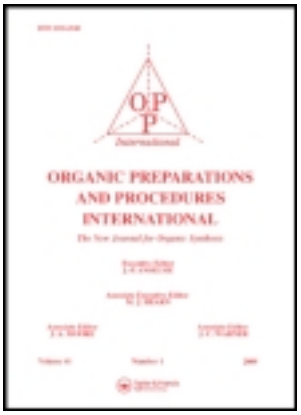

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OPPI BRIEF

Simple, Improved Synthesis of 3-Azaspiro[5,5]undecane-2,4-dione, the Precursor of Gabapentin

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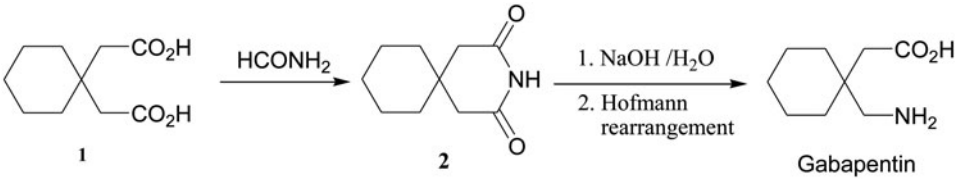
3-Azaspiro-[5,5]-undecane-2, 4-dione (**2,** *Scheme 1*) is an important intermediate for the preparation of *gabapentin*,[1–3] which is widely used in the treatment of epilepsy and other various cerebral disorders.



Scheme 1

Earlier, compound **2** had been prepared by heating a mixture of 1,1-cyclohexane –diacetic acid (**1**) and ammonium acetate in acetic anhydride.[1] Acetic anhydride is a controlled chemical listed in the UN convention against illicit traffic in narcotic drugs and psychotropic substances.[4] As a result of this convention, the availability of acetic anhydride is severely restricted and its use on an industrial scale is becoming difficult. Handley *et al*. had prepared **2** by heating an intimate mixture of **1** and urea at 170–190°C, [5] the same method was adopted and modified in a recent PCT application.[2] In this process, the solid mixture of **1** and urea was heated first to about 90°C and the melt mix then slowly heated to about 140°C, the molten mixture was stirred for about two hours until the evolution of gases had ceased. However, this process is not suitable for industrial scale because it is difficult

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to dry heat a solid powder mixture on a large scale. Furthermore, the process requires the installation of scrubbers to handle the copious quantities of carbon dioxide and ammonia gases evolved. This present note reports a new and simple process for the preparation of **2** which is suitable for industrial scale (*Scheme 1*).

Earlier, Chirac *et al*. prepared related cyclic imides by heating cyclic carboxylic anhydrides or corresponding dicarboxylic acids with formamide at 170–180°C for 5–6 h.[6] *N*-methyl-2-pyrrolidone (NMP) was used as additional solvent for substrates which had poor solubility in formamide. In these reactions, formic acid is formed as by-product. A similar method is also reported for the preparation of certain substituted 2,6-dioxopiperidines.[7] In the present work, although **1** is not soluble in formamide, no additional solvent is required as the initial suspension liquefied after heating. Further heating at 150–160°C was sufficient to complete the reaction in about 4 h as monitored by HPLC; formic acid and water are formed as the by-products. Pouring the hot reaction mixture into water (40 mL) gives **2** as a precipitate which is washed with water and dried to give **2** in high yields (>95%) and in very high purity (99.5% HPLC). The process is environmentally friendly as there is no evolution of gases during the process.

Experimental Section

All raw materials were obtained from commercial suppliers and were used as received. Melting points were determined on a Polmon MP-96 digital melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker-300 spectrometer using DMSO-d_6 as the solvent with TMS as the internal standard. Mass spectra were measured with a Thermo Scientific LCQ Fleet spectrometer. Monitoring of the reaction and the purity of the compound was analyzed using HPLC in Hypersil gold RP-18, 150 × 4.6 mm, 5 μm column with mobile phase as water: acetonitrile: trifluroacetic acid (15:85:0.01%).

3-Azaspiro-[5,5]-undecane-2, 4-dione 2. To a 100 ml three-neck flask equipped with a thermometer, mechanical stirrer and a reflux condenser was added 1,1-cyclohexanediacetic acid (**1,** 10.0 g, 50 mmol) and formamide (4.5 g, 100 mmol). The initial suspension, on heating, became a clear colorless solution and was further heated and stirred at 150–160°C for 4 h. The hot clear reaction mixture was poured cautiously into water (40 ml). The colorless precipitate obtained was collected, washed with water (10 ml) and dried under vacuum to give 8.80 g (97% yield) of **2** as a colorless solid (99.9% purity by HPLC), mp. 168–169°C, *lit*[5] 169–170°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.67 (br s, 1H), 2.42 (s, 4H), 1.30–1.41 (m, 10H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.72, 42.50, 35.29, 32.45, 25.36, 20.97. $(M + H)^+$: Calculated Mass for $C_{10}H_{15}NO_2$:182.23, Found (ESI-MS): 182.21.

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