SITE-SPECIFIC LABELING OF INDOLE DERIVATIVES: 3-(DIMETHYL-AMINOMETHYL) INDOLE-2-^{2}H (1).

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SUMMARY

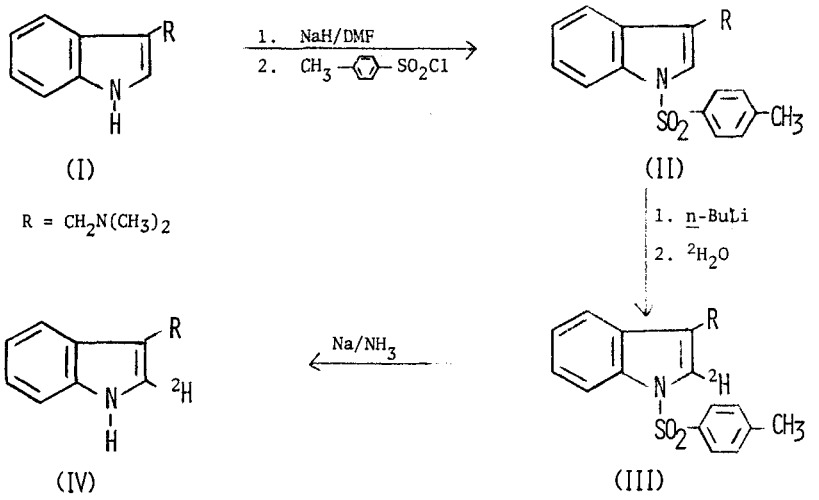
A procedure for the site-specific labeling of indole derivatives has been developed. The procedure utilizes the blocking and activating properties of the p-toluenesulfonyl group which allows for the facile metalation at the 2-position of indole with n-butyllithium and incorporation of deuterium upon reaction with ^2H_2O. Removal of the p-toluenesulfonyl group is achieved by treatment with sodium in liquid ammonia and occurs with retention of the label.

INTRODUCTION

Synthetic procedures for the site-specific introduction of a deuterium or tritium atom into biologically active indole derivatives are limited (3). Most commonly these procedures involve the introduction of the label into the parent indole nucleus or its precursor, prior to conversion to the desired derivatives, i.e., the synthesis of tryptophan-2-^{3}H and tryptamine-2-^{3}H from indole-2-^{3}H (4). More recently Raj and Hutzinger have reported (5) a method which utilizes the Raney nickel desulfurazation of 2-(2',4'-dinitrophenylthio)indoles for the introduction of hydrogen isotopes into the 2-position of indole derivatives.

We wish to describe a general method for the introduction of deuterium

or tritium into the 2-position of 3-substituted indoles. This method employs the blocking and activating properties of the p-toluenesulfonyl group which is easily attached to, and removed from, the 1-position of indole derivatives (6). Gramine, 3-(dimethylaminomethyl)indole (I), was converted to its sodium salt by treatment with sodium hydride in dimethylformamide (DMF) and alkylated with p-toluenesulfonyl chloride to give 1-(p-toluenesulfonyl)-3-(dimethylaminomethyl)indole (II). Sundberg and Russell (6) have recently prepared a variety of N-protected indoles and found the benzenesulfonyl group to be the most versatile protecting group. Site-specific exchange of the 2-proton was achieved as reported (7) and gave 1-(p-toluenesulfonyl)-3-(dimethylaminomethyl)indole-2-^{2}H (III). Removal of the p-toluenesulfonyl group was accomplished by treatment of III with sodium and liquid ammonia (8) to yield 3-(dimethylaminomethyl)indole-2-^{2}H (IV). The procedure is outlined below.



(I) (II)

R = $CH_2N(CH_3)_2$

(IV) (III)

EXPERIMENTAL

Nmr spectra were run on a Varian Associates Model HA-100 spectrometer

using deuterochloroform or deuteroacetone as the solvent and tetramethylsilane as the internal standard. Aromatic proton assignments were made by analogy to compounds previously reported (9). Mass spectra were recorded on a Varian MAT CH-7 mass spectrometer and were run using direct insertion probes. All spectra were determined at 70 eV and samples were heated to the minimum temperature necessary to produce a spectrum. One dimensional thin-layer chromatography (TLC) was carried out on silica gel G precoated plates (Analtech, Inc., Newark, Delaware), using a solvent system consisting of 1.5% ammonia in methanol. All thin-layer chromatograms were developed 12 cm and visualized with alkaline potassium permanganate or iodine vapor. Melting points were measured on a Mel-Temp capillary melting point apparatus.

1-(p-toluenesulfonyl)-3-(dimethylaminomethyl)indole (II) 3-(Dimethylaminomethyl)indole (3.48 g, 20 mmoles) dissolved in 30 ml of dry, freshly distilled DMF was added dropwise to a 200 ml three-necked roundbottom flask containing sodium hydride (1.06 g, 25 mmoles) dissolved in 50 ml of DMF which was placed under a nitrogen atmosphere. The resulting solution was allowed to stir 3 hrs at room temperature prior to the dropwise addition of p-toluenesulfonyl chloride (3.80 g, 20 mmoles) which was dissolved in 30 ml of DMF. Stirring was continued overnight. The reaction mixture was poured into 1500 ml of water, the aqueous solution extracted with 3 x 200 ml of ether, and the combined ether extracts washed with 4 x 250 ml of water prior to drying over anhydrous $MgSO_4$. Removal of the ether under reduced pressure gave a viscous oil which solidified upon standing. Conversion to the hydrochloride gave 6.07 g (84%) of colorless plates, m.p. 224-226°, following recrystallization from methanol/ethyl acetate. TLC gave R_f 0.64. The mass spectrum gave a correct $M^{\cdot+}$ at m/e 328 for $C_{18}H_{20}N_2O_2S$. Nmr (free base) ($CDCl_3$): δ 2.16 (s, 6H, $N(CH_3)_2$), 2.59 (s, 3H, CH_3Ar), δ 3.45 (s, 2H, CH_2N), δ 6.94-7.32 (m, 4H, Ar), δ 7.42 (s, 1H, indole H-2), δ 7.50-7.74 (m, 3H, Ar), and δ 7.86-8.0 (m, 1H, indole H-4).

1-(p-toluenesulfonyl)-3-(dimethylaminomethyl)indole-2-^{2}H (III). This reaction was conducted with oven-dried glassware which was assembled and placed under a continuous flow of dry nitrogen gas prior to the introduction of any reaction component. 1-(p-Toluenesulfonyl)-3-(dimethylaminomethyl)-indole (0.52 g, 1.58 mmoles) was dissolved in 60 ml of freshly distilled (from $LiAlH_4$) THF and cooled to -78° in CO_2/acetone prior to treatment with n-butyllithium (1.0 ml of 2.34 M solution, 2.34 mmoles). An immediate yellow color was produced. The reaction was allowed to stir for 30 min at -78° before quenching with ^2H_2O (0.1 ml, 5.0 mmoles). The THF was removed under reduced pressure, the resulting oil was dissolved in 50 ml of ether and dried over anhydrous $MgSO_4$. Removal of the ether under reduced pressure gave 0.47 g (91%) of product. TLC gave R_f 0.64. The mass spectrum gave a correct M^+ at m/e 329 for $C_{18}H_{19}{}^2H_1N_2O_2S$. Nmr ($CDCl_3$): δ 2.18 (s, 6H, $N(CH_3)_2$), 2.62 (s, 3H, CH_3Ar), 3.46 (s, 2H, CH_2N), δ 6.98-7.34 (m, 4H, Ar), δ 7.50-7.76 (m, 3H, Ar), and 7.87-8.0 (m, 1H, indole H-4).

3-(Dimethylaminomethyl)indole-2-^{2}H (IV). 1-(p-Toluenesulfonyl)-3-(dimethylaminomethyl)indole-2-^{2}H (2.0 g, 6.1 mmoles) was dissolved in 20 ml of dry THF and slowly added to a 300 ml three-necked roundbottom flask which contained 80 ml of liquid ammonia and was placed under a nitrogen atmosphere. The starting material was incompletely dissolved at this stage. Small sodium beads were added slowly to the vigorously stirred solution until a blue-green color persisted. The reaction was quenched by the addition of solid NH_4Cl and the excess ammonia allowed to evaporate. The resulting residue was dissolved in 50 ml of water and treated with 10 ml of 10% Na_2CO_3 solution prior to 3 x 40 ml extraction with ether. The combined ether extracts were dried over anhydrous $MgSO_4$. Removal of the ether under reduced pressure gave a crystalline solid. Recrystallization from acetone gave 0.92 (86%) of colorless plates, m.p. 138-139°. TLC gave R_f 0.25. The mass spectrum gave

a correct $M^{+\cdot}$ at m/e 175 for $C_{11}H_{13}{}^{2}H_{1}N_{2}$. Nmr ($CD_3\overset{O}{\overset{\|}{C}}CD_3$): δ 2.18 (s, 6H, $N(CH_3)_2$), δ 3.56 (s, 2H, CH_2N), δ 6.85-7.08 (m, 2H, Ar), 7.24-7.38 (m, 1H, Ar), and 7.58-7.70 (m, 1H, indole H-4). The incorporation of deuterium at the 2-position was >95% as determined by nmr.

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