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SYNTHESIS AND REACTIVITY OF 6-(FLUOROMETHYL)INDOLE AND 6-(DIFLUOROMETHYL)INDOLE

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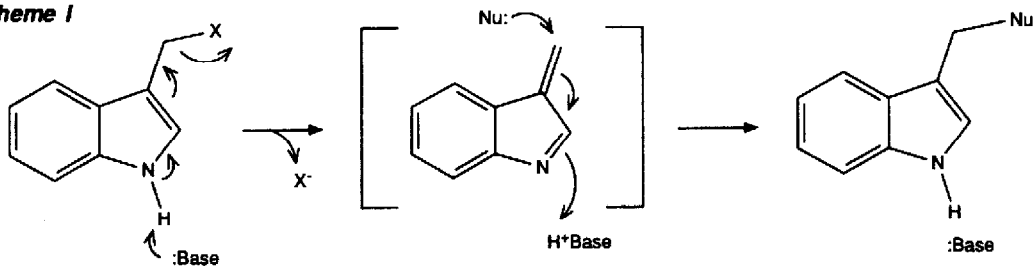
Summary: The N-1 BOC protected precursors of 6-(fluoromethyl)indole and 6-(difluoromethyl)indole were prepared and deprotected via flash vacuum thermolysis. The stability of these newly prepared, unprotected indole derivatives has been characterized and compared to that of a previously known compound, 6-(trifluoromethyl)indole.

The tryptophan processing enzymes, tryptophanase and tryptophan synthase, catalyze the reversible C-3 alkylation of indole through a mechanism proposed to include N-1 deprotonation.[1] Synthetic work in our laboratory has been directed at developing substrate analogues for the characterization of this base-dependent event. Halomethyl-containing compounds have proven useful in the identification of carbanionic intermediates formed during enzyme turnover,[2] and a similar analysis may be applicable to our heteroatomic system. Accordingly, we have developed syntheses for 6-(fluoromethyl)indole and 6-(difluoromethyl)indole.

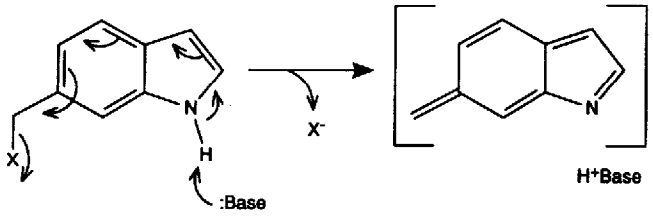
As depicted in Scheme I, we were initially interested in preparing a 3-(halomethyl)indole. If this type of compound were appropriately activated by the enzymes of interest, halide elimination would be stimulated and an electrophilic indole methide would be generated *in situ*. Our attempts to reproduce the few literature syntheses of 3-(bromomethyl)- or 3-(chloromethyl)indole were not successful.[3] While N-protected 3-(halomethyl)indoles may be prepared and are moderately stable,[4] deprotection of these compounds led to uncharacterizable mixtures. This instability even extended to the fluoromethyl analogue.

Scheme I



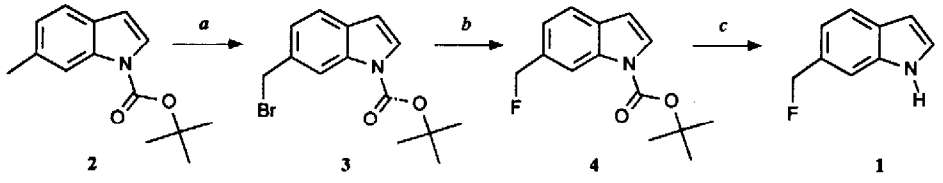
Our focus therefore turned towards the design of a derivative in which halide elimination would require disrupting the aromaticity of both the benzene and pyrrole rings of indole (Scheme II). This was expected to increase the kinetic barrier for fluoride release and thus allow for isolation of an unprotected indole. The syntheses of 6- and 7-(fluoromethyl)indole were undertaken for the purpose of enzymatic evaluation and for comparison of their reactivity to that of the previously described 6-(trifluoromethyl)indole.[5]

Scheme II



The heterocyclic nitrogen of 6-methylindole was protected using di-*tert*-butyl dicarbonate and catalytic 4-DMAP to give 1-(*tert*-butoxycarbonyl)-6-methylindole **2** in 86% yield.[6] Scheme III depicts the subsequent transformations. Irradiation of the protected methylindole **2** in the presence of NBS and dibenzoyl peroxide provided the 6-(bromomethyl) derivative **3** (69% yield).[7,8] Treatment of the brominated compound with excess AgF then gave 1-(*tert*-butoxycarbonyl)-6-(fluoromethyl)indole **4** (30% yield).[9]

Scheme III

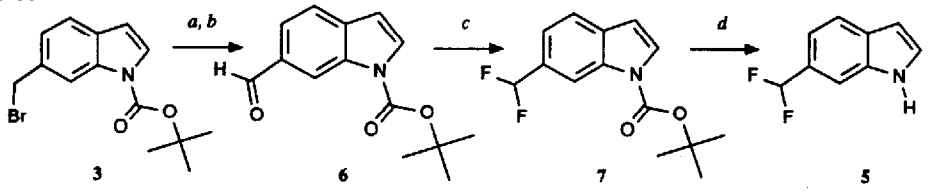


a) NBS, hν, CCl_4, 25 min, 80°; *b*) AgF, CH_3CN, 2 hr, 25°; *c*) FVT, benzene-d_6, 400°

Conventional methods for removing the BOC protecting group proceeded with concomitant loss of the halomethyl functionality.[10] Flash vacuum thermolysis[11] (400°C) of a 5-10% (wt/vol) benzene-d_6 solution of 1-(*tert*-butoxycarbonyl)-6-(fluoromethyl)indole **4** did, however, provide a compound consistent with the desired 6-(fluoromethyl)indole **1**.[12] This molecule proved to be too unstable for further manipulation.

The synthesis of 6-(difluoromethyl)indole **5** (Scheme IV) was then examined for the added stability that a second fluorine substituent should lend to this heterocyclic system. Oxidation of 6-(bromomethyl)-1-(*tert*-butoxycarbonyl)indole with DMSO/$NaHCO_3$ generated indole-6-carboxaldehyde in a crude yield of 86%; as indicated, the BOC group was lost under the conditions of this reaction (20 minutes at 150°C). Treatment of the reprotected indole-6-carboxaldehyde **6** with DAST (neat) overnight afforded a 65% yield of the 6-(difluoromethyl) derivative **7**. Flash vacuum thermolysis of **7** then gave the deprotected 6-(difluoromethyl)indole **5** in 51% yield after column purification.[13]

Scheme IV



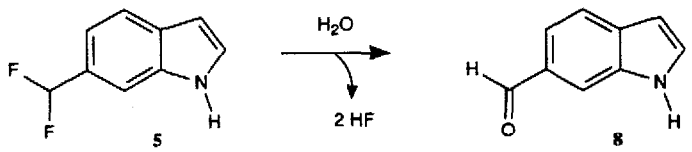
a) $NaHCO_3$, DMSO, 20 min, 150°; *b*) $(BOC)_2O$, DMAP, CH_3CN, 10 min, 25°;
c) neat DAST, 12 hr, 30°; *d*) FVT, benzene-d_6, 400°

Functionalization at the C-7 position was also our goal; fluoride elimination from this position would generate an indole methide that might trap the putative enzymatic base responsible for N-1 deprotonation. 7-(Fluoromethyl)indole[12] could be prepared in a route parallel to that developed for the 6-(fluoromethyl) derivative, and, as for 6-(fluoromethyl)indole, decomposed with a half-life of <3 hr at 25 °C in benzene. Attempts to prepare 7-(difluoromethyl)indole from 1-(*tert*-butoxycarbonyl)indole-7-carboxaldehyde and neat DAST were not successful despite reaction times of two days at 45°C; the lack of reaction is presumably due to the congestion imposed by the BOC protecting group.

The efficiency of fluoride elimination varies widely in the series of mono-, di-, and trifluoromethyl-substituted indoles. As described, 6- and 7-(fluoromethyl)indole decomposed quite readily. In contrast, there was no indication of fluoride elimination from 6-(trifluoromethyl)indole when treated with 100 mM NaOH at 25°C (*i.e.*, there was no hydrolysis to indole-6-carboxylate); this was monitored by both UV spectroscopy and TLC over a two hour period.[14]

A balance in reactivity was demonstrated by 6-(difluoromethyl)indole. This compound was stable to silica gel chromatography and storage as an ethanol solution at -20°C for at least one month. Under aqueous conditions, 6-(difluoromethyl)indole hydrolyzed to indole-6-carboxaldehyde **8** (Scheme V) with a rate constant of 1.0 x 10^{-2} min^{-1} (0.2 M potassium phosphate buffer, pH 8.0).[15] Additionally, this process was found to be independent of both pH and buffer concentration within a pH range of 3-12; above pH 13 aldehyde formation was greatly stimulated. Enzymological evaluation of the di- and tri-substituted compounds is now in progress.

Scheme V



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References and Notes

1. a) Phillips, R. S.; Miles, E. W.; Cohen, L. A. *Biochemistry* **1984**, *23*, 6228-6234; b) Kiick, D. M.; Phillips, R. S. *Biochemistry* **1988**, *27*, 7339-7344; c) Phillips, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 727-730.
2. a) Dirmaier, L. J.; Garcia, G. A.; Kozarich, J. W.; Kenyon, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 3149-3150; b) Lin, D. T.; Powers, V. M.; Reynolds, L. J.; Whitman, C. P.; Kozarich, J. W.; Kenyon, G. L. *J. Am. Chem. Soc.* **1988**, *110*, 323-324; c) Reynolds, L. J.; Garcia, G. A.; Kozarich, J. W.; Kenyon, G. L. *Biochemistry* **1988**, *27*, 5530-5538.
3. Eryshev *et al.* prepared 3-(bromomethyl)indole via Hunsdiecker bromination-decarboxylation of indole-3-acetic acid: Eryshev, B. Ya.; Dubinin, A. G.; Buyanov, V. N.; Suvorov, N. N. *Khim. Geterotsikl. Soedin.* ***1974***, 1493-1495. Although 3-(chloromethyl)indole has been reported as a synthetic intermediate, the formation of this molecule has never been explicitly described: a) Denny, G. H.; Saari, W. S. U. S. Patent 4 065 464, 1977; *Chem. Abstr.* **1978**, *88*, 513; b) Davis, B. *J. Labelled Cmpd. Radiopharm.* **1987**, *24*, 199-204.

4. See for example, a) Hino, T.; Nakamura, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1975**, *23*, 2990-2997; b) Schöllkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. Chem.* ***1985***, 413-417; c) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1986**, *29*, 1637-1643.
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6. Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed. Eng.* **1984**, *23*, 296-301.
7. A similar bromination of 1-(*tert*-butoxycarbonyl)-3-methylindole without irradiation resulted in the formation of the 2-bromo-3-(bromomethyl) derivative. No monobrominated compounds were evident even when substoichiometric amounts of NBS were used.
8. To prohibit decomposition, 1% (v/v) triethylamine was added to the column eluant during flash silica purification.
9. Praly, J. P.; Descotes, G. *Tetrahedron Lett.* **1987**, *28*, 1405-1408.
10. Techniques examined to deprotect 1-(*tert*-butoxycarbonyl)-7-(fluoromethyl)indole included acidic hydrolysis (2 M TFA in CH_2Cl_2 and HCl-saturated ethyl acetate), heating neat to 180°C, and stirring with such reagents as Nafion® NR50, boron trifluoride etherate, or trimethylsilyl iodide.
11. See Magrath and Fowler for a description of the flash vacuum thermolysis technique and apparatus: Magrath, J.; Fowler, F. W. *Tetrahedron Lett.* **1988**, *29*, 2171-2174. Rawal and Cava have described the thermolytic removal of the BOC protecting group from a variety of indoles and pyrroles in a condensed phase: Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141-6142.
12. ^{1}H NMR analysis of the material collected after the thermolysis of 1-(*tert*-butoxycarbonyl)-6-(fluoromethyl)indole **4** (crude yield 94%) provided the expected aromatic and fluoromethylene signals and demonstrated that deprotection was complete. However, 6-(fluoromethyl)indole **1** (estimated to be present in 43%) decomposed during isolation. ^{1}H NMR data for 7-(fluoromethyl)indole (benzene-d_6): δ 5.17 (d, J = 48.30 Hz, 2H), 6.46 (br s, 1H), 6.56 (t, J = 2.36 Hz, 1H), 6.82 (dd, J = 7.04 Hz, 2.52 Hz, 1H), 7.02 (t, J = 7.54 Hz, 1H), 7.5 (br abs, N-1 H), 7.61 (d, J = 8.06 Hz, 1H).
13. ^{1}H NMR data: 6-(bromomethyl)-1-(*tert*-butoxycarbonyl)indole **3** (CD_3CN), δ 1.67 (s, 9H), 4.79 (s, 2H), 6.64 (d, J = 3.87 Hz, 1H), 7.31 (dd, J = 8.19 Hz, 1.71 Hz, 1H), 7.59 (d, J = 7.80 Hz, 1H), 7.68 (d, J = 3.74 Hz, 1H), 8.24 (s, 1H); 1-(*tert*-butoxycarbonyl)-6-(fluoromethyl)indole **4** (CD_3CN), δ 1.67 (s, 9H), 5.51 (d, J = 48.31 Hz, 2H), 6.66 (d, J = 3.56 Hz, 1H), 7.30 (dd, J = 8.06 Hz, 1.46 Hz, 1H), 7.64 (d, J = 7.97 Hz, 1H), 7.69 (dd, J = 3.58 Hz, 0.77 Hz, 1H), 8.22 (s, 1H); 1-(*tert*-butoxycarbonyl)indole-6-carboxaldehyde **6** (CD_3CN), δ 1.68 (s, 9H), 6.71 (d, J = 3.58 Hz, 1H), 7.73 (d, J = 1.25 Hz, 2H), 7.84 (d, J = 3.65 Hz, 1H), 8.59 (s, 1H), 10.04 (s, 1H); 1-(*tert*-butoxycarbonyl)-6-(difluoromethyl)indole **7** (CD_3CN), δ 1.68 (s, 9H), 6.71 (d, J = 3.53 Hz, 1H), 6.93 (t, J = 56.37 Hz, 1H), 7.43 (d, J = 8.13 Hz, 1H), 7.73 (d, J = 8.14 Hz, 1H), 7.77 (d, J = 3.44 Hz, 1H), 8.34 (s, 1H); 6-(difluoromethyl)indole **5** (CD_3CN), δ 6.57 (dd, J = 3.07 Hz, 0.87 Hz, 1H), 6.88 (t, J = 56.65, 1H), 7.24 (d, J = 8.22 Hz, 1H), 7.41 (t, J = 2.72 Hz, 1H), 7.66 (s, 1H), 7.71 (dd, J = 8.23 Hz, 0.66 Hz, 1H), 9.6 (br s, 1H).
14. Bornstein *et al.* have reported that ethyl 6-(trifluoromethyl)indole-2-carboxylic acid is hydrolyzed to the diacid within 4 hr at 80-90°C in 10 N NaOH: Bornstein, J.; Leone, S. A.; Sullivan, W. F.; Bennett, O. F. *J. Am. Chem. Soc.* **1957**, *79*, 1745-1748.
15. UV spectroscopy was used to follow the hydrolysis: indole-6-carboxaldehyde **8** (H_2O) λ_{max} 304 nm (ε 12,200 $M^{-1}cm^{-1}$).

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