Synthetic Methods

DOI: 10.1002/anie.200604276

Domino Ring-Opening/Recyclization Reactions of Doubly Activated Cyclopropanes as a Strategy for the Synthesis of Furoquinoline Derivatives**

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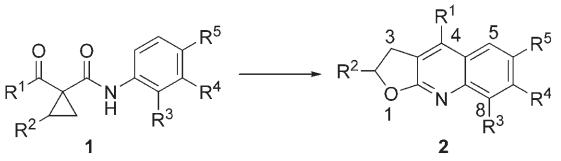
Furoquinoline alkaloids,[1] widely distributed among plants of the Rutaceae family,[2] have attracted considerable attention because of their diverse pharmacological and biological properties.[1–3] The development of efficient syntheses of furoquinolines has been the focus of much research for many decades and continues to be an active and rewarding research area.[4] However, most of the existing methods suffer from the limited availability of substrates or require multistep procedures to construct the pyridine and furan rings individually. Recently, in conjunction with drug development, new synthetic routes to furoquinoline derivatives have been developed.[5] For example, furoquinolines were synthesized in a single step by a multicomponent domino reaction of an *ortho*-alkynyl aniline, an isocyanoacetamide, and an aldehyde[5a] and by the tandem radical annulation of unsaturated *N*-aryl thiocarbamates,[5b] although there are limitations in terms of the starting materials, expensive reagents are involved, and the regioselectivity is not controllable in some cases. Herein, we report a new strategy for the synthesis of furo[2,3-*b*]-quinoline derivatives **2** in a single step from doubly activated cyclopropane precursors in the form of readily available 1-acyl *N*-aryl cyclopropanecarboxamides **1** (Scheme 1). The mechanistic details of this highly chemo- and regioselective domino ring-opening/recyclization process are also discussed.

Cyclopropanes are extremely versatile building blocks in organic synthesis owing to their ready accessibility and good reactivity.[6,7] Since the first report by Cloke in 1929 that



Scheme 1. Synthesis of furo[2,3-*b*]quinolines **2** from doubly activated cyclopropanes **1**.

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[**] Financial support of this research by the Key Grant Project of the Chinese Ministry of Education (10412), the NNSFC (20672019), and the Science Foundation for Young Teachers of Northeast Normal University (20060301) is gratefully acknowledged.

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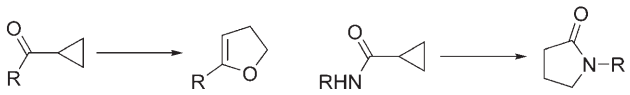
cyclopropyl ketones can be transformed into dihydrofuran derivatives,[8] such reactions have been well studied (Scheme 2).[9] Although there have been fewer studies on the synthetic utility of cyclopropyl amides, some interesting results have been obtained,[10] including the formation of ring-expanded products, such as *N*-substituted pyrrolidin-2-ones (Scheme 2).[10a]



Scheme 2. Ring opening/recyclization of cyclopropyl ketones and amides.

So far, to the best of our knowledge, there have been no reports on the synthetic applications of cyclopropane derivatives with both acyl and carbamoyl activating groups, although doubly activated cyclopropanes have proven very useful,[11] especially in the synthesis of tetrahydro-1,2-oxazines[11c,d] and 4-nitro-/4-cyanodihydropyrroles.[11e] During our research on the synthesis of carbocyclic and heterocyclic compounds via α-alkenoyl α-carbamoyl ketene dithioacetals derived from the corresponding 3-oxobutanamides,[12] we prepared a series of 1-acyl *N*-aryl cyclopropanecarboxamides **1** in good to excellent yields from cheap starting materials (acetoacetanilides and 1,2-dibromoethane or 1,2-dibromopropane)[13] and investigated their synthetic potential.

We first focused on the reactivity of the doubly activated cyclopropane precursor 1-acetyl-*N*-(2-methoxyphenyl)cyclopropanecarboxamide (**1a**),[13] which was obtained in 99% yield from the reaction of *N*-(2-methoxyphenyl)-3-oxobutanamide and 1,2-dibromoethane (K_2CO_3, *N*,*N*-dimethylformamide, room temperature, 11 h) in the presence of a Lewis acid. After many attempts, it was found that the furoquinoline derivative 8-methoxy-4-methyl-2,3-dihydrofuro[2,3-*b*]quinoline (**2a**) could be isolated in 88% yield when **1a** was treated with $SnCl_4 \cdot 5H_2O$ (1.2 equiv) in xylene at 120°C for 4.5 h (Scheme 3; Table 1, entry 1). Other Lewis acids, including $FeCl_3 \cdot 6H_2O$ and $BF_3 \cdot OEt_2$, gave **2a** in lower yields (Table 1, entries 2 and 3). When $TiCl_4$ was used as the catalyst, and the reaction was carried out in nitromethane at room temperature, instead of **2a**, the ring-opened product 2-(2-chloroethyl)-*N*-(2-methoxyphenyl)-3-oxobutanamide (**3a**) was obtained in 75% yield (Scheme 3).[13] Surprisingly, the reactions mediated by anhydrous $FeCl_3$ and $SnCl_4$ provided **2a** in lower yields than those with the hydrated Lewis acids

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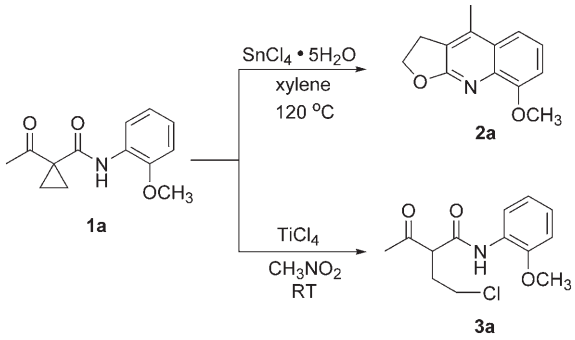


Scheme 3. Reaction products obtained from **1a** depending on the reagents used.

Table 1: The reaction of **1a** in the presence of a Lewis acid under different conditions.

Entry	Lewis acid (equiv)	Solvent	T [°C]	t [h]	Yield of **2a** [%][a]
1	$SnCl_4 \cdot 5H_2O$ (1.2)	xylene	120	4.5	88
2	$FeCl_3 \cdot 6H_2O$ (1.2)	xylene	120	6.0	52
3	$BF_3 \cdot OEt_2$ (1.2)	xylene	120	5.0	28
4	anhydrous $FeCl_3$ (1.2)	xylene	120	7.0	27
5	anhydrous $SnCl_4$ (1.2)	xylene	120	4.5	45
6	$SnCl_4 \cdot 5H_2O$ (0.5)	xylene	120	0.5	11[b]
7	$SnCl_4 \cdot 5H_2O$ (1.2)	toluene	110	8.0	58
8	$SnCl_4 \cdot 5H_2O$ (1.2)	benzene	80	40.0	63
9	$SnCl_4 \cdot 5H_2O$ (1.2)	nitromethane	101	10.0	45

[a] Yield of the isolated product. [b] The yield was not increased with a longer reaction time (6 h).

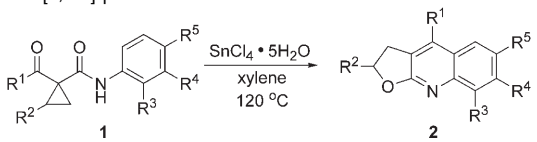
(Table 1, entries 4 and 5). Furthermore, the reaction was not efficient when only a small amount of $SnCl_4 \cdot 5H_2O$ (for example, 0.5 equivalents) was used (Table 1, entry 6). The reaction could also be carried out in toluene, benzene, and nitromethane, but the yields of **2a** were lower than when xylene was used (Table 1, entries 7–9).

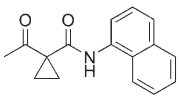
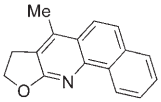
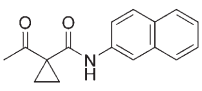
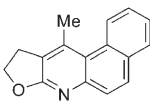
In contrast to usual ring-opening/recyclization reactions of cyclopropyl ketones[9] and amides[10] (Scheme 2), in the transformation from **1a** to **2a** the oxygen atom on the dihydrofuran ring of the product originates from the carbamoyl group of **1a**. As this transformation constitutes one of the simplest routes to a furo[2,3-*b*]quinoline derivative,[1–5] and the corresponding doubly activated cyclopropanes can be produced readily from very cheap raw materials,[13] we next investigated the scope of the reaction.

Precursors **1** with one or two electron-donating groups on the aryl ring were reactive under the optimized conditions given in Table 1, entry 1, and the corresponding products **2** were obtained in excellent yields (Table 2, entries 1, 2, 5, and 7).[14] In the case of precursors **1e** and **1g** with an electron-withdrawing chloro group on the aryl ring, the desired products **2e** and **2g** were also obtained in good yields (Table 2, entries 4 and 6). However, substrate **1i** with a strongly electron-withdrawing acetyl group on the aryl ring did not react to give the desired product **2i** (Table 2, entry 8), but the product of the hydrolysis of **1i**, 4-acetylaniline, was produced in 80% yield. The naphthalene derivatives **1j** and **1k** underwent the desired reaction smoothly to provide **2j** and **2k**, respectively, in high yields (Table 2, entries 9 and 10).

The reactions described exhibit very high regioselectivity. For example, precursors **1g**, **1h**, and **1k** reacted to give **2g**, **2h**, and **2k** as single regioisomers (Table 2, entries 6, 7, and 10); **1l** and **1m** (with a methyl group on the cyclopropane ring) also gave the single regioisomers **2l** and **2m** (with a methyl group at the 2-position) in excellent yields (Table 2, entries 11 and 12). In a study on acid-catalyzed cyclization by Ashrof and Raman, **2l** was also obtained in 92.7% yield from α-allylacetoacetanilide. However, a mixture of the corresponding furo- and pyrano[2,3-*b*]quinolines was produced in 19% combined yield from α-(but-2-enyl)acetoacetanilide, and no furo[2,3-*b*]quinolines were obtained from other α-allylacetoacetanilides.[4i] In our studies, besides the 1-acetyl *N*-aryl cyclopropanecarboxamides **1a**–**1h** and **1j**–**1m**, 1-(4-methoxybenzoyl)-*N*-phenylcyclopropanecarboxamide (**1n**; with a substituted benzoyl group as one of the activating groups) was used successfully as a substrate to prepare the furoquinoline **2n** in moderate yield under identical conditions

Table 2: Synthesis of furo[2,3-*b*]quinolines **2** from **1**.[a]



Entry	Substrate **1**						t [h]	Product	Yield [%][b]
	1	R^1	R^2	R^3	R^4	R^5			
1	**1b**	Me	H	Me	H	H	4.0	**2b**	90
2	**1c**	Me	H	Me	H	Me	5.5	**2c**	87
3	**1d**	Me	H	H	H	H	1.0	**2d**	75
4	**1e**	Me	H	H	H	Cl	0.5	**2e**	57
5	**1f**	Me	H	H	H	Me	1.5	**2f**	86
6	**1g**	Me	H	H	Cl	H	0.5	**2g**	56
7	**1h**	Me	H	H	Me	H	1.3	**2h**	91
8	**1i**	Me	H	H	H	CH_3CO	0.5	**2i**	0
9	**1j**						0.5		68
10	**1k**						0.5		75
11	**1l**	Me	Me	H	H	H	1.5	**2l**	93
12	**1m**	Me	Me	OMe	H	H	5.0	**2m**	85
13	**1n**	*p*-$MeOC_6H_4$	H	H	H	H	0.5	**2n**	45

[a] Reactions were carried out with $SnCl_4 \cdot 5H_2O$ (1.2 mmol) and **1** (1.0 mmol) in xylene (3 mL) at 120°C for 0.5–5.5 h. [b] Yield of the isolated product.

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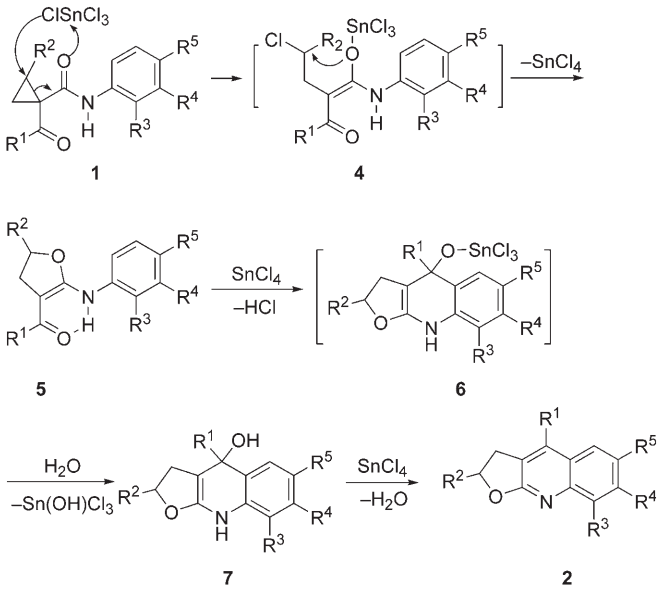
(Table 2, entry 13). Our results show the wide scope of the novel domino ring-opening/recyclization reaction with respect to a range of substituents R^1, R^2, R^3, R^4, and R^5 (Tables 1 and 2). Thus, this new synthetic strategy provides an efficient route to furo[2,3-*b*]quinolines.

In general, β-ketoanilides are the precursors of 2-quinolones in the Knorr synthesis.[4i,15] To gain an understanding of the mechanism of the ring-opening/recyclization reaction, some further experiments were conducted. The reaction of **1a** with $SnCl_4 \cdot 5H_2O$ (1.2 equiv) in xylene at 120 °C for 10 min gave the dihydrofuran **5a**, compound **7a**, and the furoquinoline **2a** in yields of 42, 20, and 33%, respectively, and the reaction of **5a** under the same conditions with a reaction time of 2 h produced **7a** (31%) and **2a** (47%; Scheme 4). Under



1 4 5 6 7 2

Scheme 4. Proposed mechanism for the synthesis of furo[2,3-*b*]-quinolines **2**.

otherwise identical conditions but with 0.2 equivalents of $SnCl_4 \cdot 5H_2O$, the reaction of **7a** for 2 h gave **2a** in quantitative yield, and the reaction of **5a** for 4.5 h produced **2a** in only 5% yield. These results suggest that **5** and **7** are involved as reaction intermediates, and that a stoichiometric amount of $SnCl_4 \cdot 5H_2O$ is required for the transformation of **5** into **7**. To probe the effect of the ratio of $SnCl_4$ to water on the yield of furoquinolines **2** (Table 1, entries 1 and 5), water was added to the reaction mixture with **1a** for further investigations.[16] Under otherwise identical conditions to those described in entry 5 of Table 1, when $SnCl_4$ and water were present in the reaction mixture in a ratio of 1:3, 1:5, and 1:7, **2a** was isolated in 45 (with **5a** (30%) and 2-methoxybenzenamine (24%)), 81 (with trace amounts of **5a** and 2-methoxybenzenamine), and 35% yield (with **5a** (20%) and 2-methoxybenzenamine (33%)), respectively. These results indicate that water is involved in the reaction. On the basis of all of the results described, a possible mechanism for this domino reaction is proposed in Scheme 4.

The overall transformation may involve the $SnCl_4 \cdot 5H_2O$-initiated opening of the cyclopropane ring in **1** (**1**→**4**), followed by a novel annulation to form the dihydrofuran intermediate **5**. Furoquinolines **2** were then produced through a Combes-type annulation.[17] Further evidence for this mechanism was provided by the annulation reaction of **3a**. Both **5a** and **2a** were obtained in 45% yield when **3a** was heated for 0.5 h under the conditions described in entry 1 of Table 1. Thus, the conversion of **1** into **2** involves a novel tandem ring-opening and annulation process (doubly activated cyclopropane→furan→furoquinoline).

In conclusion, we have developed a new strategy for the synthesis of furoquinoline derivatives **2** through an $SnCl_4$-mediated tandem ring-opening/recyclization reaction of the doubly activated cyclopropanes **1**. The advantages of this method, which include high chemo- and regioselectivity, high efficiency, operational simplicity, and the ready availability of a wide range of substrates from cheap starting materials, make this new strategy very powerful. Further studies towards the expansion of the scope of the reaction to various heterocyclic substrates are in progress.

Received: October 18, 2006
Published online: January 19, 2007

Keywords: cyclization · cyclopropanes · domino reactions · furoquinolines · synthetic methods

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