to develop more efficient and straightforward approaches to oxazino[4,3-*a*] indoles.



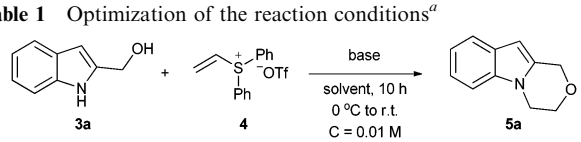
Scheme 1 Examples of N-fused indole derivatives.

In terms of reaction efficiency, cascade or tandem reactions have been established as powerful tools for the rapid assembly of complex polycyclic architectures.[9] Notably, vinyl sulfonium salts[10] have been identified as valuable and versatile intermediates. For instance, Aggarwal and co-workers[11] described an excellent epoxy-annulation cascade, affording five-, six-, and seven-membered epoxide-fused heterocycles from diphenyl vinyl sulfonium salts and amido aldehydes/ketones.[11a–c] In addition, they further developed a concise strategy for the synthesis of morpholines, thiomorpholines, and piperazines from readily available amino alcohols/thiols/amines and vinyl sulfonium salts.[11d,e]

As part of our ongoing program on carbo- and heterocycle oriented methodology development,[12] we herein describe an efficient synthesis of oxazino[4,3-*a*]indoles by means of a cascade addition-cyclization reaction of (1*H*-indol-2-yl)methanols and vinyl sulfonium salts.

We began our investigation by examining the reaction of (1*H*-indol-2-yl)methanol **3a** and diphenyl vinyl sulfonium triflate **4**. As shown in Table 1, the choice of base was important to this cascade process, and the reaction did not take place in the absence of base (Table 1, entry 1). After screening several organic and inorganic bases, potassium hydroxide was found to give the best results (Table 1, entries 2–5). A simple survey of solvents revealed that the reaction media had a significant effect on the reaction efficiency. The variation of solvent from CH_2Cl_2 to $ClCH_2CH_2Cl$ or CH_3CN led to decreased yields (Table 1, entries 5–7). The reaction

Table 1 Optimization of the reaction conditions[a]



Entry	Base	Equiv.	Solvent	Yield (%)[b]
1	—	—	CH_2Cl_2	—
2	DBU	3.0	CH_2Cl_2	39
3	NaH	3.0	CH_2Cl_2	71
4	*t*BuOK	3.0	CH_2Cl_2	63
5	KOH	3.0	CH_2Cl_2	83
6	KOH	3.0	$ClCH_2CH_2Cl$	77
7	KOH	3.0	CH_3CN	58
8	KOH	2.5	CH_2Cl_2	93
9	KOH	2.0	CH_2Cl_2	84
10	KOH	1.0	CH_2Cl_2	64

[a] Conditions: **3a** (0.30 mmol), **4** (0.36 mmol), base (1.0–3.0 equiv.), solvent (30 mL). [b] Yield of isolated product.

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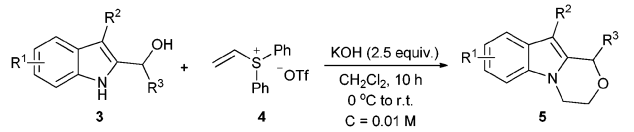
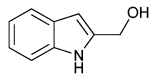
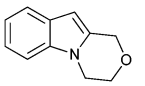
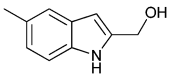
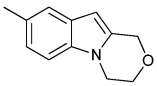
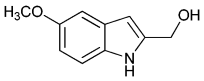
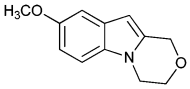
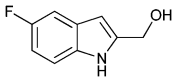
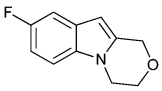
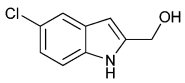
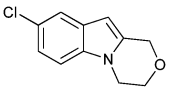
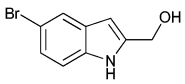
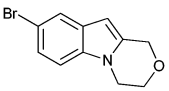
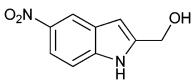
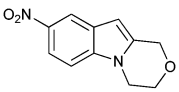
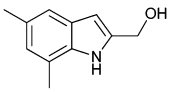
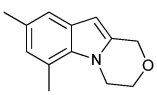
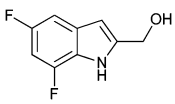
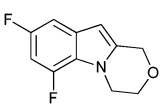
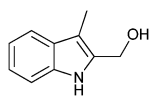
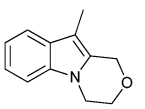
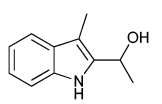
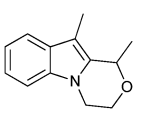
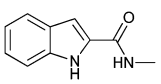
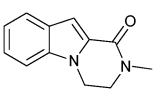
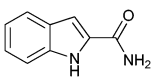
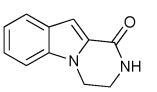
† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data. CCDC 800928. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03823g

Table 2 Synthesis of oxazino[4,3-*a*]indoles using diphenyl vinyl sulfonium salt **4**[a]



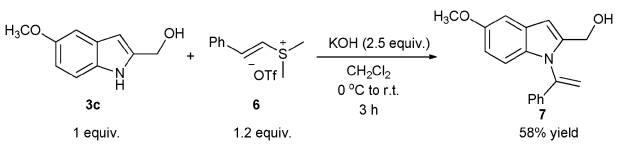
Entry	Substrate	Product	Yield (%)[b]
1	 **3a**	 **5a**	93
2	 **3b**	 **5b**	73
3	 **3c**	 **5c**	75
4	 **3d**	 **5d**	81
5	 **3e**	 **5e**	74
6	 **3f**	 **5f**	76
7	 **3g**	 **5g**	74
8	 **3h**	 **5h**	60
9	 **3i**	 **5i**	61
10	 **3j**	 **5j**	74
11	 **3k**	 **5k**	62
12	 **3l**	 **5l**	80
13	 **3m**	 **5m**	90

[a] Conditions: **3** (0.50 mmol), **4** (0.60 mmol), KOH (1.25 mmol), CH_2Cl_2 (50 mL). [b] Yield of isolated product.

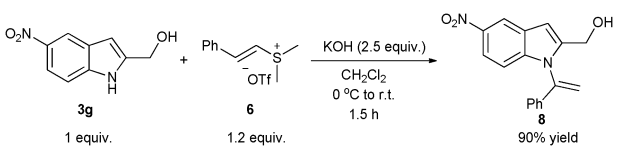
conditions were further optimized by adjusting the amount of the base; for example, 2.5 equivalents of KOH produced **5a** in 93% yield (Table 1, entries 5, 8–10).

With the optimal conditions in hand, the scope of the (1*H*-indol-2-yl)methanol compounds was explored. As highlighted in Table 2, significant structural variations in the (1*H*-indol-2-yl)methanol components were well tolerated and furnished the corresponding N-fused indoles in moderate to good yields. As revealed in entries 2 and 3, the substrates with electron-rich substituents at the C(5)-indole position could be successfully utilized in this transformation. Moreover, the electron-deficient substrates in the context of 5-halogen- and 5-nitro-substituted indoles also exhibited high reaction activities (Table 2, entries 4–7). These results clearly indicated that the electronic modification of the indole ring can be accomplished with little influence on the outcome of the reaction. Importantly, these halogenated oxazino[4,3-*a*]indoles (*e.g.* **5e** and **5f**) can be further functionalized with the use of organometallic technologies,[13] and in doing so generate diverse polycyclic indoles with more molecular complexity (Table 2, entries 4–6, and 9). When disubstituted (1*H*-indol-2-yl)methanol substrates were employed, cyclization products were obtained in slightly lower yields (Table 2, entries 8–9). Furthermore, the substrate with a methyl at the 3-position of indole was applicable as well (Table 2, entry 10), and the secondary alcohol substrate **3k** also smoothly cyclized to afford the corresponding product in moderate yield (Table 2, entry 11). Significantly, *N*-methyl-1*H*-indole-2-carboxamide **3l** and 1*H*-indole-2-carboxamide **3m** could also successfully participate in this cyclization and afforded the corresponding products **5l**[14] and **5m** in 80% and 90% yield respectively, both of which are precusors of the bioactive pyrazino[1,2-*a*]indoles (Table 2, entries 12 and 13).

In order to clarify the mechanism, (1*H*-indol-2-yl)methanol substrates **3c** and **3g** were tested with dimethyl[(*E*)-2-phenyl-1-ethenyl]sulfonium trifluoromethane-sulfonate **6** under the optimized conditions. As illustrated in eqns (1) and (2), the fact that only the olefin products **7** and **8**[15] were isolated in high yields indicated that the cascade reaction was initiated by the addition of the nitrogen anion of the indole ring to the sulfonium salt.



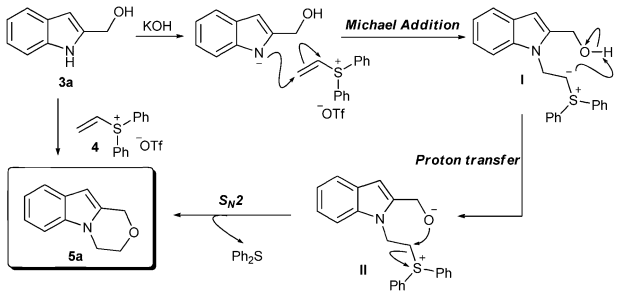
(1)



(2)

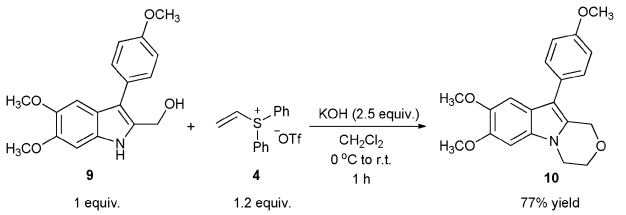
As shown in Scheme 2, the conjugated addition of the nitrogen anion to the electrophilic sulfonium salt affords an intermediate sulfur ylide I. Intra- or intermolecular proton shift followed by S_N2 substitution gave the cyclization product.[11d,e]

Finally, the synthetic utility of this transformation was highlighted in the synthesis of 3,4-dihydro-7,8-dimethoxy-10-(4-methoxyphenyl)-1*H*-[1,4]oxazino[4,3-*a*]indole **10**, a drug candidate



Scheme 2 Proposed mechanism for the cascade reaction.

for the treatment of tumors of the blood. The reaction of vinyl sulfonium **4** with substituted (1*H*-indole-2-yl)methanol **9** under our standard conditions generated **10** in 77% yield (eqn (3)). Compared with a conventional three-step synthesis of **10** (49% yield),[3b] the current one-step procedure represents a significant improvement in terms of the criteria of green chemistry.



(3)

In summary, we have developed an addition-cyclization reaction of (1*H*-indole-2-yl)methanols and vinyl sulfonium salts, providing biologically and pharmaceutically important oxazino[4,3-*a*]indoles in good to excellent yields. This methodology can also be used in the preparation of pyrazino[1,2-*a*] indole derivatives.

We are grateful to the National Science Foundation of China (20872043) for support of this research.

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14 Crystal data for **5l**: $C_{12}H_{12}N_2O$, M = 200.24, monoclinic, $P2_1/c$, a = 10.5035(12) Å, b = 8.0361(9) Å, c = 12.2743(14) Å, α = 90°, β = 98.375(2)°, γ = 90°, V = 1025.0(2) Å^3, Z = 4, T = 298(2), $F000$ = 424, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0489, wR_2 = 0.1371, R indices (all data): R_1 = 0.0679, wR_2 = 0.1458. CCDC 800928. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

15 The conjugate addition of the nitrogen anion to sulfonium salt **6** gave an ylide, which would undergo 1,2-proton shift and an elimination to form the olefin products. Also see ref. 10*l* and 10*m*.