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One-Step Synthesis of the Tricyclic Core of Martinellic Acid from 2-(Cyanomethyl)-3-oxo-*N*-arylbutanamides

Zhiguo Zhang, Qian Zhang,* Zihong Yan, and Qun Liu*

Department of Chemistry, Northeast Normal University, Changchun 130024, China

zhangq651@nenu.edu.cn; liuqun@nenu.edu.cn

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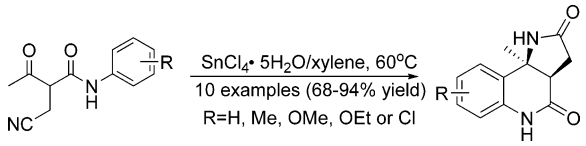

A $SnCl_4 \cdot 5H_2O$-mediated facile and efficient one-step synthesis of the tricyclic core of martinellic acid from readily available 2-(cyanomethyl)-3-oxo-*N*-arylbutanamides was developed and a mechanism involving consecutive hydrolysis of a cyano group and a double annulation process is proposed.

The pyrrolo[3,2-*c*]quinoline ring system is known as a core structure unit of bioactive molecules of either synthetic[1] or natural source[2] for many years. Several derivatives of such a tricyclic angular heterocycle possess a wide spectrum of biological activities,[3] including most notably antitumor properties,[4] gastric (H^+/K^+)-ATPase inhibitor,[5] hypotensive,[6] anti-inflammatory activities,[7] and others. The relatively recent isolation of martinella alkaloids (Figure 1) from the organic extracts of Martinella iquitosensis roots,[2] which evidenced antagonist properties against bradykinin receptors,[8] renewed interest from several research groups to plan new synthetic approaches.[9,10] Among these methods, the simplicity of the core connectivity of martinellic acid produced in two steps from arylthio-substituted succinic anhydrides and imines deserves special mention although some limitations in terms of the starting materials and efficiency exist (Scheme 1).[9j]

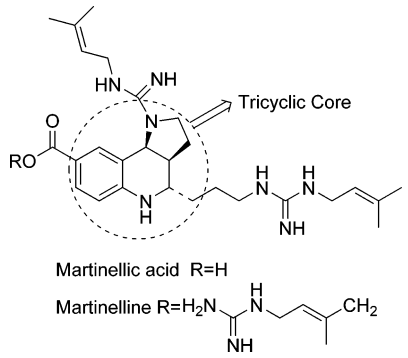

FIGURE 1. Structures of martinellic acid and martinelline.

Domino reactions are highly efficient processes that allow the synthesis of complex molecules starting from simple, inexpensive starting materials, in a straightforward fashion.[11] In the last two decades, various types of domino reactions have been developed and employed in the synthesis of heterocyclic compounds.[12] During our research on syntheses of carbocyclic[13] and heterocyclic compounds[14] by domino reactions, we devel-

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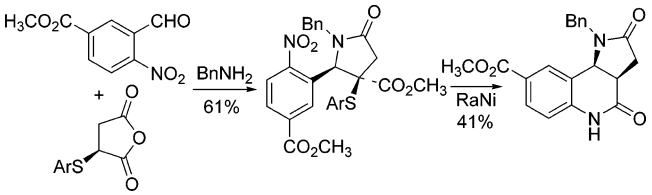
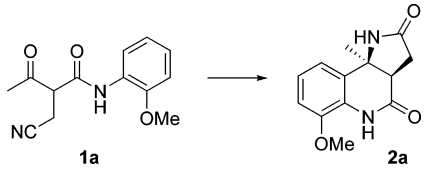
SCHEME 1



SCHEME 2. Synthesis of Pyrrolo[3,2-*c*]quinoline 2a from 1a

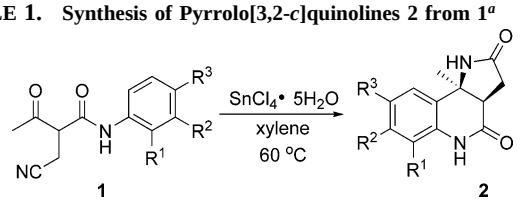


oped new strategies for the preparation of furo[2,3-*b*]quinolines and highly substituted pyridin-2(1*H*)-ones through a novel $SnCl_4$-mediated tandem ring-opening/recyclization reaction and the Vilsmeier−Haack reaction, respectively, starting from the easily available 1-acetyl *N*-aryl cyclopropanecarboxamides.[15] The successful synthesis of furo[2,3-*b*]quinolines[15a] prompted us to pay special attention to the development of new synthetic strategies for the preparation of fused quinoline derivatives by suitably selecting the substituents on the active methylene group of 1-acetyl *N*-arylcarboxamides. In this paper, we describe a one-step, atom economical procedure for the preparation of the tricyclic core of martinellic acid **2** from the readily available 2-(cyanomethyl)-3-oxo-*N*-arylbutanamides **1**.

Our initial studies were focused on the $SnCl_4{\cdot}5H_2O$-mediated reaction of 2-(cyanomethyl)-*N*-(2-methoxyphenyl)-3-oxobutanamide (**1a**), which was obtained in 88% yield from *N*-(2-methoxyphenyl)-3-oxobutanamide and 2-bromoacetonitrile based on known methods.[15a,16] After the optimization of the reaction conditions, including the reaction temperature, the solvent, and the amount of $SnCl_4{\cdot}5H_2O$, we were pleased to discover that in the presence of 1.2 equiv of $SnCl_4{\cdot}5H_2O$, **1a** could be efficiently transformed into a pyrrolo[3,2-*c*]quinoline derivative **2a** in 92% yield at 60 °C in xylene for 6.0 h (Scheme 2, Table 1, entry 1). The structure of **2a** was confirmed by the X-ray single crystal analysis, showing the expected cis ring fusion (Figure 2). It is noteworthy that the above transformation from **1a** to **2a** represents one of the simplest routes to the tricyclic core of martinellic acid.[9,10]

Next, a series of 2-(cyanomethyl)-3-oxo-*N*-arylbutanamide substrates **1** were prepared (in yields of 64−90% by alkylation of the commercially available 3-oxo-*N*-arylbutanamides with 2-bromoacetonitrile[15,16]) and subjected to the above optimal reaction conditions with the aim to determine its scope. Some of the results are summarized in Table 1. It is clear that the substrates **1** with one or two electron-donating groups on the aryl ring are reactive and lead to the corresponding pyrrolo-[3,2-*c*]quinoline derivatives **2** in excellent yields (Table 1, entries 1−3, 5−7, and 10). In the case of precursors **1h** and **1i** with an electron-withdrawing chloro group on the aryl ring, the desired products **2h** and **2i** are also obtained in high yields with prolonged reaction times (Table 1, entries 8 and 9). In addition,

TABLE 1. Synthesis of Pyrrolo[3,2-*c*]quinolines 2 from 1[a]



entry	1	substrate R^1	substrate R^2	substrate R^3	time (h)	product 2	yield[b] (%)
1	**1a**	OMe	H	H	6.0	**2a**	92
2	**1b**	Me	H	H	7.5	**2b**	88
3	**1c**	Me	H	Me	7.0	**2c**	83
4	**1d**	H	H	H	7.0	**2d**	93
5	**1e**	H	H	OMe	22	**2e**	85
6	**1f**	H	H	OEt	24	**2f**	85
7	**1g**	H	H	Me	6.0	**2g**	82
8	**1h**	H	H	Cl	77	**2h**	71
9	**1i**	H	Cl	H	72	**2i**	68
10	**1j**	H	Me	H	8.0	**2j** + **3j**[c]	94[c]

[a] Reactions were carried out with $SnCl_4{\cdot}5H_2O$ (1.2 equiv) and **1** (2.0 mmol) in xylene at 60 °C. [b] Isolated yield. [c] **3j** is the regioisomer of **2j** and the ratio of the two regioisomers (**2j**:**3j**) is about 5:1 (estimated by ^1H NMR spectrum).

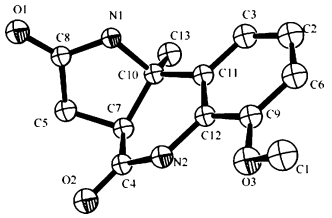
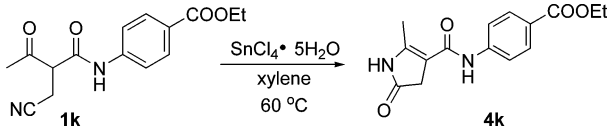


FIGURE 2. ORTEP drawing of **2a**.

SCHEME 3



high regioselectivity is observed in the transformation from **1i** to **2i** (Table 1, entry 9). However, for the substrate **1k** with a strongly electron-withdrawing COOEt group on the aryl ring, no desired **2k** was observed. Instead, an annulation product **4k** was produced in 61% yield (Scheme 3).

On the basis of all of the above results and our previous work,[15] the overall transformation may involve the hydrolysis of the cyano group of 2-(cyanomethyl)-3-oxo-*N*-arylbutanamide **1**,[17] followed by proton (generated from the hydrolysis of $SnCl_4$[18]) catalyzed aza-annulation and dehydration to form the pyrrolinone intermediate **4**. The next $SnCl_4$ mediated Micheal addition of a water to the intermediate **4** provides a cis-fused ring intermediate **7**, which undergoes an intramolecular annulation to produce the pyrroloquinolines **2** (Scheme 4). In our research, the above proposed mechanism was proven by some further experiments. Under otherwise identical conditions as described in Table 1, entry 1, but with catalytic quantity of

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

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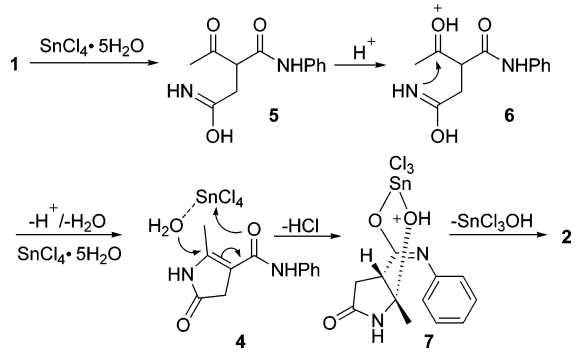
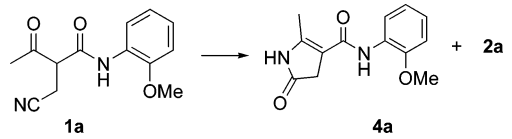
(18) The constitution of aqueous Tin(IV) chloride has been studied in detail, please see: Taylor, M. J.; Coddinfton, J. M. *Polyhedron*, **1992**, *11*, 1531−1544 and references cited therein.

SCHEME 4. The Proposed Mechanism for the Synthesis of Pyrrolo[3,2-*c*]quinolines 2



SCHEME 5. Reaction of 1a in the Presence of 0.2 or 0.5 equiv of $SnCl_4 \cdot 5H_2O$



$SnCl_4 \cdot 5H_2O$ (0.2 equiv) for 12 h, the reaction of **1a** gave a pyrrolinone **4a**[16] in 66% yield and a trace amount of **2a** (Scheme 5). Furthermore, with 0.5 equiv of $SnCl_4 \cdot 5H_2O$ for 6 h, 39% **4a** and 38% **2a** were obtained from **1a**, respectively. In addition, the quantitative transformation from **4a** to **2a** was achieved with 1.0 equiv of $SnCl_4 \cdot 5H_2O$ at 60 °C for 6 h. However, upon treatment of **4a** with 1.0 equiv of anhydrous $SnCl_4$ at 60 °C for 12 h, no reaction occurred. These above results suggest that **4** is involved as the intermediate in the transformation from **1** into **2**, and during the transformation from **4** into **2**, water plays an important role and a stoichiometric amount of $SnCl_4 \cdot 5H_2O$ is also required.

In conclusion, we have developed a new strategy for the synthesis of the tricyclic core of martinellic acids **2** through a $SnCl_4$-mediated domino reaction of the 2-(cyanomethyl)-3-oxo-*N*-arylbutanamides **1**. The advantages of this method, which include high yields, mild conditions, high regioselectivity, and the ready availability of substrates from cheap starting materials, make this new method very powerful. The extension of the scope of the methodology including the introduction of a hydrogen atom instead of the angular methyl group in the tricyclic core and the examination of biological activity of the pyrrolo[3,2-*c*]quinolines are currently under investigation in our laboratory.

Experimental Section

General procedure for the preparation of pyrrolo[3,2-*c*]-quinoline 2 from 2-(cyanomethyl)-3-oxo-*N*-arylbutanamide 1 (2a as an example): A mixture of 2-(cyanomethyl)-*N*-(2-methoxyphenyl)-3-oxobutanamide (**1a**) (492 mg, 2.0 mmol) and $SnCl_4 \cdot 5H_2O$ (840 mg, 2.4 mmol) was well stirred for 6.0 h at 60 °C in xylene (2 mL). Cooling the reaction mixture to 0 °C was followed by basification with 5 mL of sodium hydroxide solution (15%). Then the mixture was filtrated and washed with water (10 mL) and dichloromethane (3 mL) and dried in vacuum to afford compound **2a** as a white solid (450 mg, 92%).

Selected data for **2a**: mp 140−141 °C; ^{1}H NMR (500 MHz, DMSO) δ 1.43 (s, 3H), 2.26 (q, J = 10.5 Hz, 1H), 2.51 (q, J = 10.5 Hz, 1H), 3.05 (t, J = 10.0 Hz, 1H), 3.79 (s, 3H), 6.91−6.93 (m, 1H), 7.01−7.05 (m, 2H), 8.79 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 29.4, 35.1, 47.9, 56.5, 59.9, 111.1, 119.0, 123.8, 124.2, 128.0, 146.2, 168.6, 174.0; MS calcd *m*/*z* 246.1, found 247.1 $[(M + 1)]^+$; IR (KBr, neat) ν 3206, 3073, 2973, 2852, 1689, 1497, 1422, 1265, 1181, 1053, 985, 867, 787, 738 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.33; H, 5.61; N, 11.48.

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Supporting Information Available: Experimental procedures, full characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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