Reactions of Cyclopropyl Aryl Ketones with Sulfonamides Mediated by $Zr(OTf)_4$: Cascade Preparation of 5-Aryl-3,4-dihydro-2*H*-pyrrole

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Abstract: We found that the Lewis acid $Zr(OTf)_4$ can effectively promote the ring-opening reaction of cyclopropyl aryl ketones with sulfonamides. By controlling the reaction conditions, we could obtain the ring-opened products **3** and the cyclized products **5** in moderate to good yields. This process provides a novel and efficient route for the synthesis of 5-aryl-3,4-dihydro-2*H*-pyrrole in the presence of a Lewis acid.

Key words: cyclopropyl aryl ketones, Lewis acid, $Zr(OTf)_4$, ring-opening reaction, sulfonamides, cyclization, 5-aryl-3,4-dihydro-2*H*-pyrrole

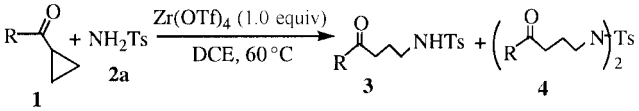
In recent years, ring-opening reactions of cyclopropyl ketones for the preparation of enolates have attracted much attention from synthetic organic chemists, and these reactions have been investigated extensively.[1,2] However, the ring-opening reactions of monoactivated cyclopropane derivatives are generally sluggish due to their low reactivities towards nucleophiles. Several examples have been so far reported under severe reaction conditions, for example, assisted by stronger nucleophiles such as I^- and stronger Lewis acids such as $TiCl_4$,[2a] or assisted by the β-effect of silicon atom of trimethylsilyl group.[2b] Thus, it is necessary to develop a method for the ring-opening reaction of simple monoactivated cyclopropane derivatives under mild conditions. Herein, we present a Lewis acid-mediated ring-opening reaction of arylcarbonyl activated cyclopropanes (monoactivated cyclopropane) with sulfonamides under mild conditions.

The ring-opening reaction of cyclopropyl phenyl ketone (**1a**, 0.5 mmol) with NH_2Ts (**2a**, 1.0 mmol) proceeded smoothly in 1,2-dichloroethane (DCE) in the presence of Lewis acid $Zr(OTf)_4$ (100 mol%)[3] to give product **3a** in 85% yield along with trace amount of product **4a** for 1.5 hours at 60 °C (Table 1, entry 1).[4] Under these reaction conditions, we examined an array of cyclopropyl aryl ketones with **2a**. The results are summarized in Table 1. In all cases the corresponding ring-opened products **3** were obtained in moderate to good yields (Table 1, entries 2–6). For cyclopropyl methyl ketone (**1g**), no reaction occurred (Table 1, entry 7).

Interestingly, we found that if this reaction was carried out for a long time (about 2 d), the cyclized products **5** (5-aryl-3,4-dihydro-2*H*-pyrrole) were formed in good yields. The results are summarized in Table 2 (Table 2, entries 1 and 3–7).[5] In this cyclization reaction, $Zr(OTf)_4$ (50 mol%) is also an effective Lewis acid mediator. Using Lewis acid $BF_3{\cdot}OEt_2$ (50 mol%) as a promoter, the corresponding cyclized product **5a** was obtained in somewhat lower yield (52%, Table 2, entry 2). Their structures were determined by ^1H and ^{13}C NMR spectroscopic data and microanalysis.

For sulfonamide **2b** similar results were obtained, although this reaction was slower than that of **2a** (Scheme 1). The corresponding ring-opened product **6** was obtained in 30% yield along with the cyclized product **5a** in 26% yield after 10 hours at 60 °C in DCE in the presence of $Zr(OTf)_4$ (100 mol%). When this reaction was carried out for 24 hours in the presence of 50 mol% of $Zr(OTf)_4$, the cyclized product **5a** was formed in 63% yield as the sole product (Scheme 1).

Table 1 Reaction of Various Cyclopropyl Aryl Ketone (0.5 mmol) with NH_2Ts (**2a**, 1.0 mmol) Mediated by $Zr(OTf)_4$ (100 mol%)



Entry	R	Time (h)	Yield (%)[a]	
			3	**4**
1	C_6H_5 (**1a**)	1.5	**3a**, 85	**4a**, trace
2	*p*-FC_6H_4 (**1b**)	1.5	**3b**, 68	0
3	*p*-MeC_6H_4 (**1c**)	2	**3c**, 65	0
4	3,5-$(Me)_2C_6H_3$ (**1d**)	2	**3d**, 41	0
5	*p*-$MeOC_6H_4$ (**1e**)	2	**3e**, 36[b]	0
6	2-thiophenyl (**1f**)	3	**3f**, 62[b]	0
7	methyl (**1g**)	10	NR	

[a] Isolated yields.
[b] Determined by ^1H NMR spectroscopy.

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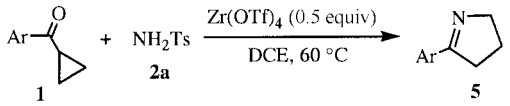
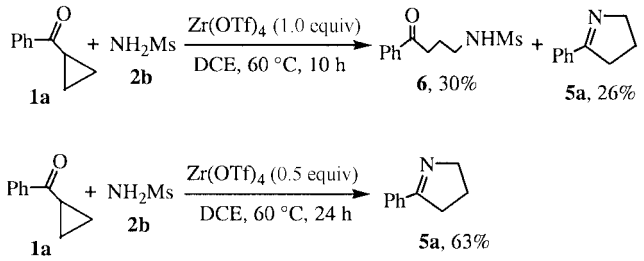
Table 2 Reaction of Various Cyclopropyl Aryl Ketone (0.5 mmol) with NH_2Ts (1.0 mmol) Mediated by $Zr(OTf)_4$ (50 mol%) for a Long Reaction Time



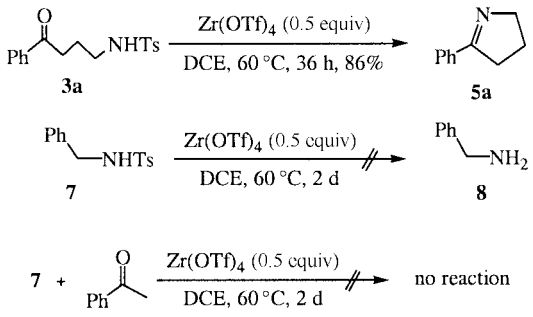
Entry	Ar	Time (h)	Yield (%)[a] 5
1	C_6H_5 (**1a**)	48	**5a**, 80
2[b]	C_6H_5 (**1a**)	72	**5a**, 73
3	*p*-FC_6H_4 (**1b**)	36	**5b**, 74
4	*p*-MeC_6H_4 (**1c**)	48	**5c**, 77
5	3,5-$(Me)_2C_6H_3$ (**1d**)	48	**5d**, 82
6	*p*-$MeOC_6H_4$ (**1e**)	48	**5e**, 47
7	2-thiophenyl (**1f**)	48	**5f**, 82

[a] Isolated yields.
[b] Mediated by $BF_3{\cdot}OEt_2$ (0.5 equiv).



Scheme 1

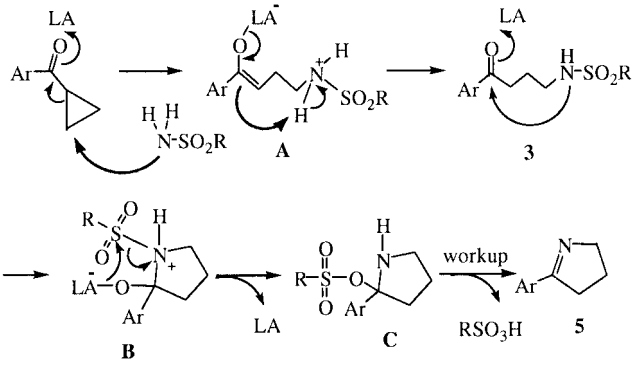
In the presence of $Zr(OTf)_4$, we confirmed that **3a** could be transformed to cyclized product **5a** in DCE at 60 °C in 86% yield after 36 hours (Scheme 2). The cyclized product **5** was therefore indeed derived from the ring-opened product **3** in the presence of $Zr(OTf)_4$. On the other hand, we found that *p*-toluenesulfonyl (Ts) protected benzylamine **7** remained intact under the same conditions for 2 days. In addition, in the presence of acetophenone, no reaction occurred (Scheme 2). These results suggested that sulfonyl groups (Ts and Ms groups) were removed during the ring-closing process.



Scheme 2

Based on the above results, a plausible reaction mechanism for the formation of **3** and **5** is shown in Scheme 3. The sulfonamide attacks the Lewis acid activated cyclopropyl aryl ketone **1** to give the ring-opened zwitterionic intermediate **A**. The ring-opened product **3** was then formed from intermediate **A**. In the presence of Lewis acid, the further intramolecular attack of the nitrogen atom in $NHSO_2R$ to the carbonyl group of **3** produces the zwitterionic intermediate **B**. The intramolecular elimination gives another intermediate **C** and regenerates the Lewis acid. Usual work-up furnishes the cyclized product **5** (Scheme 3).

In conclusion, we have found that Lewis acid $Zr(OTf)_4$ can effectively promote the ring-opening reaction of cyclopropyl aryl ketones with sulfonamides to give the products **3** and cyclized products **5** in moderate to good yields during different reaction time. This process provides a novel and efficient route for the synthesis of 5-aryl-3,4-dihydro-2*H*-pyrrole in the presence of Lewis acid. Efforts are in progress to elucidate the mechanistic details of this reaction and to determine its scope and limitations.



Scheme 3 A plausible reaction mechanism for the reaction of cyclopropyl aryl ketone with sulfonamide catalyzed by Lewis acid

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(3) In the presence of catalytic amount of $Zr(OTf)_4$, a prolonged reaction time was required. During a prolonged reaction time, this reaction accompanied the cyclized product **5**. In order to accelerate the reaction rate and let the reaction complete within a short time to give the ring-opened compound **3** as a major product, $Zr(OTf)_4$ (100 mol%) was employed.

(4) A variety of Lewis acids and solvent have been tested in this reaction (unpublished results from our laboratory). As a result of these investigations, we found that $Zr(OTf)_4$ is the best Lewis acid for this reaction.

(5) For other examples of the synthesis of 5-aryl-3,4-dihydro-2*H*-pyrrole, see: (a) Stevens, R. V.; Ellis, M. C.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5576; and references cited therein. (b) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. (c) Keely, S. L. Jr.; Tahk, F. C. *J. Am. Chem. Soc.* **1968**, *90*, 5584.

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