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Convenient Synthesis of Cerpegin

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CONVENIENT SYNTHESIS OF CERPEGIN

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convenient procedure for the preparation of cerpegin is described.

Keywords: Cerpegin; dihydrofuranone; dimethylformamiddimethylacetal

The alkaloid from Ceropegia juncea Roxb., cerpegin, is a rare, naturally occurring pyridine. Cerpegin structure was elucidated as 1,1,5-trimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (3).^[1] Ceropegia juncea is reported to be a tranquilizing, antiinflammatory, analgesic, and antiulcer Indian plant.^[2] Because of the application of cerpegin, its preparation has been the subject of detailed studies.^[3-9]

In an extension of our synthetic studies on chemically and biologically interesting cerpegin, we report here a convenient synthesis of cerpegin starting from 3-(N-methyl)carbamoyl-4,5,5-trimethyl-2,5-dihydrofuran-2-one (1).^[10]

1,1,5-Trimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (cerpegin, 3) was prepared by the reaction of 3-(N-methyl)carbamoyl-4,5,5-trimethyl-2,5-dihydrofuran-2one (1) with N,N-dimethylformamiddimethylacetal (2). A mixture of 1 (1 equiv.) and 2 (1.1 equiv.) in absolute benzene was boiled for 35 h, producing 3 with 89% yield. The formation of cerpegin (3) occurs via the methyl group of compound 1 condensation with N,N-dimethylformamiddimethylacetal (2) followed by cyclization of the intermediate enamine with dimethylamine evolution.

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The chemical science community of Armenia has carried heavy loss with the passing of Prof. Aida Avetisyan on October 19, 2009. Professor Avetisyan was an extraordinary person, and all her life was devoted to the service of chemical science and its teaching in the walls of the Yerevan State University. She forever has connected scientific activity with the chemistry of heterocyclic compounds containing oxygen, nitrogen, and sulfur atoms. Professor Avetisyan has brought a significant contribution to education and professional training of many students and young specialists. Professor Avetisyan's students, colleagues, and friends will remember for a long time her image—an image of the multitalented scientist and teacher.

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EXPERIMENTAL

The melting point was determined by the open capillary method. Infrared (IR) spectra were recorded on a Specord 751 R spectrometer in mineral oil; NMR spectra were recorded on a Varian Mercury 300 instrument (at 300 MHz for ¹H CMR and 75, 46 MHz for ¹³C NMR) using tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on a Nermag Riber R10–10H with 70-eV electron impact ionization. The purity of the synthesized compound was controlled by means of thin-layer chromatography (TLC) on Silufol UV-254 plates; the eluent acetone/ benzene ratio was 1:2, developed by iodine vapors.

1,1,5-Trimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (Cerpegin, 3)

A mixture of 1 g (0.01 mol) of 3-(N-methyl)carbamoyl-4,5,5-trimethyl-2,5dihydrofuran-2-one (1) and 1.5 mL (0.011 mol) N,N-dimethylformamiddimethylacetal (2) in absolute benzene was boiled for 35 h until dimethylamine evolution had ceased. The evolved dimethylamine was absorbed with hydrochloric acid (35%). After removal of the solvent, water was poured on the crystalline residue, and the formed precipitate was filtered off and washed with water. The product was obtained as pale yellow needles (CH₂Cl₂-EtOH) in 89% yield, mp: 268–270 °C (mp 268– 270 °C^[1]). IR, γ_{max} , cm⁻¹: 1760 (C=O), 1670 (C=O), 1630 (C=C), 1620 (C=C). ¹H NMR (DMSO-d₆/CCl₄: 1/3) δ_{H} : 1.48 s (6H, 2CH₃), 3.4 s (3H, NCH₃), 4.9 d (1H, ³*J*=4.9, CCH=CHN), 5.65 d (1H, ³*J*=4.9, CCH=CHN). ¹³C NMR (DMSO-d₆/ CCl₄: 1/3) δ_{C} : 24.18 (2CH₃), 37.75 (N-CH₃), 82.51, 98.38, 112.17, 145.96, 157.90, 166.88, 170.86. MS (70 eV) *m*/*z*: 193 [M⁺] (34.58), 178 [M-CH₃]⁺ (100), 150 [M-CH₃CO]⁺ (4.79), 136 (3.65),108 (12.87), 79 (5.79), 42 (49.67). Found (%): C, 62.36; H, 5.95; N, 7.49. C₁₀H₁₁NO₃(193.20) calculated (%): C, 62.17; H, 5.74; N, 7.25.

This easy and convenient synthesis provides an example of an efficient route to furo[3,4-c]pyridine-3,4(1H,5H)-dione and provides a potential route to the cerpegin analogs.

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