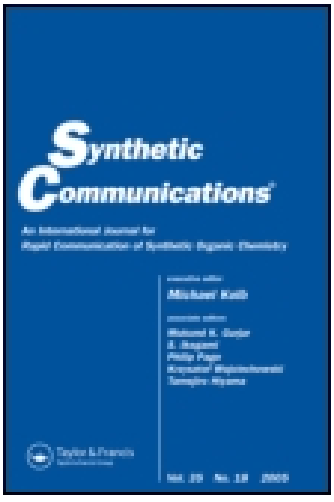

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Ibotenic Acid Decarboxylation to Muscimol: Dramatic Solvent and Radiolytic Rate Acceleration

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Abstract: The decarboxylation of ibotenic acid to muscimol in DMSO with ^3H_2O or D_2O is discussed.

Keywords: Decarboxylation, deuterium, DMSO, ibotenic acid, muscimol, tritium

Both ibotenic acid (**1**) and muscimol (**2**) have been isolated from several fungal species including *Amanita muscaria*[1] and are active CNS agents of the NMDA and GABA receptor systems respectively. It has also been demonstrated that under certain circumstances **1** can decarboxylate to **2**, but the scope of the reaction was largely unexplored.[2] A number of years ago colleagues in our laboratory, likely influenced by the conditions of the classic Krapcho reaction,[3] first reported in a talk that simply stirring **1** in a solution of DMSO with high specific activity ^3H_2O overnight at ambient temperature afforded a very reasonable radiochemical yield of **3a** with exclusive tritium incorporation in the amino methylene as established by tritium NMR.[4] Since then we have performed this simple yet robust synthesis many times, providing valuable radioligand **3a** to the neurochemical community

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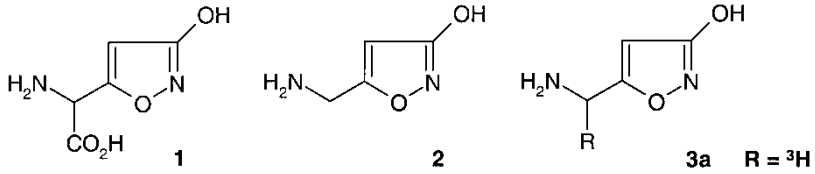
and supporting literally hundreds of key published studies in the GABA area. A representative synthesis is described in the experimental section.



Years later, Nielsen and coworkers independently explored the nonenzymatic decarboxylation of ibotenic acid, reporting that **1** was stable in water even at 37°C overnight and only after its exposure to boiling water at pH extremes over the course of several hours was any decarboxylation to **2** noted.[5] Until recently we were unaware of this surprising observation and it clearly demonstrates that our mild ambient temperature decarboxylation of **1** to **3a** with DMSO/^3H_2O is a far more intriguing and remarkable result than first recognized. It is certainly a rare event to so markedly accelerate a reaction by a mere solvent change[6] and we were prompted to further examine this interesting transformation more closely.

We first confirmed and extended the observation of the Danish workers, noting that when **1** is dissolved in D_2O at ambient temperature and monitored by HPLC, it is stable for more than two weeks, showing only minimal (0.2%) conversion to **3b**. We next examined the stability of **1** in DMSO-d_6 and D_2O (10:1), a concentration identical to the tritiation reaction. In this solvent system at ambient temperature and monitored by HPLC, approximately 90% of **1** was gradually and fairly cleanly converted to **3b** over the course of a week. This result was repeated several times and interestingly shows that the addition of DMSO to water clearly facilitates the decarboxylation of **1.** However, and perhaps even more important, the use of ^3H_2O (in lieu of water) with DMSO dramatically accelerates the decarboxylation process.

Further work on the mechanism of this intriguing reaction will be reported in due course.

EXPERIMENTAL

General

Evaporations were carried out on a Buchi evaporator (Model RE 111) at bath temperatures of less than 40°C. Analytical TLC was performed on Analtech 5 × 15 cm glass plates. Autoradiography was performed at 0°C after spraying with 2,5-diphenyloxazole (PPO) and exposing the plates to X-ray film. The TLC plates were also scanned for applied radioactivity using a

Vanguard Autoscanner. Analytical and preparative HPLC were performed on a Waters instrument with peak detection done simultaneously by UV (280 nm Waters 440 UV detector) and a liquid scintillation flow monitor. NMR spectra were obtained on a Bruker 300 MHz instrument and chemical shift values are expressed in parts per million downfield from TMS. The mass spectra were obtained on a Finnigan LCQ Deca instrument with direct injection. All chemicals used were reagent grade and muscimol was obtained from Sigma (catalogue #M 1523). Deuterated solvents were obtained from Aldrich.

[Methylene-^{3}H] Muscimol (3a)

A solution of 10 mg (0.06 mmol) of **1** (Sigma catalogue # I-2765) in 0.3 mL of dry DMSO with 100 Ci of ^3H_2O (at 58 Ci/mmol) was stirred overnight at ambient temperature. After this time volatile tritium was removed under vacuum with several evaporations of 0.1 mL of water. A TLC [avicel plate developed with butanol–acetic acid–water (25 : 4 : 10)] showed that there was no evidence of **1** remaining. The crude product (1003 mCi) was purified by preparative HPLC on a Zorbax SCX column eluted with 50 mmol aqueous potassium phosphate (pH 3), affording 109 mCi (a 6% radiochemical yield based on **1**) of product **3a**, which was demonstrated to be 97% radiochemically pure and cochromatograph with authentic **2** by HPLC (same system as above) with a specific activity of 29.5 Ci/mmol as measured by mass spectrometry based on the ratio of the unlabelled, single-tritiated and double-tritiated M + 1 peaks at 115, 117, and 119 m/e respectively. It also provided a proton-decoupled tritium NMR (D_2O) showing a multiplet at 4.13 ppm.

Stability of 1 in Deuterated Solvents

As described above, the stability of **1** was examined at ambient temperature in various deuterated solvents and monitored by HPLC (same system as above with a flow rate of 1 mL/min). Both **1** and **3b** were baseline separated in this system with retention times of 3 and 7 min, respectively. Besides cochromatography with **2, 3b** was also identified by mass spectrometry showing a M + 1 peak of 117 m/e for the deuterated isotopomer $C_4H_4D_2N_2O_2$ as well as the characteristic isoxazole ring proton NMR (DMSO-d_6) resonance at 5.80 ppm.

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