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A New Efficient Synthesis of Pyranoquinolines from 1-Acetyl *N*-Aryl Cyclopentanecarboxamides

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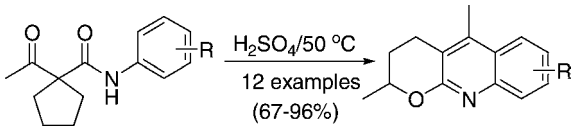
ABSTRACT



A new efficient synthesis of pyrano[2,3-*b*]quinoline derivatives is developed via the H_2SO_4-mediated tandem cyclization/ring-opening/recyclization reaction of readily available 1-acetyl *N*-aryl cyclopentanecarboxamides, during which a novel ring-cleavage fashion of the cyclopentane unit is involved and possible mechanisms are discussed.

Pyranoquinoline alkaloids, widely distributed among plants of the Rutaceae family, have attracted considerable attention because of their broad pharmacological and biological properties.[1] The development of efficient syntheses of pyranoquinolines has been the focus of much research for several decades and continues to be an active and rewarding research area. However, most of the existing methods suffer from limited scope or availability of starting materials, or require multistep procedures.[1,2] In this Letter, we describe an efficient synthesis of pyrano[2,3-*b*]quinolines **3** from the readily available 1-acetyl *N*-aryl cyclopentanecarboxamides **1** via a novel tandem cylization/ring-opening/recyclization reaction (Scheme 1).

Small carbon ring compounds, cyclopropanes and cyclobutanes, are extremely versatile building blocks in organic synthesis due to their ready accessibility and good reactivity originating from the inherent ring strain. Cyclopropanes/cyclobutanes activated by electron-withdrawing substituents are capable of undergoing a variety of ring-cleavage reactions.[3−5] In contrast, the ring-cleavage reactions of the activated cyclopentanes and their applications in organic synthesis are very rare owning to the stability of the five-membered cyclopentane ring.[6] Although in the works of Langer and co-workers,[6a,b] hydroxyspiro[5.4]decenones could be transformed to bicyclo[4.4.0]deca-1,4-dien-3-ones in the presence of trifluoroacetic acid, the ring-cleavage of the cyclopentane unit was through a well-known Wagner−Meerwein rearrangement. Herein, the first ring-cleavage fashion of activated cyclopentanes, which is similar to that of activated cylcopropanes,[3,4] is provided and a terminal

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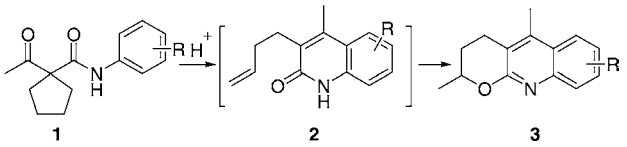
Scheme 1. Synthesis of Pyrano[2,3-*b*]quinolines **3** from Activated Cyclopentanes **1**

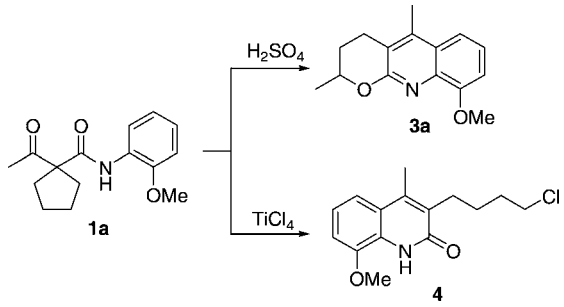


alkene intermediate **2** was presumably generated during the transformation from **1** to **3** (Scheme 1).

During our research on the synthesis of carbocyclic[7] and heterocyclic compounds[8] by domino reactions,[9] we developed a new strategy for the preparation of furo[2,3-*b*]quinolines through $SnCl_4$-mediated ring-opening/recyclization reactions of the activated cyclopropanes,[10] which prompted us to attempt new procedures for the synthesis of fused quinoline derivatives from activated cycloalkane precursors. Accordingly, 1-acetyl-*N*-(2-methoxyphenyl)cyclopentanecarboxamide (**1a**) was prepared in 92% isolated yield by the reaction of *N*-(2-methoxyphenyl)-3-oxobutanamide and 1,4-dibromobutane.[10] To our surprise, mediated by $TiCl_4$ (3.0 equiv), **1a** could be transformed to 3-(4-chlorobutyl)-8-methoxy-4-methylquinolin-2(1*H*)-one (**4**) in 9% yield at 50 °C for 40 h and 85% of **1a** was recovered (Scheme 2). It should be noted that during the transformation from **1a** to **4**, a novel ring-cleavage fashion of the cyclopentane unit was involved, which was similar to the homo-Michael reaction of activated cylcopropanes with nucleophiles[3,4] (for example, the transformation from **A** to **B**[10]). So far, to our knowledge, there is no report of this type of reaction based on activated cyclopentanes. Therefore, we showed great interest in this new ring-cleavage reaction of cyclpentane and the synthetic utility of activated cyclopentanes **1**.

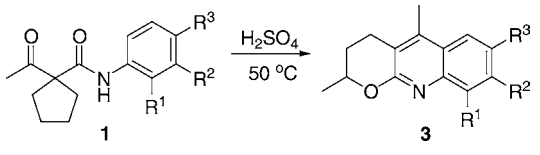
After many attempts, we were pleased to discover that by simply dissolving **1a** (1.0 mmol) in a small amount of 98% concentrated H_2SO_4 (0.5 mL) at 50 °C for 1.5 h, the pyrano-[2,3-*b*]quinoline derivative **3a** (Scheme 2) was obtained in 96% yield.[11] As there was a methyl group in the pyran ring of **3a**, an extra rearrangement may be involved from **1a** to

Scheme 2. Reaction Products Obtained from **1a** Depending on the Reaction Conditions



3a with the ring-cleavage of the cyclopentane unit. Gratifyingly, the new transformation of **1a** to **3a** was successfully expanded. The synthesized cyclopentane precursors **1b**−***l*** with both electron-donating and electron-withdrawing group(s) on the aryl ring (starting from acetoacetanilides and 1,4-dibromobutane)[11] could undergo this reaction to afford the desired pyrano[2,3-*b*]quinolines **3b**−***l*** in high to excellent yields (Table 1, entries 2−12). Furthermore, high regioselectivity was observed in the transformation from **1k** to **3k** and **1*l*** to **3*l*** (Table 1, entries 11 and 12). Therefore, we provided here an efficient and practical route to pyrano[2,3-*b*]quinolines **3** from activated cyclopentanes **1**.

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



	substrate **1**						
entry	**1**	R^1	R^2	R^3	time (h)	product **3**	yield[b] (%)
1	**1a**	OMe	H	H	1.5	**3a**	96
2	**1b**	Me	H	H	1.5	**3b**	90
3	**1c**	Cl	H	H	4.0	**3c**	76
4	**1d**	Me	H	Me	1.5	**3d**	85
5	**1e**	H	H	OMe	1.5	**3e**	88
6	**1f**	H	H	OEt	1.5	**3f**	83
7	**1g**	H	H	Cl	4.0	**3g**	67
8	**1h**	H	H	Me	1.5	**3h**	92
9	**1i**	H	H	NHAc	2.0	**3i**	82
10	**1j**	H	H	H	1.5	**3j**	87
11	**1k**	H	Cl	H	4.0	**3k**	77
12	**1*l***	H	Me	H	1.5	**3*l***	92

[a] Reactions were carried out with **1** (1.0 mmol) in 0.5 mL of 98% concentrated H_2SO_4 at 50 °C. [b] Isolated yield.

On the basis of all of the above results and our previous work,[10] a plausible mechanism of this domino reaction is presented in Scheme 3. The overall transformation commences from a H_2SO_4 -mediated Combes-type annulation[10,12] of **1** to provide an alcohol intermediate **5**. With the

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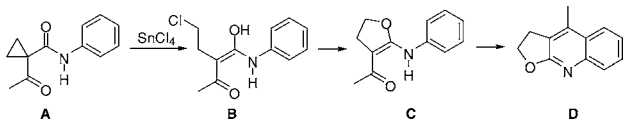
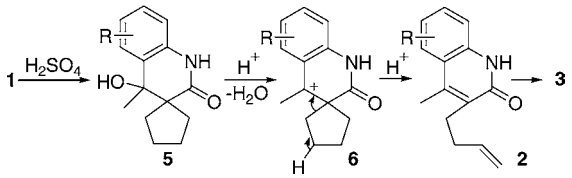
(10) Zhang, Z.; Zhang, Q.; Sun, S.; Xiong, T.; Liu, Q. *Angew. Chem., Int. Ed.* **2007**, *46*, 1726−1729 and references cited therein. A proposed mechanism as follows:



(11) For the reaction procedure in detail please see the Supporting Information.

Scheme 3. Proposed Mechanism for the Formation of Pyrano[2,3-*b*]quinolines **3**



elimination of water, a tertiary benzylic cation intermediate **6** is formed. The next elimination of a proton from intermediate **6** may directly provide a terminal alkene intermediate **2**, which can undergo an intramolecular Markovnikov addition to finally produce pyrano[2,3-*b*]quinoline **3**. In addition, in the present study, we could not exclude an alternative mechanism via a corner protonated cyclopropane intermediate[13,14] and the subsequent rearrangement in the transformation from the intermediate **6** to **2**. Further evidence for the formation of the tertiary benzylic cation intermediate **6** in the above proposed mechanisms was provided by the

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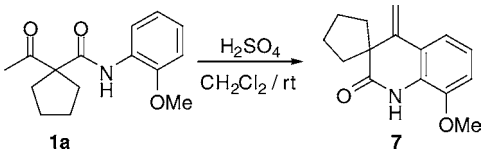
Scheme 4. Reaction of **1a** in the Presence of 1.0 equiv of 98% Concentrated H_2SO_4



reaction of **1a** in the presence of 1.0 equiv of 98% concentrated H_2SO_4 in dichloromethane (Scheme 4).[11] As a result, **1a** was transformed to a quinoline derivative **7**, which may originate from the intermediate **6** (Scheme 3) through eliminating a proton from the methyl group.

In conclusion, we have developed a new efficient synthesis of pyrano[2,3-*b*]quinolines via the H_2SO_4-mediated domino cyclization/ring-opening/recyclization reaction of readily available activated cyclopentanes, during which a novel ring-opening fashion of the cyclopentane unit was involved. This ring-opening fashion of activated cyclopentanes may open a new way to understand the special behavior of cycloalkanes with normal ring sizes and broaden their synthetic applications. Further studies are in progress.

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Supporting Information Available: Experimental details and spectral data for **1a**−***l***, **3a**−***l***, **4**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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