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An Efficient Synthesis of 5-Azidotryptophan

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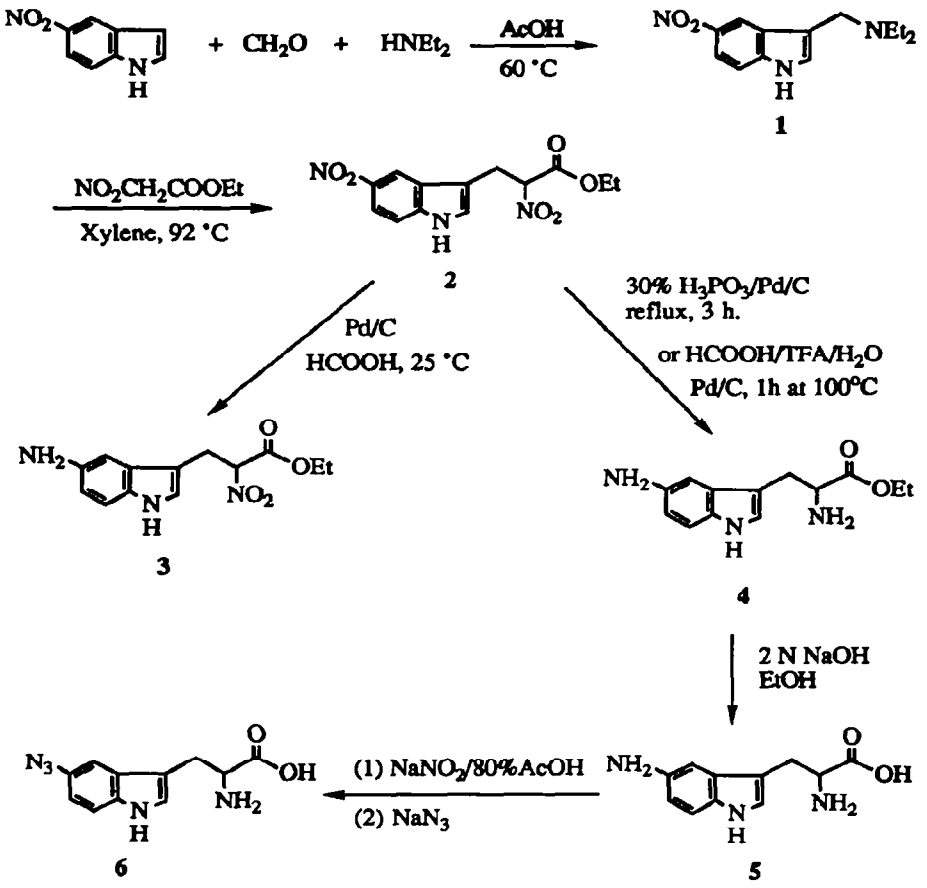
Abstract: An efficient synthesis of a potentially useful photoaffinity labeling reagent, 5-azidotryptophan, is described.

During our search for photoactive analogues of 5-bromotryptophan, a recently discovered potent antisickling agent,[1] as effective photoaffinity labeling reagents, we needed to synthesize 5-azidotryptophan through diazotization of 5-aminotryptophan.

Starting from 5-nitroindole, we used a modified procedure of the original method of Cavallini and Ravenna[2] (Scheme 1) and obtained 5-nitrogramine in high yield. The substituted and unsubstituted gramines have been employed in the C-alkylation of acetamidomalonate and/or nitroacetate, en route to the synthesis of tryptophan and its derivatives.[2b,2c,3] We chose the reaction between ethyl nitroacetate and 5-nitrogramine to prepare the desired ethyl 1-nitro-2-(5-nitro-3-indolyl)propionate (2), since we expected that the two nitro groups could be reduced in a single step, rendering it more efficient than alternate routes. Initial runs were carried out, therefore, according to the procedure of Lyttle and Weisblat for the synthesis of 1-nitro-2-(3-indolyl)propionate.[3a] The crude oil obtained in the reaction was dissolved in chloroform and extracted with 5% NaOH solution. The latter solution was acidified and extracted with chloroform. However, only a small amount of brown oily material was retrieved after removal of the solvent. The workup procedure was thus changed, along with some modification of the major reaction course. Our final optimized procedure is quite simple: (1) heating a mixture of 5-nitrogramine and ethyl nitroacetate in xylenes at 92 °C for 15 h, (2) washing the resulting solution (after mixed with methylene chloride) with 2 N HCl and water, and (3) removal of the solvents yielding the crystalline product (2) in 86% yield.[4]

Reduction of 2 using the standard procedures of catalytic hydrogenation[5] (10% Pd/C, 40-50 psi) resulted only in a complex mixture. An alternative reduction method employing Pd/C in conjunction with such hydrogen donors as formic acid or phosphorous acid[6] appeared promising for our purpose. It was found, however, that when 2 was treated with formic acid in the presence of 10% Pd/C at room

Scheme 1



temperature, only the nitro group on the indole ring was completely converted to an amino while the α-nitro group remained intact (see **3** in Scheme 1). When the reaction was conducted at 100 °C, a complex mixture was obtained. We reasoned that this might be caused by the initially formed amino group on the indole ring, the reactivity of which (presumably towards the ester functionality) could not be suppressed by

protonation of the weak formic acid. Indeed, when 2 was reduced either with phosphorous acid/Pd/C or with HCOOH/Pd/C in the presence of aqueous trifluoroacetic acid, the desired diamino compound (4) was formed fairly cleanly in 60-70% yields.[7] The latter procedure was more convenient as the product was easily isolated by evaporation of the volatile reagents. Compound 4 was then hydrolyzed with 2N NaOH/EtOH (1/2, v/v) to give 5-aminotryptophan (5), followed by conversion into 5-azidotryptophan (6)[8] according to the procedure of Melhado and Leonard for the preparation of 6-azidotryptophan[9] (Scheme 1) in a one-pot fashion (total 49% yield from 4).[10] This compound (6), along with 4-, 6-, and 7-azidotryptophan, was previously synthesized using tryptophan synthetase in very poor yield and on a very small scale.[11] Furthermore, these compounds were not fully characterized (e.g., no NMR spectra were given), presumably due to very limited quantities obtained. The present method, however, affords a reasonably good yield and is readily scaled up. 5-Cyanotryptophan[12] should also be obtainable via diazotization of 5 and subsequent reaction with CuCN. It is expected that the general route should also be applicable for synthesis of 4- and 7-azidotryptophan.

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2. (a) The workup procedures were modified: after heating at 60 °C for 2.5 h, the reaction mixture was evaporated to near dryness. The wet crystalline residue was suspended in a small amount of $CHCl_3$ and collected by filtration. The crystals were washed with a slight amount of cold alcohol and dried in vacuo (84%). The crystals were determined to be in the form of 1·2AcOH, which, suspended in water, were converted quantitatively to the neutral form with Na_2CO_3. (b) Cavallini, G.; Ravenna, V. *Il Farmaco (Pavia) Ed. Sci.* **1958**, 13, 105-112. (c) *CA20126d* (1958).

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4. The product was purified by recrystallization from methanol/cyclohexane or by preparative TLC (silica gel; ethyl acetate/hexane, 1/1, v/v): mp 127-128 °C; NMR ($CDCl_3$) δ 8.58 (s, 1H), 8.53 (s, 1H, broad), 8.16 (dd, J_1 = 8.9 Hz, J_2 = 2.0 Hz), 7.44 (d, 1H, J = 8.9 Hz), 7.26 (s, 1H), 5.45 (m, 1H), 4.33 (q, 1H, J = 7.0 Hz), 3.74 (m, 2H), 1.32 (t, 3H, J = 7.0 Hz); IR (KBr) 3427, 1748, 1562, and 1325 cm^{-1}; EIMS m/z 115 (100), 129 (73), 215 (81), 260 (82), 307 (30). Anal. Calcd for $C_{13}H_{13}N_3O_6$: C, 50.82; H, 4.26; N, 13.68. Found: C, 50.86; H, 4.43; N, 13.36.

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7. Analytically pure product was obtained by convrsion to its HCl salt (4·2HCl) (in $CHCl_3$ with HCl gas): mp > 250 °C; ^{1}H-NMR (DMSO-d_6) δ 11.54 (s, 1 H), 10.44 (s, 3 H, broad), 8.80 (s, 3 H, broad), 7.54-7.40 (m, 3 H), 7.14 (d, 1 H, J = 8.6 Hz), 4.15 (m, 1 H), 4.08 (q, 2 H, J = 6.8 Hz), 3.31 (m, 2 H), 1.04 (t, 3 H, J = 6.8 Hz); FABMS m/z $[M + H]^+$ 248.2. Anal. Calcd for $C_{13}H_{19}N_3O_2Cl_2$: C, 48.76; H, 5.98; N, 13.12. Found: C, 48.78; H, 5.85; N, 12.87.

8. The product (6) was recrystallized from H_2O: mp 150 °C (dec); NMR (CD_3CO_2D/D_2O, 4/1, v/v) δ 7.43 (d, 1 H, J = 8.6 Hz), 7.33 (s, 1 H), 7.31 (d, 1 H, J = 1.5 Hz), 6.87 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 1.5 Hz), 4.35 (m, 1 H), 3.56-3.32 (m, 2 H); IR (KBr) 2120 cm^{-1}; UV (CH_3CO_2H/H_2O, 4/1, v/v) λ_{max} 251 (4.29).

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10. Compound 4 was hydrolysed for 1 h at room temperature in the presence of five equivalent of NaOH. The alkaline solution was neutralized and evaporated to dryness. The residue was dissolved in 80% acetic acid solution for the next step.[9]

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