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Metalation of Pi-Deficient Heterocycles A Facile Synthesis of Cerpegin

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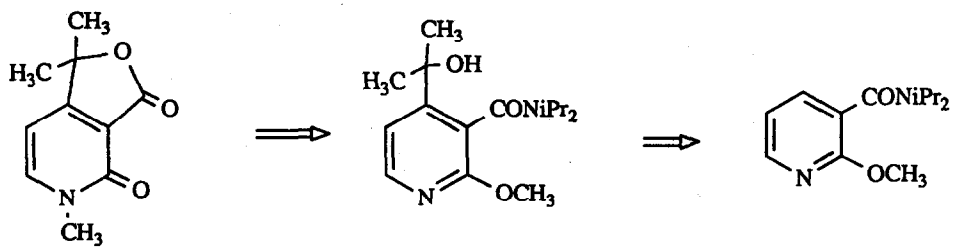
Key Words: Cerpegin; synthesis; metalation

Abstract: *The first total synthesis of the naturally occuring cerpegin is described. Metalation of a pyridine derivative has been used in the key step.*

Cerpegin **1** is an alkaloid isolated from the plant *Ceropegia juncea.*[1] Its structure has been assigned to a fused oxo-pyrido-furanone on the basis of crystallographic studies [1] and spectroscopic methods.[2] The plant from which cerpegin is extracted, is used in indian indigenous medicine as tranquillizer, anti-inflammator and antiulcer.

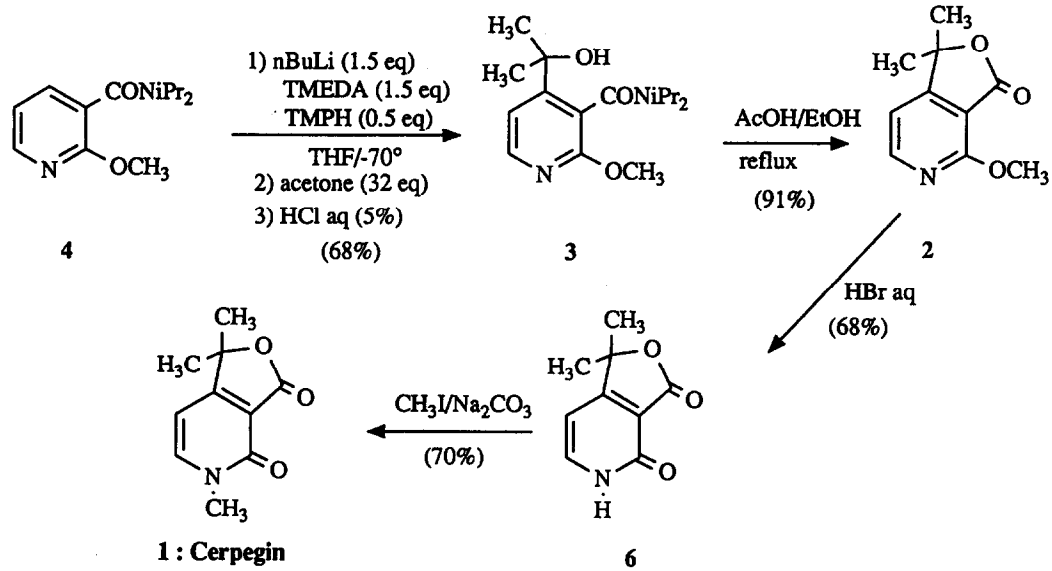
Within the framework of our research on the metalation of π-deficient heterocycles [3] and applications to the synthesis of natural products [4], we report here the first synthesis of cerpegin. The key step of the synthesis is the preparation of the hydroxyamide **3**. The retrosynthetic approach integrates pyridine carboxamide ortho-metalation and lactonization (scheme below).



1 **3** **4**

3-N,N-diisopropylcarbamoyl-2-methoxypyridine 4 is prepared in good overal-yield (82%) starting from the readily available 2-chloronicotinic acid 5 [5].

The secondary carboxamide moiety provides an excellent possibility for the regiospecific ortho-lithiation and subsequent electrophilic substitution of the pyridine ring [6]. The ortho-methoxy-N,N-diisopropylamide 4 reacts with TMPLi in THF in presence of TMEDA at -70°C to generate the lithiated amide [5]. Treatment of the lithiated species with acetone gives alcohol 3 (68%). Cyclization of the latter compound by reflux in an ethanol/acetic acid mixture affords the lactone 2 in good yield (91%). The use of boron tribromide as demethylating reagent failed but treatment of the methoxy-lactone 2 with 48% HBr led to the expected pyridone 6 (68%). Cerpegin 1 was obtained by methylation of the 2-[1H]-pyridone with methyliodide in refluxing EtOH (70%). The overall yield of the above synthesis is 28% [7].



4 3 2

1 : Cerpegin 6

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7. Physical and spectral data for 1: Solid F = 271°C (Lit[2] 268-270 °C). GC-MS Ei: 193(M), 178, 150, 136, 109, 78. ^{1}H NMR (DMSO-d6, HMDS , 200 MHz): δ 1.51 (s,6H,CH_3), 3.47 (s,3H,N-CH_3), 6.61 (d,1H,H-5 J_{5-6}: *6.74Hz*), 8.17 (d,1H,H-6 J_{6-5}: *6.74Hz*). IR (KBr cm^{-1}): 1550, 1600, 1665, 1750.

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