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Indole Synthesis

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Synthesis of Indoles through Highly Efficient Cascade Reactions of Sulfur Ylides and *N*-(*ortho*-Chloromethyl)aryl Amides**

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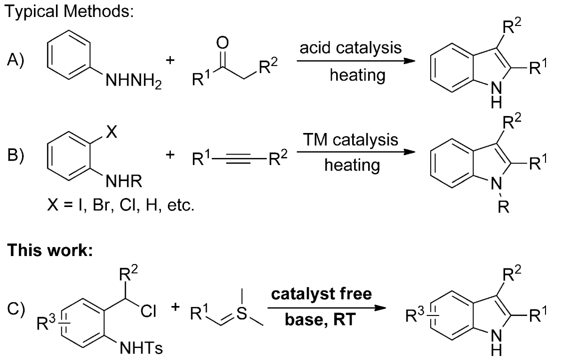
As a consequence of its prevalence as a "privileged" structure in many natural isolates and therapeutic agents, the indole framework has continued to capture the interest of chemists worldwide.[1] Consequently, numerous efforts have been devoted to the development of efficient methods to construct the indole architecture.[2] Work on this problem dates back to the seminal studies by Fischer and Jourdan,[3] which led to the synthesis of indoles by heating phenylhydrazines with ketones or aldehydes in the presence of a protic acid or a Lewis acid catalyst (Scheme 1 A). Despite its extensive applications[4] and various improvements,[5] the Fischer indole synthesis has several limitations, including poor regioselectivity with nonsymmetric ketones, a restricted range of starting materials, and harsh reaction conditions such as the use of strong acids and/or elevated temperatures.[2] As a consequence, the demand for alternative efficient methods has encouraged the development of new methods for the synthesis of indoles. Over the past several decades, protocols have emerged that rely on transition-metal-catalyzed processes. For example, heteroannulation and cyclization reactions of 2-alkynylanilines,[6] reductive cyclizations,[7] C−H activations,[8] and other processes[9] have become extremely attractive methods for the formation of indoles (Scheme 1 B). Despite these achievements, the further development of efficient and practical procedures to construct the indole skeleton that minimize the use of special reagents, cost, time, and steps remains highly desirable. Herein, we disclose an unprecedented cascade process of sulfur ylides and *N*-(*ortho*-chloromethyl)aryl amides under very mild conditions, which allows a highly efficient synthesis of structurally diverse indoles (Scheme 1 C).



Scheme 1. Strategies for the synthesis of indoles. TM = transition metal.

As pioneered by Corey and Chaykovsky,[10] sulfur ylides are versatile synthetic reagents in synthetic organic chemistry.[11] For example, the research groups of Aggarwal,[12] Tang,[13] Xiao,[14] and others[15] have developed many elegant reactions of sulfur ylides to generate functionalized cyclic compounds. As part of our ongoing research program on methods to synthesize carbo- and heterocycles,[16] we have devised and tested a general strategy for the synthesis of indoles that relies on cascade reactions of sulfur ylides.

In the initial phase of this study we investigated the reaction of dimethyl (2-oxo-2-phenylethyl)sulfonium ylide (**1a**) with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide (**2a**) in CH_2Cl_2 and in the presence of Cs_2CO_3 (2.5 equiv) at room temperature. Interestingly, a cascade reaction took place to afford (1*H*-indol-2-yl)-(phenyl)methanone (**3aa**) in 48 % yield (Table 1, entry 1). An increase in the amount of the base to 5.0 equivalents caused a sharp increase in the yield of this reaction to 73 % (Table 1, entry 2). The solvent was found to have a dramatic impact on the efficiency of the reaction (Table 1, entries 2–8). Notably, xylenes were identified as optimal for the formation of **3aa** (Table 1, entry 8). Other bases (Table 1, entries 8–11) and changing the substrate concentrations (Table 1, entries 8, 12, and 13) did not lead to an improvement in the reaction efficiency.

With the optimal reaction conditions established (Table 1, entry 8; 5.0 equiv Cs_2CO_3 in xylenes at RT), we next investigated the substrate scope of the reaction by employing a variety of sulfur ylides (**1**). As summarized in Table 2, various sulfur ylides were found to participate in this cascade process. For example, sulfur ylides bearing electron-neutral (Table 2, entry 1), electron-rich (Table 2, entries 2 and 3), and electron-deficient (Table 2, entries 4–9) substituents on the aryl ring underwent this reaction to furnish the corresponding products in generally high yields (75–92 %). In addition, the

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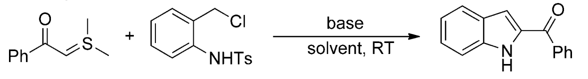
Table 1: Optimization of the reaction conditions.[a]

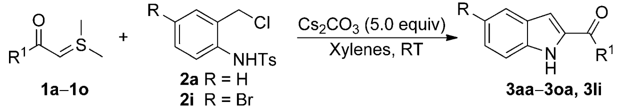


1a **2a** **3aa**

Entry	Solvent	Conc. [M]	Base	Equiv.	Yield [%][b]
1	CH_2Cl_2	0.05	Cs_2CO_3	2.5	48
2	CH_2Cl_2	0.05	Cs_2CO_3	5.0	73
3	Et_2O	0.05	Cs_2CO_3	5.0	trace
4	MeCN	0.05	Cs_2CO_3	5.0	58
5	THF	0.05	Cs_2CO_3	5.0	64
6	MeOH	0.05	Cs_2CO_3	5.0	trace
7	toluene	0.05	Cs_2CO_3	5.0	75
8	**xylenes**	**0.05**	$\mathbf{Cs_2CO_3}$	**5.0**	**82**
9	xylenes	0.05	KOH	5.0	67
10	xylenes	0.05	*t*BuOK	5.0	trace
11	xylenes	0.05	TMG	5.0	33
12	xylenes	0.1	Cs_2CO_3	5.0	70
13	xylenes	0.025	Cs_2CO_3	5.0	77

[a] Reaction conditions: **1a** (0.33 mmol), **2a** (0.3 mmol), base, solvent (3, 6 or 12 mL), RT. [b] Yield of isolated product. TMG = tetramethylguanidine.

Table 2: Synthesis of indoles from various sulfur ylides.[a]



1a–1o **2a** R = H **2i** R = Br **3aa–3oa, 3li**

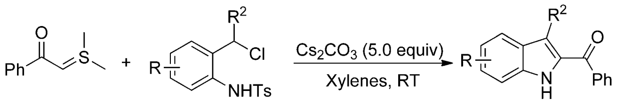
Entry	R^1	Product	Yield [%][b]
1	Ph (**1a**)	**3aa**	82
2	*p*-$MeOC_6H_4$ (**1b**)	**3ba**	75
3	*p*-MeC_6H_4 (**1c**)	**3ca**	81
4	*m*-BrC_6H_4 (**1d**)	**3da**	78
5	*p*-ClC_6H_4 (**1e**)	**3ea**	81
6	*p*-$NO_2C_6H_4$ (**1f**)	**3fa**	87
7	*p*-FC_6H_4 (**1g**)	**3ga**	86
8	*o*-FC_6H_4 (**1h**)	**3ha**	92
9	*m*-$NO_2C_6H_4$ (**1i**)	**3ia**	91
10	2-thioenyl (**1j**)	**3ja**	65
11	2-furanyl (**1k**)	**3ka**	87
12[c]	OEt (**1l**)	**3la**	25 (30)
13[c,d]	OEt (**1l**)	**3li**	40 (60)
14[e]	*t*Bu (**1m**)	**3ma**	63
15[c]	$PhCH_2CH_2$ (**1n**)	**3na**	68
16[c]	Ph-CH=CH (**1o**)	**3oa**	34 (61)
17[f]	Ph (**1a**)	**3aa**	74

[a] Reaction conditions: **1** (0.33 mmol), **2a** (0.3 mmol), Cs_2CO_3 (5.0 equiv), xylenes (6 mL), RT. [b] Yield of isolated product. Values in parentheses are the yields of one-pot procedures. See the Supporting Information for more details. [c] RT for 2 h, and then 60 °C. [d] **2i** was used in place of **2a**. [e] KOH (5.0 equiv) was used in place of Cs_2CO_3. [f] Gram scale: **1a** (8.8 mmol, 1.59 g), **2a** (8 mmol, 2.37 g), Cs_2CO_3 (40 mmol, 13 g), xylenes (40 mL).

scope of this reaction was extended to include a variety of stable sulfur ylides, such as those containing heteroaryl (Table 2, entries 10 and 11) and ethoxy substituents (Table 2, entries 12 and 13). Furthermore, alkylacyl-substituted sulfur ylides, such as **1m** and **1n**, gave the corresponding products in moderate yields (Table 2, entries 14 and 15), and alkenylacyl-substituted substrate could also be tolerated under the model reaction conditions (Table 2, entry 16). Finally, to demonstrate preparative utility, the reaction was carried out on a gram scale. To our delight, the reaction proceeded efficiently to afford the desired product without an apparent loss in the reaction yield (Table 2, entry 17).

Of equal importance is the observation that significant structural variation of the *N*-(*ortho*-chloromethyl)aryl amide substrate is possible. As shown in Table 3, electron-rich and electron-poor *N*-(*ortho*-chloromethyl)aryl amides, with different substitution patterns on the benzene ring, all participated in the process, thereby providing the corresponding indoles in moderate to high yields (Table 3, entries 2–9). Incorporation of methyl and chloro substituents at the *ortho*, *meta*, or *para* positions relative to the sulfonanilide nitrogen atom did not retard the cascade reaction, thus demonstrating that steric effects in the *N*-aryl amide component did not alter the efficiency of the process (Table 3, entries 2, 3, and 6–8). Furthermore, disubstituted *N*-(*ortho*-chloromethyl)aryl amide substrates were found to react to form cyclization products in high yields (Table 3, entries 4 and 5). In addition, substrates with substituents at the benzylic position also underwent the transformation to produce the corresponding products in excellent yields (Table 3, entries 10 and 11). To our knowledge, such cyclic adducts can not be obtained by Friedel–Crafts reactions of 2-acylindoles. A similar result was observed when a free hydroxy group was introduced into the indole framework (Table 3, entry 12), and the product **3al** was reported to be a novel CaMKII inhibitor.[17a] Moreover, (5-methoxy-1*H*-2-indolyl)phenylmethanone (**3am**), which has been identified to be as active as paclitaxel and exhibit antiangiogenic activity,[17b] can be synthesized in only one step in 87% yield (Table 3, entry 13).

Table 3: Synthesis of indoles from various *N*-(*ortho*-chloromethyl)aryl amides.[a]

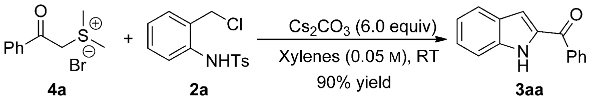


1a **2a–2m** **3aa–3am**

Entry	R	R^2	Product	Yield [%][b]
1	H	H (**2a**)	**3aa**	82
2[c]	5-Me	H (**2b**)	**3ab**	78
3[c]	3-Me	H (**2c**)	**3ac**	90
4[c]	3,4-Me_2	H (**2d**)	**3ad**	95
5[c]	4,5-$(MeO)_2$	H (**2e**)	**3ae**	84
6	6-Cl	H (**2f**)	**3af**	76
7	5-Cl	H (**2g**)	**3ag**	87
8	4-Cl	H (**2h**)	**3ah**	71
9	5-Br	H (**2i**)	**3ai**	57
10[c]	H	Me (**2j**)	**3aj**	95
11[c]	5-Cl	Ph (**2k**)	**3ak**	95
12	5-OH	H (**2l**)	**3al**	45
13	5-OMe	H (**2m**)	**3am**	87

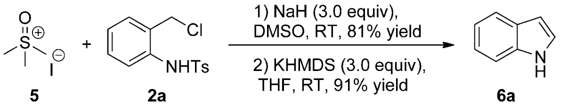
[a] Reaction conditions: **1a** (0.33 mmol), **2** (0.3 mmol), Cs_2CO_3 (5.0 equiv), xylenes (6 mL), RT. [b] Yield of isolated product. [c] RT for 2 h, and then 60 °C.

Importantly, the reaction of sulfonium salt **4a** with **2a** was also found to be applicable to the synthesis of 2-benzoylindole, thus simplifying the procedure further [Eq. (1)]. This one-pot procedure was also applied successfully to the



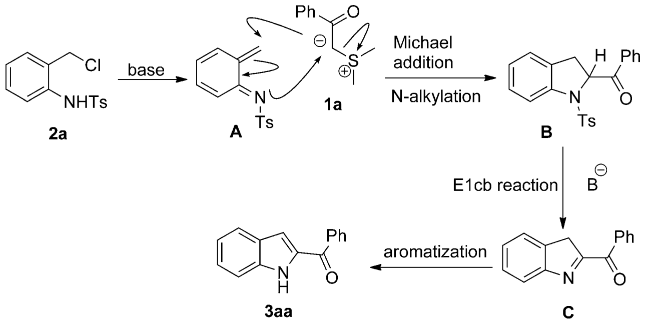
(1)

synthesis of other indoles such as **3la**, **3li**, and **3oa** (Table 2, entries 12, 13, and 16). Furthermore, the process is not limited to stable carbonyl ylides. Dimethyloxosulfonium methylide, generated in situ from trimethylsulfoxonium iodide **5**, reacted well with **2a** to form indoline in 81% yield, which was followed by an E1cb elimination to afford unsubstituted indole **6a** in 91% yield [Eq. (2); DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane].



(2)

A possible mechanism for the cascade reaction that leads to formation of the indole ring is depicted in Scheme 2. The process is initiated by addition of sulfur ylide **1a** to the aza-*o*-quinodimethane intermediate **A**, generated in situ from *N*-(*ortho*-chloromethyl)aryl amide **2a** under the basic conditions.[18a–d] This step is followed by cyclization with loss of dimethylsulfide to generate indoline **B**, which then undergoes an E1cb elimination to afford **C**. This is then aromatized to give the indole **3aa**.[18e] Observations made in two additional experiments provided evidence to support the proposed mechanism.[19]



Scheme 2. Possible mechanism for the cascade reaction.

In summary, an unprecedented and robust method for the synthesis of indoles from stable sulfur ylides and *N*-(*ortho*-chloromethyl)aryl amides, which takes place by a cascade reaction sequence, has been developed. This process occurs under mild conditions, utilizes simple operations, and affords indole products in generally high yields. Further studies to expand the scope of the sulfur ylides are currently ongoing.

Experimental Section

Representative procedure: After stirring a solution of sulfur ylide **1a** (0.33 mmol) and Cs_2CO_3 (1.5 mmol) in xylenes (6 mL) for 0.5 h, *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide (**2a**; 0.3 mmol) was added. The mixture was stirred at room temperature. Upon completion of the reaction, as monitored by TLC, the crude mixture was subjected to flash chromatography on silica gel (silica: 200–300; eluent: petroleum ether/ethyl acetate = 10:1) to provide pure indole **3aa** in 82% yield.

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[19] For some mechanism studies, see the Supporting Information.

Indole Synthesis

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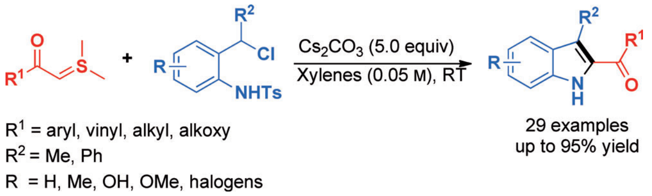
Synthesis of Indoles through Highly Efficient Cascade Reactions of Sulfur Ylides and *N*-(*ortho*-Chloromethyl)aryl Amides



Batting the ylides: A simple procedure carried out under mild conditions allows the direct and efficient synthesis of structurally diverse indoles. This approach involves a cascade reaction of sulfur ylides and *N*-(*ortho*-chloromethyl)-aryl amides (see scheme).