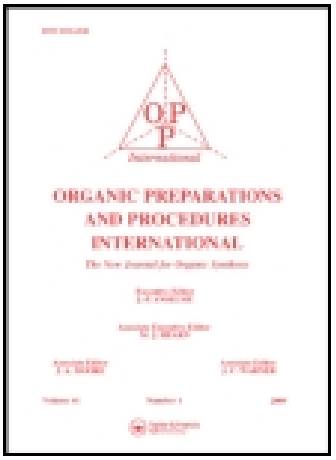

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OPPI BRIEF

A Novel Procedure for the Synthesis of Ammonium Glufosinate

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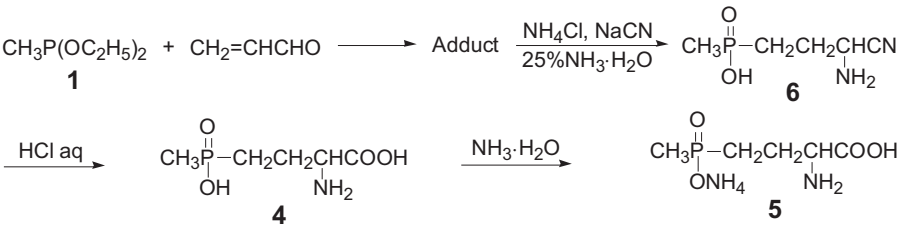
Ammonium glufosinate [**5**, ammonium 2-amino-4-(hydroxymethylphosphinyl)butanoate] is a highly effective and non-selective herbicide widely used in genetically modified and glufosinate-tolerant crops.[1] Various processes for preparation of ammonium glufosinate have disadvantages, such as the use of high pressure[2] and expensive and unstable materials,[3–5] lengthy operational steps and low yields.[6–8] Ammonium glufosinate is generally obtained (*Scheme 1*)[9] from the addition of diethyl methylphosphonite (**1**) with acrolein, followed by a Strecker synthesis and subsequent hydrolysis of the aminonitrile, and addition of aqueous ammonia. However, this method requires the use of and also generates large excess amounts of ammonium chloride (about 4–5 equivalents to **5**), which cannot be easily separated from the product and may cause environmental pollution.



Scheme 1

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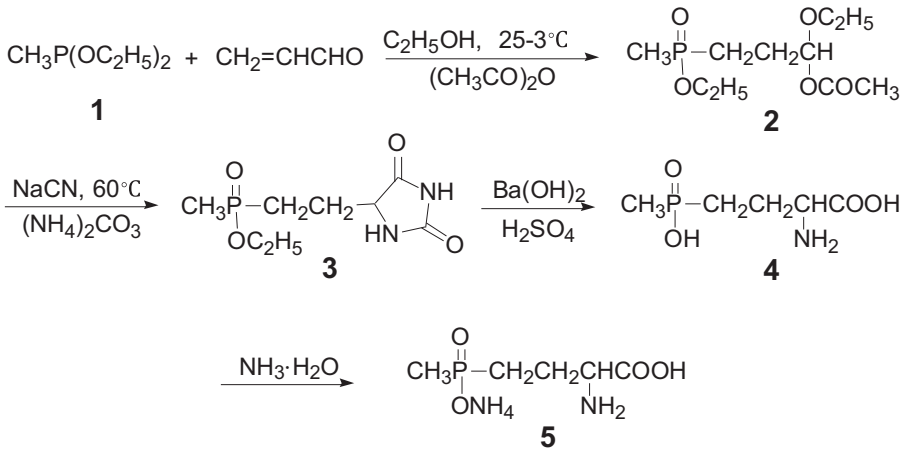

Scheme 2

The present report describes a novel procedure for the preparation of **5**. 1-Acetoxy-1-ethoxy -3-(ethoxymethylphosphinyl)propane (**2**) was obtained in 95% yield from the reaction of **1** with acrolein in the presence of ethanol and acetic anhydride at 25°C to 30°C (*Scheme 2*). The treatment of **2** with sodium cyanide and ammonium carbonate yielded 5-[2-(ethoxymethylphosphinyl)ethyl]hydantoin (**3**) in 78% yield. Finally, **3** was hydrolyzed with aqueous barium hydroxide for 30 h to afford 2-amino-4-(hydroxymethylphosphinyl)butanoic acid (**4**) which was converted to **5** in 96% yield by addition of aqueous ammonia. The fact that the mp. of **5** is above 200° (and thus not a reliable criterion) and close to that reported for the acid **4**,[10] prompted us to isolate and characterize phosphinothricin **(4)**. It was then converted to **5** to confirm its identity as ammonium glufosinate **(5)** (see ***Exterimental Section***].

The proposed synthesis of **5** *via* a hydantoin intermediate **(3)** avoids the use and generation of ammonium chloride in contrast with the previous method (*Scheme 1*), reduces waste generation and simplifies the purification of the product.

Experimental Section

^{1}H Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AC-500 instrument. Spectra from gas chromatography–mass spectrometry (GC–MS) were acquired using Agilent 6890 N GC system equipped with a 5973 N mass-selective detector. Atmospheric-pressure chemical ionization–mass spectrometry (ACPI–MS) spectra were determined using a LCQ Deca XP Plus ion-trap mass spectrometer equipped with an ACPI source and controlled by Xcalibur software. The purity of the products was determined using a Hitachi L-7000 high-performance liquid chromatograph (HPLC) with SAX Nucleosil 100-5 SB column (250 mm × 4.6 mm) and Thermo Scientific gas chromatograph with TR SMS SQC column (15 m × 0.25 mm). The melting points were obtained on a Buchi Melting Point B-545 and are uncorrected. Spectra from high-resolution mass spectrometry (HRMS)

were obtained using Agilent 6210 TOF LC–MS. Elemental analyses were performed using an EA-1110 instrument.

Preparation of 1-Acetoxy-1-ethoxy-3-(ethoxymethylphosphinyl)propane (2). A solution of freshly distilled acrolein (5.60 g, 0.10 mol) and acetic anhydride (10.20 g, 0.10 mol) at room temperature was added dropwise to a solution of **1** (13.60 g, 0.10 mol) in ethanol (4.60 g, 0.10 mol) under N_2 atmosphere at 25°C to 30°C for 20 min. The mixture was then stirred for 2 h at 30°C and evaporated under vacuum to remove volatiles to leave **2** (25.50 g, 95% yield, 94.1% purity) as a colorless liquid that was further purified by high-vacuum distillation (boiling point, 93–95°C/23 Pa).

^{1}H NMR (500 MHz, DMSO-d_6): δ1.12 (3H, t, $J = 7.0$ Hz), 1.22 (3H, t, $J = 7.0$ Hz), 1.40 (3H, d, $J = 13.8$ Hz), 1.71–1.79 (4H, m), 2.05 (3H, s), 3.47–3.53 (1H, m), 3.61–3.67 (1H, m), 3.90–3.95 (2H, m), and 5.78–5.80 (1H, m). ^{31}P NMR (500 MHz, DMSO-d_6): δ 53.39; MS (m/e): 209, 193, 165, 136, 119, 79, 57, and 43. HRMS (ESI): Calcd for $C_{10}H_{21}NaO_5P$: 275.1024, Found: 275.1029.

Anal. Calcd for $C_{10}H_{21}O_5P$: C, 47.62; H, 8.39. Found: C, 47.56; H, 8.43.

Preparation of 5-[2-(Ethoxymethylphosphinyl)ethyl]hydantoin (3). A mixture of **2** (26.80 g, 0.10 mol, 94.1% purity), ethanol (80 ml), and sodium cyanide (4.90 g, 0.10 mol) into a 250 ml four-necked flask was stirred at room temperature for 20 min. Then an aqueous solution of ammonium carbonate (19.20 g, 0.20 mol) in water (80 ml) was added and the reaction mixture was heated at 60°C for 4 h and then at 75°C for 0.5 h. Ethanol and water were removed under reduced pressure. The residue was dissolved in ethyl acetate (150 ml), and insoluble materials were removed by filtration. The filtrate was evaporated under vacuum to afford **3** (20.50 g, 78% yield, 89.2% purity) as a yellow oil. It was purified by chromatography on a silica column (ethyl acetate:ethanol 4/1) to yield a colorless oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20–1.23 (3H, m), 1.41 (3H, d, $J = 13.8$ Hz), 1.65–1.90 (4H, m), 3.90–3.96 (2H, m), 4.08 (1H, t, $J = 5.6$ Hz), 7.99 (1H, s), 10.68 (1H, s). ^{31}P NMR (500 MHz, DMSO-d_6): δ 53.73. MS (m/e): 235, 218, 207, 190, 164, 136, 127, 119, and 99. HRMS (ACPI) Calcd for $C_8H_{15}N_2O_4P$ $[M + H]^+$: 235.0842, Found: 235.0839.

Anal. Calcd for $C_8H_{15}N_2O_4P$: C, 41.03; H, 6.46. Found: C, 41.09; H, 6.41.

Preparation of Ammonium Glufosinate (5) and Isolation of Phosphinothricine (4). A mixture of **3** (26.20 g, 0.10 mol, 89.2% purity), barium hydroxide octahydrate (31.60 g, 0.10 mol), and water (200 ml) into a 500 ml three-necked flask was heated to reflux for 30 h with stirring. After cooling to 60°C, the mixture was neutralized to 30% H_2SO_4 (32.7 g, 0.10 mol) and the precipitate was filtered and washed with water (50 ml × 2). The pH of the combined filtrate and washes was adjusted to ~9 by addition of 25% aqueous ammonia. The solution was then evaporated to dryness under vacuum and the residue was recrystallized from methanol to give **5** as a white solid [19.30 g, 96% yield, 98.5% purity (HPLC)], mp. 214–215°C, lit.[11] 215°C. ^{1}H NMR (500 MHz, D_2O): δ 1.26 (3H, d, $J = 13.5$ Hz), 1.54–1.70 (2H, m), 2.00–2.14 (2H, m), 3.79 (1H, t, $J = 6.0$ Hz). ^{31}P NMR (500 MHz, D_2O): δ 41.99.

Anal. Calcd for $C_5H_{15}N_2O_4P$: C, 30.31; H, 7.63; N, 14.14. Found: C, 30.24; H, 7.66; N, 14.21.

For the isolation and identification of phosphinothicine (**4**), a small portion of the filtrate and washes obtained after the addition of 30% sulfuric acid as described above, was evaporated to dryness under vacuum and the solid residue was recrystallized from

1:1 EtOAc-ethanol to give **4** as a white solid, mp. 209–212°C, lit.[10] 211–213°C, ^{1}H NMR (500 MHz, D_2O): δ 1.55 (3H, $J = 14$ Hz, 1.89–2.04 (2H, m, 2.19–2.28 (2H, m), 4.18 (1H, t, $J = 6.0$ Hz). It was dissolved in methanol and 25% aqueous ammonia was added to adjust the pH to 9. The resulting solution was evaporated to dryness under vacuum to afford ammonium glufosinate (**5**), identical with the sample prepared directly above.

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