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A concise synthesis of chilenine via a sequential reaction process

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Abstract

A new short synthesis of chilenine has been achieved in two steps. The precursor amide was readily prepared by the condensation of the corresponding amine and acid. Treatment of the amide with oxalyl chloride in the presence of $AlCl_3$ at room temperature afforded the desired product chilenine through sequential Friedel–Crafts acylation, amide cyclization to imide, and intramolecular Friedel–Crafts type reaction. The synthesis suggests a new potential of oxalyl chloride for a two-carbon synthon.

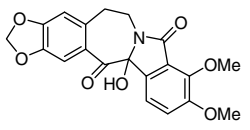
Keywords: Chilenine; Oxalyl chloride; Friedel–Crafts reaction; Sequential reaction

One of isoindolobenzazepine alkaloid chilenine **1** has been isolated from *Berberis empetrifolia* Lam as a racemic form (Fig. 1).[1] Due to its unique carbonyl–hydroxyl functional groups in the tetracyclic ring, many groups have shown synthetic interests to suggest several attractive ways for the ring skeleton as well as total synthesis.[2–12]

As an extension of our study for exploring successive ring formation of alkaloids,[13–16] herein, we describe a new sequential process for the synthesis of chilenine by using oxalyl chloride. The reagent has been known to react with aroylacetic esters to provide a quinone skeleton under Friedel–Crafts reaction conditions.[17]

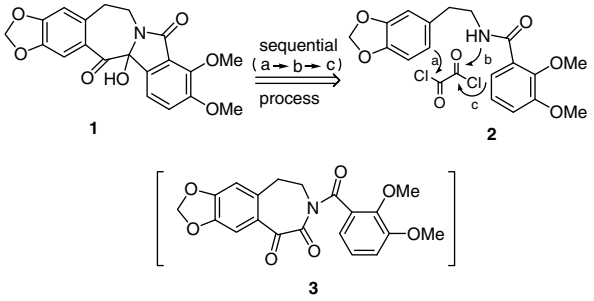
In the approach, we envisioned that Friedel–Crafts reaction of **2** (path a) would be followed by amide-acyl chloride cyclization (path b), affording intermediate **3**, and the subsequent intramolecular Friedel–Crafts type alkylation to the resulting carbonyl-imide functional group would afford the desired product **1** in a concise manner (Scheme 1).

The requisite precursor **2** was readily prepared by the condensation of 3,4-methylenedioxyphenlethyl amine and 2,3-dimethoxybenzoic acid in 73% yield. As a preliminary study, we wanted to examine up to which step the reaction would proceed in a pot, and so we added one equivalent of oxalyl chloride to a solution of **2** in methylene chloride at room temperature. Surprisingly, we could separate out the desired product **1**, though, in small yield. And we considered that the reaction could occur sequentially to yield



1: Chilenine

Fig. 1.



Scheme 1.

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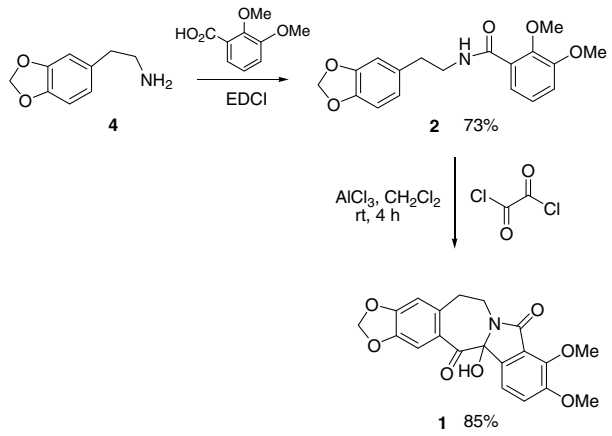
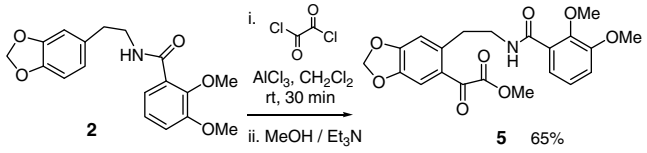


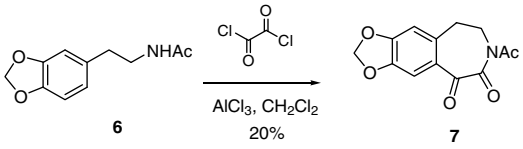
Scheme 2.



Scheme 3.

the final product. Then, we found an optimized condition which yielded **1** in 85% yield, addition of 10 equiv of oxalyl chloride to the solution of **2** containing 3 equiv of $AlCl_3$ at 0 °C and stirring the mixture for 4 h at room temperature (Scheme 2). The spectral data of **1**, mp 158–159 °C (lit.,[9] mp 157–158 °C), were identical to those reported in the literature.[9]

Although we could finish the synthesis of chilenine **1** in two steps, it would be worthwhile supporting the proposed reaction steps by showing the reaction intermediates. When the reaction was quenched with MeOH and Et_3N early in 30 min, we could separate compound **5** in 65% yield (Scheme 3). We assumed that **5** should be made from an acyl chloride intermediate obtained through Friedel–Crafts reaction of **2** with oxalyl chloride (Scheme 1, path a). However, we could not find intermediate **3**, which would be formed by the next reaction (Scheme 1, path b). It might be because of the immediate consumption of **3** for the final step (Scheme 1, path c). Therefore we synthesized compound **6**, which has an acetyl group on nitrogen instead of a dimethoxy-benzoyl group and treated it with oxalyl chloride under the same condition, and could separate the tricarbonyl compound **7**[18] in ca. 20% yield (Scheme 4), which is assumed to support path b and path c suggested in Scheme 1. $AlCl_3$ seemed to act as an efficient catalyst in each step of the reactions and therefore enable the process in a sequential manner.



Scheme 4.

In conclusion, we have suggested a concise way to isoindolobenzapine alkaloid chilenine in two steps. Oxalyl chloride has been used as a two-carbon synthon and a source of two carbonyl functional groups in proper position for the synthesis. Lewis acid $AlCl_3$ has enabled the three-step process to proceed sequentially, affording the product in good yield under mild condition.

Acknowledgments

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18. ^1H NMR (400 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.84 (m, 1H), 3.05 (m, 1H), 3.53 (m, 1H), 4.52 (m, 1H), 5.99 (m, 1H), 6.00 (m, 1H), 6.59 (s, 1H), 6.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 28.9, 37.3, 90.8, 101.5, 105.2, 108.2, 125.8, 127.5, 147.1, 148.8, 152.0, 158.3.