

A concise synthesis of chilenine via a sequential reaction process

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Received 14 January 2008; revised 9 February 2008; accepted 12 February 2008

Available online 14 February 2008

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.

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

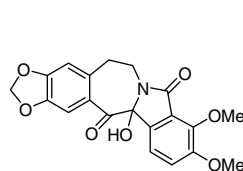
One of isoindolobenzazepine alkaloid chilenine **1** has been isolated from *Berberis empetrifolia* Lam as a racemic form (Fig. 1).¹ Due to its unique carbonyl–hydroxyl functional groups in the tetracyclic ring, many groups have shown synthetic interests to suggest several attractive ways for the ring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

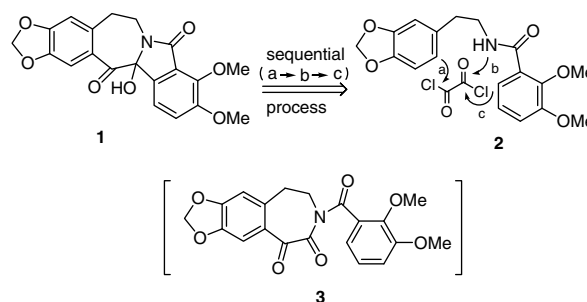
cyclization (path b), affording intermediate **3**, and the subsequent intramolecular Friedel–Crafts type alkylation to the resulting carbonyl–imide functional group would afford the desired product **1** in a concise manner (Scheme 1).

The requisite precursor **2** was readily prepared by the condensation of 3,4-methylenedioxyphenylethyl 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



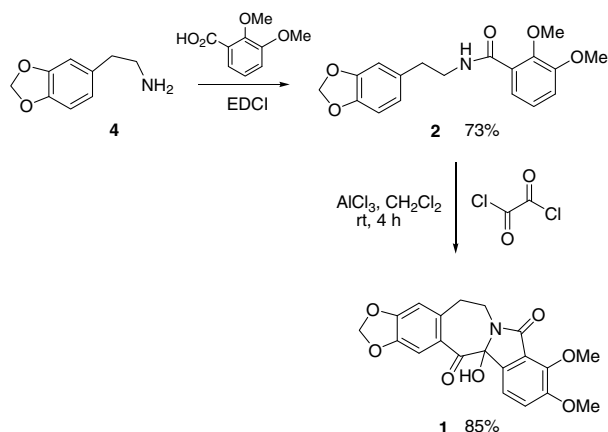
1: Chilenine

Fig. 1.

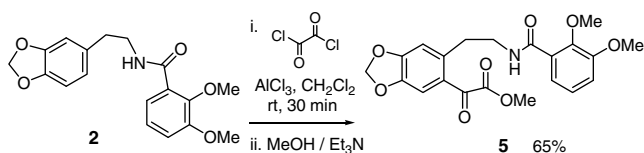


Scheme 1.

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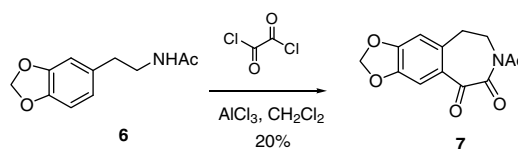
Scheme 2.



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 $158\text{--}159^\circ\text{C}$ (lit.,⁹ mp $157\text{--}158^\circ\text{C}$), 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

This work was supported by grant (R01-2007-000-20037-0) from the Basic Research Program of Korea Science and Engineering Foundation, and we appreciate the Center for Research Facilities, CNU, for the permission to NMR.

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- 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); ¹³C 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.