5-(α-FLUOROVINYL)-*N*-TOSYLINDOLE

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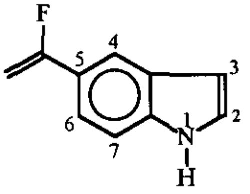
Abstract- A α-fluorovinyl (or α-fluoroethene) substituent was introduced into the indole 5-position using an "atypical" Heck reaction. 5-Iodoindole (**4**) is preferred over 5-bromoindole as the starting material. Protection of the indole nitrogen is necessary.

The fluorovinyl group has been suggested to be a peptide bond isostere since it mimics both the steric and the electronic features of a peptide bond.[1] It has been successfully incorporated in some peptides which have been analyzed for chemical and biological stability and for receptor binding affinity.[2] We decided to investigate the fluorovinyl group as a potential isostere of the carboxyamido group in aromatic compounds. Thus 5-(α-fluorovinyl)tryptamines could be good bioisosteres of 5-carboxyamido-tryptamines (**3**), potent 5 HT_1 agonists. 5-(α-fluorovinyl)indole (**1**), which can serve as the starting material to make 5-(α-fluorovinyl)tryptamines (**2**) and other tryptamine analogs, can be made by introducing a α-fluorovinyl group into the indole 5-position. Here we report the synthesis of 5-(α-fluorovinyl)-*N*-tosyl indole in full detail.

There are a few methods reported in the literature to introduce an α-fluorovinyl group into aromatic systems.[3-5] Because of potential shortcomings anticipated with these methods, like severe reaction conditions, number of steps involved and the availability of the starting materials, we decided to investigate the "atypical" Heck reaction discovered by Heitz and Knebelkamp.[6]



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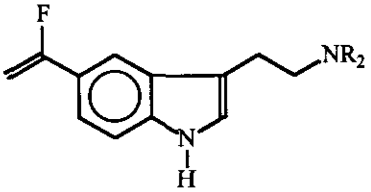

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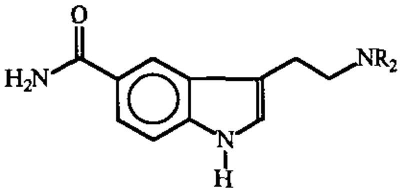

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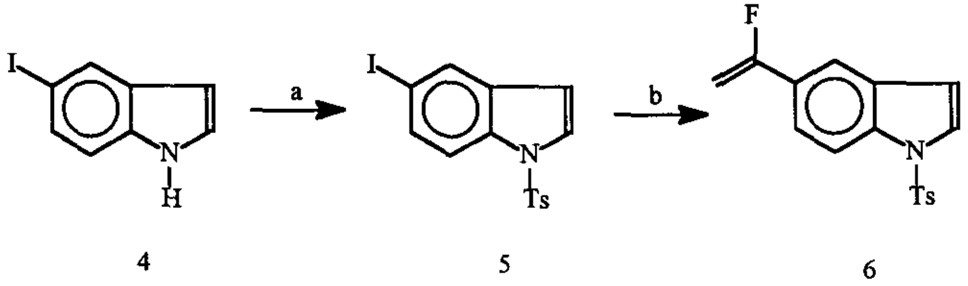
The reaction conditions here are much simpler, the starting materials are readily available and it is a single step reaction from 5-iodoindole (**4**). Commercially available 5-bromoindole was initially employed as the aryl halide to react with 1,1-difluoroethylene gas in presence of palladium acetate as the coupling catalyst at 1000 psi and 120°C. All that was recovered was unidentifiable, sticky, tarry, complex residue. Protection of the indole nitrogen with *p*-toluenesulfonyl group[7] avoided this apparent polymerization but the reaction was too sluggish. GCms analysis of the reaction mixture after 96 h still showed 35% of the aryl halide unreacted and only 20% product formation. This prompted us to examine the use of 5-iodoindole (**4**) as the aryl halide since aryl iodides are known to be more reactive in the Heck reaction.[6] **4** was prepared by the literature method[8] and its nitrogen was protected by *p*-toluenesulfonyl group. The reaction of 5-iodo-*N*-tosyl indole (**5**) with 1,1-difluoroethylene under similar reaction conditions (except much lower pressure, about 250 psi) was much faster, with complete consumption of **6** in 24 h (Scheme 1). The yield was only 35-37% on our first few attempts but was finally improved to 50% by increasing the pressure of the 1,1-difluoroethylene gas in the reaction vessel to 800 psi at 120°C. The product, 5-α-fluorovinyl-*N*-tosylindole (**6**) was obtained in white crystalline form after work up and purification. The *N*-tosyl group can be removed in nearly quantitative yield using sodium methoxide/methanol whenever required. The unprotected 5-(α-fluorovinyl)indole was found to be unstable to atmospheric conditions, possibly explaining the failure to isolate characteristic products either when 5-bromo- or 5-iodoindole were employed as aryl halide.

Scheme 1.



Reagents: a. *p*-TsCl, $(n\text{-}Bu)_4NHSO_4$, 15% NaOH, toluene, room temperature, 3 h.
b. 1,1-difluoroethylene, $Pd(OAc)_2$, Et_3N, DMF, 24 h.

p-TsCl = *p*-toluene sulfonyl chloride

EXPERIMENTAL

Chemicals and Methods: 1,1-Difluoroethylene (99+ %) in a lecture bottle was obtained from Aldrich chemical company. Melting points were determined with an Electrothermal Capillary melting point apparatus and are uncorrected. Proton nmr spectra were obtained using Varian Gemini 200 (MHz) spectrometer. EI mass spectra were obtained on Hewlett Packard 5970 MSD spectrometer. Elemental analysis was performed by Desert Analytics, Tucson, AZ. The pressure reaction vessel used was a 600 ml Parr Pressure Reaction Apparatus, model no. 4563M.

5-Iodo-*N*-tosylindole (5) 5-Iodoindole[8] (8.33 g, 35 mmol), *p*-toluenesulfonyl chloride (9.98 g, 52.5 mmol) and tetrabutylammonium bisulfate (1.76 g, 5.18 mmol) were dissolved in 102 ml of toluene in 1 litre flask. The clear solution was cooled in an ice bath. To this was added 102 ml of 15% aqueous NaOH. The two phase mixture was stirred vigorously at room temperature for 3 h. The organic phase was separated and washed with 56 ml of 1N HCl followed by saturated $NaHCO_3$ and water. After drying the organic phase with anhydrous Na_2SO_4, it was evaporated under reduced pressure to obtain 11.8 g (86%) of light tanned crystalline solid. mp 136-138°C. Mass spectrum: m/z 397 (M^+ 81%), 242 (37%), 155

(86%), 115 (73%), 91 (100%), 65 (56%). ^{1}H-Nmr (200 MHz,$CDCl_3$): δ 2.35 (3H, s, tosyl-CH_3), 6.59 (1H, dd, indole 3-H, J = 0.7 and 3.8 Hz), 7.22 (2H, d, tosyl H adjacent to methyl, J = 8.7 Hz), 7.39 (1H, dd, indole 6-H, J = 2.2 and 9.4 Hz), 7.56 (1H, d, indole 2-H, J = 3.8 Hz), 7.65 (1H, d, indole 4-H, J = 2.2 Hz), 7.73 (2H, d, tosyl H adjacent to sufonyl, J = 8.7 Hz), 7.87 (1H, d, indole 7-H, J = 9.4 Hz). *Anal.* Calcd. for $C_{15}H_{12}NO_2IS$: C, 45.35; H, 3.04; I, 31.94; N, 3.52; S, 8.07. Found: C, 45.05; H, 3.02; I, 31.90; N, 3.48; S, 8.04.

5-(α-Fluorovinyl)-*N*-tosylindole (6) 5-Iodoindole-*N*-tosylindole (**5**) (11.76 g, 30 mmol), Et_3N (7.57 g, 75 mmol), palladium acetate (0.2 g, 0.9 mmol) were placed in a pressure reaction vessel along with 70 ml of dimethylformamide (DMF). The reaction vessel was degassed twice, cooled in a dryice-ether bath to about -60°C and at this point was introduced 1,1-difluoroethylene gas till the pressure guage reached up to 100 psi. The temperature at this point rose to -35°C. Then the reaction mixture was allowed to attain room temperature. The pressure read 350 psi. The reaction mixture was heated up to 120°C and allowed to stir vigorously at this temperature for 24 h. Then it was cooled to room temperature and poured into 200 ml of ice water to give a dark yellow sticky precipitate. This was extracted in ether (100 ml x 3). The ether extract was concentrated to give a dark brown viscous residue which was chromatographed on silica gel (Hexane:EtOAc = 9:1) to obtain 4.5 g (48%) of light yellow oil which solidified on refrigeration. Rf = 0.4 (10% EtOAc/Hexane). mp 84-86°C. Mass spectrum : m/z 315 (M^+, 100%), 155 (78%), 163 (15%), 133 (21%), 91 (99%), 65 (22%). ^{1}H-Nmr (200 MHz, $CDCl_3$) : δ 2.32 (3H, s, tosyl CH_3), 6.65 (1H, d, indole 3-H), 7.21 (2H, d, tosyl H adjacent to methyl, J = 8.2 Hz), 7.5 (1H, dd, indole 6-H, J = 2.08 and 8.4 Hz), 7.58 (1H, d, indole 2-H, J = 3.7 Hz), 7.71 (1H, d, indole 4-H, J = 2.1 Hz), 7.76 (2H, d, tosyl H adjacent to sulfonyl, J = 8.2 Hz), 7.96 (1H, d, indole 7-H, J = 8.4 Hz). *Anal.* Calcd. for $C_{17}H_{14}NO_2FS$: C, 64.74; H, 4.47; N, 4.44; F, 6.02; S, 10.16. Found: C, 64.91; H, 4.43; N, 4.47; F, 6.15; S, 10.18.

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REFERENCES

1. T. Allmendinger, P. Furet, and E. Hungerbuhler, Tetrahedron Lett., 1990, **31**, 7297
2. T. Allmendinger, E. Felder, and E. Hungerbuhler, Tetrahedron Lett., 1990, **31**, 7301.
3. K. Matsuda, J. A. Sedlak, J. S. Noland, and G.C. Glecker, J. Org. Chem., 1962, **27**, 4015.
4. L.Eckes, and M. Hanack, Synthesis, 1978, 217.
5. D. P. Mattews, R. S. Gross, and J. R. McCarthy, Tetrahedron Lett., 1994, **35**, 1027.
6. W. Heitz, and A. Knebelkamp, Makromol.Chem., Rapid Commun., 1991, **12**, 69.
7. V. O. Illi, Synthesis, 1979, 136.
8. H. F. Russell, B. J. Harris, D. B. Hood, E. G. Thompson, A. D. Watkins, and R. D. Williams, Organic Preperations and Procedures Int., 1985, 17, 391.

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