

## An Improved Synthesis of the Phosphonic Acid Analog of Tryptophan

Roland S. Rogers, Michael K. Stern\*

Chemical Sciences Department, Monsanto Corporate Research, Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, Missouri 63167, USA

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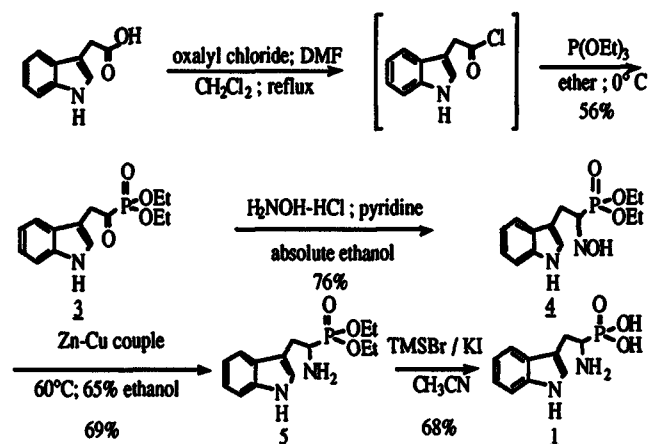
**Abstract:** An efficient and short synthesis of the phosphonic acid analog of tryptophan {[1-amino-2-(3-indolyl)]ethylphosphonic acid, **1**} from indole-3-acetic acid which utilizes a novel zinc-copper couple reduction of an oxime is described.

The phosphorous analogs of  $\alpha$ -amino acids have been studied extensively due to the finding that these class of molecules often have interesting biological activities ranging from plant growth regulators<sup>1</sup> to antibacterial agents.<sup>2</sup> In addition, the incorporation of these molecules into small peptides have produced potent inhibitors of a variety of enzymes of medicinal importance.<sup>3</sup> Thus, the 1-aminophosphonic acids represents a useful and interesting series of compounds.

Several good methods for the synthesis of these compounds have been reported. For instance, the diaryl esters of a variety of amino acid analogs can be prepared by a two step synthesis from benzyl carbamate, aldehyde, and triphenylphosphine<sup>4</sup> or via aminomethylphosphonate schiff base intermediates.<sup>5</sup> In addition, oxidation of the corresponding phosphinic acids have also been reported.<sup>6</sup> However, noticeably absent from the literature are reports of an efficient synthesis of the phosphonic acid analog of tryptophan **1**. The single reported synthesis of **1** proceeds in poor yield (10%), requires the isolation of reactive indole-3-acetyl chloride **2** and suffers a cumbersome Al-Hg reduction of oxime **4**.<sup>7</sup> Thus, we wish to report a more efficient synthesis of **1** which eliminates the need for the isolation of **2** and relies on a novel Zn-Cu reduction of **4** (Scheme 1). While our synthesis follows that of Subotkowski et. al., in general, it is important to note that our improved method provides higher overall yields (20%) and begins with commercially available indole-3-acetic acid.

Indole-3-acetyl chloride **2** was generated from indole-3-acetic acid using oxalyl chloride (1.1 eq.) in refluxing methylene chloride which contained 0.3% DMF by volume. After a solvent exchange to anhydrous diethyl ether the acid chloride was reacted with triethyl phosphite (1 eq.) at room temperature to generate the Arbuzov product, keto-phosphonate (**3**) which precipitates out of ether as a white solid in 56% yield. This compound exists primarily in the enolate form, as identified by <sup>1</sup>H-NMR. The keto-phosphonate was converted to the oxime (**4**) upon treatment with hydroxylamine hydrochloride (1.3 eq.) and pyridine (1.5 eq.) in absolute ethanol at room temperature. The ethanol was removed and the reaction was treated with 1 N HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was cooled to 0 °C which caused **4** to precipitate out as a white solid in 76% yield. Initially, the reduction of the oxime to the amine was performed with an aluminum amalgam.<sup>7</sup> However, the poor yields (20 - 40%) of the reaction and the large quantities of mercury waste generated indicated that a better route

was needed. Hydrogenation over Raney-Nickel proved ineffective. It was found that the reduction of the oxime to the racemic amine **5** could be accomplished in good yield (69%) using zinc-copper couple in warm aqueous ethanol with ultrasonic agitation.<sup>8</sup> This novel method for the reduction of oximes is vastly preferable to the aluminum-amalgam reductions previously reported. Finally, the cleavage of the phosphonate esters to form **1** was accomplished in 68% yield with TMSI, generated *in situ* by the reaction of TMSBr and KI in acetonitrile.<sup>9</sup>



Scheme 1

In summary, tryptophan phosphonic acid was synthesized in five steps from indole-3 acetic acid. This procedure has advantages over the previously published route in that the critical acid chloride is generated *in situ* and the Al-Hg reduction was replaced with a more efficient zinc-copper couple method. These advantages make this scheme amenable to production of large quantities of **1**.

### References and Notes

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