SYNTHESIS OF CERPEGIN

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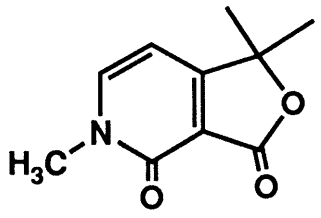
Cerpegin (**1**), a new pyridone alkaloid, was synthesized starting from the Michael reaction of phenylthioacetonitrile (**2**) and 2-methoxycarbonyl-4,4-dimethyl-2-buten-4-olide (**3**) in five steps. Catalytic hydrogenation of a nitrile group in the presence of a conjugated carbon-carbon double bond was performed by addition of 1 eq of conc. HCl.

KEYWORDS pyridone alkaloid; cerpegin; Michael reaction; phenylthioacetonitrile; catalytic hydrogenation

The structure of cerpegin, a new pyridone alkaloid isolated from *Ceropegia juncea*, was elucidated as 1,1,5-trimethylfuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (**1**). [1] *Ceropegia juncea* Roxb. is reported to be the source of "Soma," a plant drug of the Ayurvedic system of medicine with a wide variety of uses.[2] Although the total alkaloidal fraction of the alcoholic extracts of this plant exhibited promising tranquilizing, hypotensive and local anesthetic effects in experimental animals,[1] it is not clear whether **1** itself has those characteristics or not. Because of the novelty of its structure and our continuing interest in the synthesis of heterocyclic compounds possessing fused furanone moieties,[3] we undertook the synthesis of **1**. The first total synthesis of **1** was recently reported by Kelly *et al.*[4] They constructed **1** starting from 2-nicotinic acid in about five steps. We now report the alternative synthesis of **1** that involves Michael addition of phenylthioacetonitrile (**2**)[5] to 2-methoxycarbonyl-5,5-dimethyl-2-buten-4-olide (**3**).[6]



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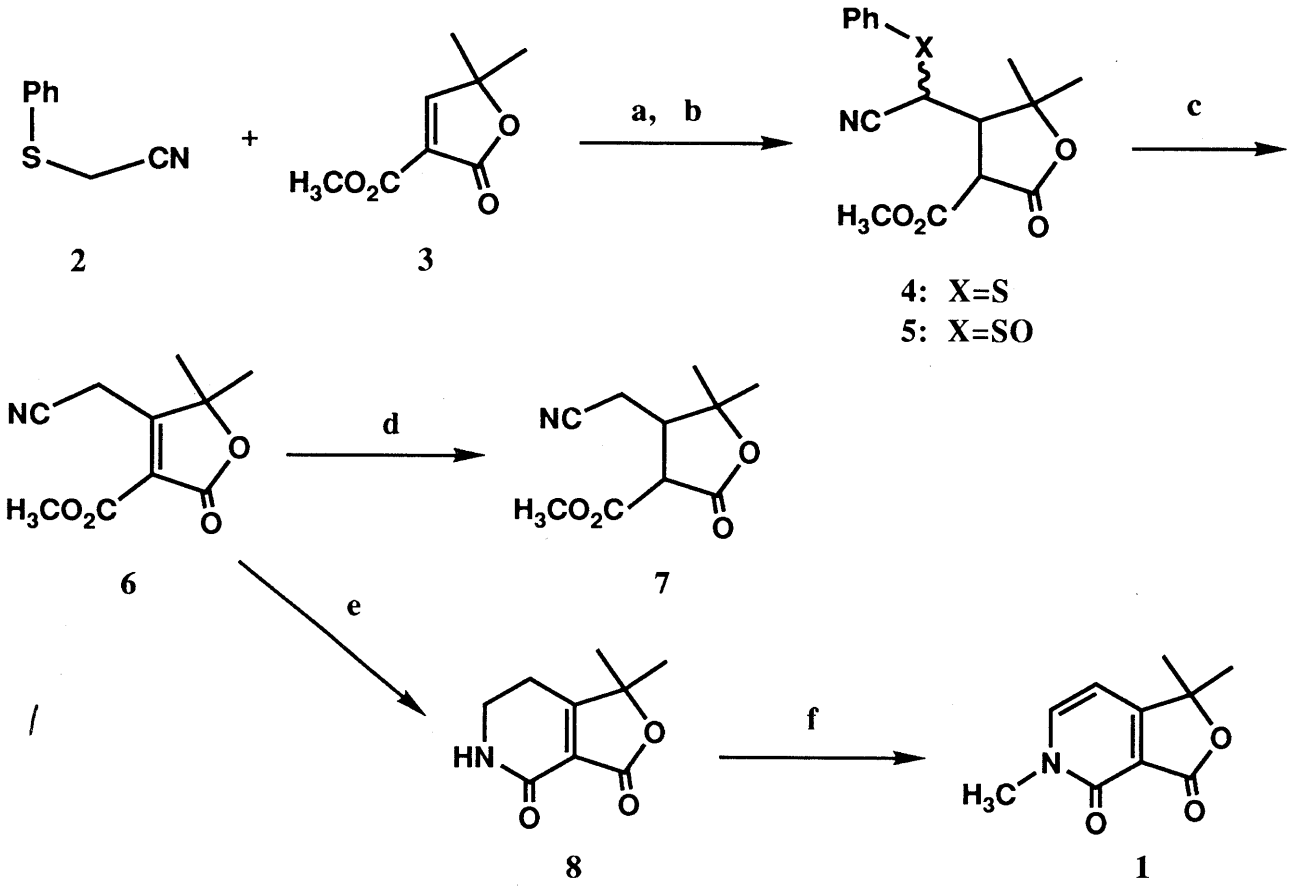
The reason we chose the above reaction at the beginning of the synthesis is as follows. Wang *et al.* reported that **2** is a good Michael donor,[7] and we have experience using **3** as a Michael acceptor.[3c] In addition, the phenylthio group is useful for the introduction of a carbon-carbon double bond after Michael addition.

Thus, 2-lithiophenylthioacetonitrile, prepared by treatment of **2** (1 eq) with lithium diisopropylamide (LDA) (1.2 eq), was reacted with **3** (1 eq) in THF at -78 °C for 5 min and then at room temperature for 3 h. Acidic workup gave the adduct **4** as a mixture of two stereoisomers in 93% yield.[8] Oxidation of **4** with *m*-chloroperbenzoic acid (MCPBA)(1 eq) in CH_2Cl_2 furnished crystalline **5** in 80% yield, which was successively heated in benzene to form the α, β–unsaturated lactone **6** (mp 100-102 °C) in 57% yield.[9] Reduction of the nitrile group to an amine in the presence of the conjugated carbon-carbon double bond of **6** was a crucial step. Reaction of **6** with $NaBH_4$, $NaBH_4$-$CoCl_2$ or BH_3-THF resulted in the recovery of **6** or formation of a complex mixture. Catalytic hydrogenation of **6** over Pd/C in acetic acid gave the undesired compound **7** (mp 127-129 °C)[10] in 79% yield. When the

catalytic hydrogenation of **6** was performed in the presence of Pd/C and an equivalent of conc. HCl in MeOH and the reaction was worked up under basic conditions (10% Na_2CO_3, pH ca. 9), the desired compound **8** (mp 226-229 °C) was obtained in 44% yield.[11] The crucial points of the catalytic reduction are to add conc. HCl just before starting the reaction and to keep the pressure of hydrogen at 1 atm. Replacement of conc. HCl with *p*-toluenesulfonic acid or Pd/C with Raney-Ni did not improve the yield. As the desired compound **8** was in hand, its *N*-methylation was examined. Reaction of



a) LDA (1.2 eq) in THF, 5 min at -78 °C, 3 h at rt (93%); **b**) MCPBA (1 eq) in CH_2Cl_2, 5 min at O °C (80%); **c**) reflux in C_6H_6, 7 h (57%); **d**) H_2 (1.6 atm), 10% Pd/C in AcOH, 2 h (79%); **e**) i) **6** (0.5 g) in c.HCl (0.2 ml) and MeOH (25 ml), H_2, Pd/C (0.25 g), 3 h; ii) 10% Na_2CO_3, pH 9 (44%); **f**) NaH (1.1 eq), methyl *p*-toluenesulfonate (1.4 eq) in DME, reflux, 1 h, (81%).

8 with CH3I in the presence of NaH in DMF at room temperature was unsuccessful and resulted in the formation of a complex mixture, which probably contains over-methylated products. Therefore, the milder reaction conditions were employed next. Treatment of **8** with methyl *p*-toluenesulfonate (1.4 eq) in the presence of NaH (1.1 eq) in DME at refluxing temperature for 1 h gave **1** (mp 267-271 °C; lit.[1] mp 268-270 °C) directly in 81% yield. IR, ^{1}H-NMR and MS spectral data of the synthetic compound **1** are identical to those of the natural one.[1,4]

In summary, pyridone alkaloid cerpegin (**1**) was synthesized starting from the Michael addition of **2** to **3** in five steps involving the catalytic reduction of the nitrile group in the presence of the conjugated carbon-carbon double bond.

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8) The structures of the newly obtained compounds were characterized by IR, ^{1}H-NMR and MS spectral data.

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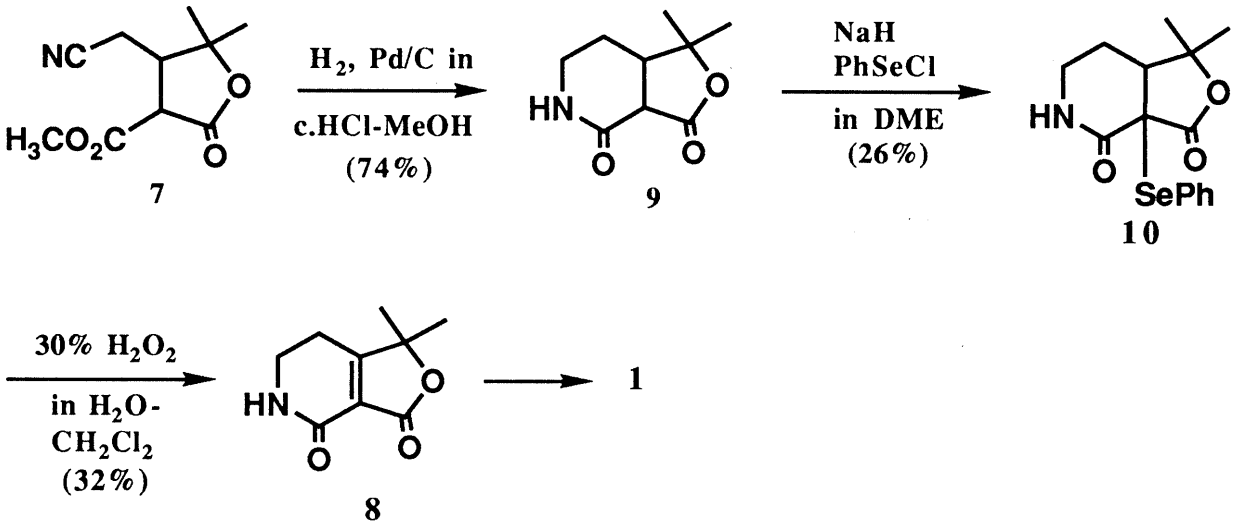
10) Transformation of the undesired compound (**7**) into **1** was tried. Thus, further catalytic reduction of **7** in the presence of conc. HCl and Pd/C in MeOH gave **9** in 74% yield. Reaction of **9** with phenylselenenyl chloride in the presence of NaH in DME gave **10** in 26% yield. Oxidative elimination reaction of **10** with 30% H_2O_2 in H_2O-CH_2Cl_2 proceeded successfully to give **8** in 32% yield, which is capable of being transformed into **1** as described in the text.



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