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'One-pot' four-step synthesis of cerpegin

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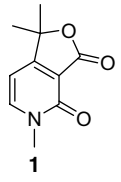
Abstract—Cerpegin (**1**) was synthesized through a 'one-pot' reaction in 71% overall yield. Lithiation of commercially available 2-methoxynicotinic acid (**2**) as its lithium salt using LTMP, followed by addition of acetone at low temperature and a specific acidic treatment of the intermediate **3** thus obtained, gave the 1,1-dimethyl-3,4-dioxo-1,3,4,5-tetrahydrofuro[3,4-*c*]pyridine (**4**). The latter was finally selectively alkylated using methyl iodide and caesium carbonate to afford cerpegin (**1**).

Ceropegia juncea Roxb. is used in traditional indian medicine as tranquillizer, anti-inflammatory, analgesic and antiulcer.[1] Cerpegin (**1**) is a rare naturally occurring pyridinone alkaloid isolated from this plant and responsible for some of its pharmacological actions;[2] its structure was established in 1991.[1,2a]



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Our laboratory reported in 1992 the first synthesis of cerpegin (**1**) in six synthetic steps and 28% overall yield.[3] Three syntheses of cerpegin employing three and four synthetic steps in moderate overall yields of 21%,[4] 15%[5] and 34%[6] have been published. Villemin and Liao documented in 1996 a really improved method consisting of a 'one-pot' three-step preparation of cerpegin in 75% overall yield.[7] Three other laborious and low yielding syntheses (17%,[8] 27%[9] and 15%[10]) in five and seven synthetic steps have since been reported.

We here report a new convenient 'one-pot' four-step synthesis of cerpegin, which proceeds in a good overall yield of 71%, starting from commercially available 2-methoxynicotinic acid. The work is an extension of our studies on the directed lithiation of unprotected pyridinecarboxylic acids[11] to the synthesis of a natural compound.

The deprotonation of 2-methoxynicotinic acid (**2**) was carried out using 3 equiv of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at −75 °C after in situ formation of its lithium salt with 1 equiv of BuLi (Scheme 1).[12] The ring deprotonation step time was optimized by recording the ^{1}H NMR spectra of samples treated with D_2O. Trapping the intermediate dilithio derivative with acetone furnished the expected 4-substituted lithium nicotinate **3** as the major product. To reach the expected furo[3,4-*c*]pyridine structure, we had to find the adequate acidic conditions, which will allow the three-step sequence including neutralization, lactonization and conversion to the pyridinone. In the first experiment attempted, the dilithium salt **3** was treated by a mixture of hydrochloric and acetic acids in refluxing ethanol.[13] After removal of the solvent and extraction with hot dichloromethane, the lactopyridinone **4** was isolated in only 48% yield, due to surprising formation of the 2-chloropyridolactone **5**[14] in 38% yield (Scheme 1). In the same way, we noticed that the 2-bromopyridolactone **6**[15] was produced in a good yield of 76% when hydrobromic acid was used in place of hydrochloric acid in the above acidic treatment of dilithium salt **3**.[16,17] The

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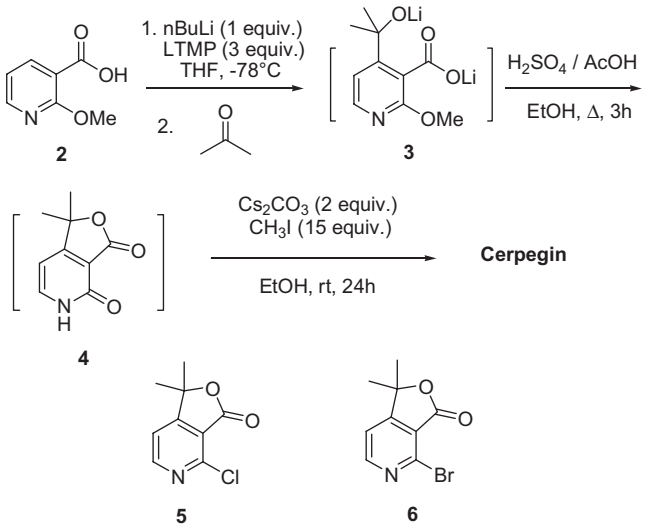

Scheme 1. 'One-pot' four-step synthesis of **1**.

halopyridolactones **5** and **6** result from surprising direct substitution of the methoxy group by the halide.[17]

In order to counter the formation of the halopyridolactone we decided to use the non-nucleophilic strong acid H_2SO_4. We observed in this case by ^1H NMR spectroscopy monitoring the total conversion of dilithium salt **3** to the desired lactopyridone **4** a 3 h reflux period. Faced with the difficulty to extract the lactopyridone **4** from ethanol, it was decided to simply remove the solvent and acetic acid under reduced pressure, and to finish cerpegin synthesis before purification. This was effected by adding to the residue an excess of methyl iodide and caesium carbonate, the latter allowing neutralization of residual H_2SO_4 and catalyzing the methylation of the nitrogen atom.[7] Cerpegin (**1**) was then isolated after removal of the solvent, extraction and purification by flash chromatography in 71% overall yield.

In conclusion, as in three of the previously described syntheses of cerpegin, our strategy utilizes lithiation as key step. However, unlike our first synthesis[3] and that of Kelly and Walsh,[4] the method we here described avoids masking the lithium carboxylic group since the lithium carboxylate was directly used as a directed metallation group. Starting with 2-methoxypyridine and employing as key step a 'one-pot' dilithiation of the pyridine ring at C3 then C4 positions, the Comins' synthesis stays certainly the most elegant strategy based upon directed lithiation of pyridine but it suffers from a modest 38% overall yield. Our present 'one-pot' synthesis of cerpegin from commercially available 2-methoxynicotinic acid is a really improved way towards cerpegin, as efficient as the Villemin's 'one-pot' judicious procedure, which is based upon a condensation of ethoxycarbonyl-α,β-insaturated-γ-lactone with triazine leading directly to cerpegin skeleton.[7]

*Typical one-pot four-step synthesis of cerpegin **1***: 2-Methoxynicotinic acid (**2**, 0.5 g, 3.2 mmol) was added to a solution of BuLi (5.2 mL, 2.5 M in hexane) and 2,2,6,6-tetramethylpiperidine (1.2 mL, 9.8 mmol) in THF (15 mL) at −78 °C under argon. The mixture was stirred for 30 min at the same temperature before dried acetone (3 mL) was added dropwise. After 30 min at −78 °C, the mixture was allowed to reach rt before hydrolysis with water (0.5 mL). After removal of the solvents under reduced pressure, EtOH (30 mL), H_2SO_4 (2 mL, 96%) and glacial AcOH (3 mL) were added to the crude material and the resulting solution was heated at reflux for 3 h. EtOH and AcOH were then removed under reduced pressure and the residue was dissolved in EtOH (30 mL). Caesium carbonate (2.1 g, 6.6 mmol) and CH_3I (3 mL) were added and the mixture was stirred for 48 h at rt. After evaporation of the solvents under reduced pressure, hot CH_2Cl_2 (10 mL) was added and the resulting solution was filtered. The organic phase was dried over Na_2SO_4. After concentration, the crude material was chromatographed on a silica gel column using CH_2Cl_2/MeOH (9:1) as eluent to give cerpegin (**1**, 2.1 g, 71%) as a beige solid.[18]

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12. These conditions were successful for 2-chloronicotinic acid; see Ref. 11.
13. After the dilithium salts **3** were hydrolyzed by adding water (0.5 mL), THF was removed under reduced pressure. A 2 M aqueous solution of HCl (0.5 mL), AcOH (5 mL) and EtOH (10 mL) were then added to the crude material and the resulting solution was heated at reflux for 3 h.
14. Spectral data of **5**: ^1H NMR (300 MHz, $CDCl_3$): 8.58 (s, 1H, H_6), 7.34 (s, 1H, H_5), 1.62 (s, 6H, 2Me); *m/z* (EI): 197–199 (70%), 182–184 (100%).
15. Spectral data of **6**: ^1H NMR (300 MHz, DMSO): 7.83 (d, 1H, H_6, J = 5.3 Hz), 6.80 (d, 1H, H_5, J = 5.3 Hz), 1.41 (s, 6H, 2Me); *m/z* (EI): 241–243 (10%), 226–228 (100%).

16. After the dilithium salts **3** was first hydrolyzed by adding water (0.5 mL), THF was removed under reduced pressure. A 33% acetic solution of HBr (10 mL) was then added to the crude material and the resulting solution was heated at reflux for 3 h.
17. We here described a new example of direct substitution of a methoxy group at C2 position of pyridine by an halide. This transformation is generally achieved directly by treating the 2-halopyridine by a halogenating agent, see: Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Fujishige, K.; Takagi, M.; Kikkawa, K.; Omori, K. *Bioorg. Med. Chem.* **2003**, *13*, 2341–2345, and references cited therein.
18. Cerpegin **1**: mp 268–269 °C (lit.[1] mp 268–270 °C); ^{1}H NMR (300 MHz, $CDCl_3$) 7.68 (d, 1H, H_6, J = 6.9 Hz); 6.24 (d, H_5, J = 6.9 Hz); 3.64 (s, 3H, Me); 1.60 (s, 6H, 2Me); ^{1}H NMR (300 MHz, DMSO) 8.19 (d, 1H, H_6, J = 6.6 Hz); 6.63 (d, 1H, H_5, J = 6.6 Hz); 3.46 (s, 3H, Me); 1.52 (s, 6H, 2Me); ^{13}C NMR (75 MHz, DMSO): 172.3, 166.7, 157.4, 148.1, 110.2, 98.7, 82.5, 37.2, 25.8. The ^{1}H NMR data in $CDCl_3$ are in agreement with those previously described.[4]