Synthesis of Substituted Indoles and Carbazoles from 2-Fluorophenyl Imines

Linas V. Kudzma*
Baxter Healthcare Corporation, Anesthesia and Critical Care, 95 Spring Street, New Providence, NJ 07974, USA
Fax +1(908)2867359; E-mail: linas_kudzma@baxter.com
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Abstract: The synthesis of a series of indole and carbazole derivatives from 2-fluorophenyl imines is reported. 2-Fluoroaniline-d₄ (13) is prepared and used to investigate the mechanism of this indolization. 2-Fluorophenyl enamino 17 gives the synthetically useful carbazole 20 via a similar indolization and in situ alkylation.

Key words: indoles, imines, enamino, benzyne, nucleophilic aromatic substitution

Synthesis of selectively functionalized indole and carbazole derivatives continues to attract interest in organic synthesis due to the extensive presence of indoles in natural products and biologically active compounds in medicinal chemistry. The method described in this article provides a new short route to 2- or 2,3-disubstituted indoles from appropriately substituted 2-fluorophenyl imines and a 2-fluorophenyl enamino. This method complements a related route to indole derivatives from 3-chlorophenyl imines and enamines.

Scheme 1 Reagents and conditions: a) 2.5 equiv LDA, THF, reflux 5 h; b) H₂O

During a large scale synthesis of a 4-anilidopiperidine opioid analgesic involving the addition of phenyllithium to imine 1, a previously overlooked minor side product was isolated and determined to be the gamma-carbolone derivative 2. Reaction conditions were modified to make this initially unexpected indole derivative the exclusive product (Scheme 1). Treatment of imine 1 with a minimum of two equivalents of the non-nucleophilic base LDA and heating the reaction mixture to reflux, cleanly gave the indole derivative 2 in nearly quantitative yield. Additional investigation found that this is a general method for preparing 2- or 2,3-disubstituted indoles in good to excellent yields from appropriately substituted 2-fluorophenyl imines (Table 1).

2-Fluorophenyl imines were easily obtained from 2-fluoroaniline and the corresponding ketone in refluxing toluene by acid-catalyzed azeotropic dehydration. The resulting 2-fluorophenyl imines can be purified by chromatography or distillation and fully characterized if so desired. Alternatively, the majority of toluene can be distilled off in vacuo and the resultant crude imine used directly, as demonstrated in the high yielding synthesis of carbazole 6. The reaction of acetophenone and 2-fluoroaniline produced an interesting unexpected side product. In this case, attempts to drive the azeotropic dehydration to completion gave varying amounts of 2,4-diphenyl-3H-1-benzazepine (9), presumably from an aldol-type condensation followed by an intramolecular SNAr ring closure under unprecedented conditions (Figure 1).

Similarly, 2-acetylthiophene and 2-fluoroaniline under acid-catalyzed azeotropic dehydration can give the analogous dithienyl-3H-1-benzazepine (10).

The mechanism and synthetic utility of this benzazepine synthesis are presently being investigated and full details will be reported separately. Despite this side reaction, it is possible to obtain the desired imines 4 and 5 in modest yield if the reaction is not driven to completion and the imines are isolated by chromatography.

To synthesize indole derivatives from 2-fluorophenyl imines, the imines were dissolved in anhydrous THF under an atmosphere of dry nitrogen, cooled to –78 °C and treated with 2.5–3 equivalents of LDA followed by heating to reflux. The reactions were monitored by TLC analysis and showed only a small amount of indolization as the reaction mixture warmed to ambient temperature. Typically, several hours at reflux under nitrogen were needed to complete the displacement of the aromatic fluorine. The need for a minimum of 2 equivalents of LDA strongly suggested that this aromatic substitution involves a benzyne rather than a SNAr mechanism. The intermediacy of a benzyne was demonstrated by the use of 2-fluoroaniline-d₄ in the synthesis.

2-Fluoroaniline-d₄ (13) was prepared (Scheme 2), from fluorobenzene-d₅ which was ortho lithiated using Schlosser’s ‘super base’ protocol and quenched with solid car-
bon dioxide to give 2-fluorobenzoic acid-d$_4$ (11) in excellent yield. This acid was then converted to 2-fluorobenzamide-d$_4$ (12) by heating with neat thionyl chloride followed by treatment of the crude acid chloride with ammonia in dichloromethane. The amide 12 was converted to 2-fluoroaniline-d$_4$ (13) under standard Hofmann rearrangement conditions without loss of deuterium label.

2-Fluoroaniline-d$_4$ (13) was reacted with 2-acetylthiophene to give the imine 14 and indolization under the typical conditions (Scheme 3) gave the deuterium labeled indole 16. This deuterated indole 16 was chosen for the labeled experiment because the $^1$H NMR resonance at C-4 was cleanly resolved from other Ar-H resonances and loss of deuterium label at this location could be easily observed. The spectrum of indole 16 only showed exchange of deuterium at $^\delta$ 7.59 (C-4), which is adjacent to the former location of the aromatic fluorine. This strongly indicates that lithiation occurs at this site, followed by elimination of fluoride to form the proposed benzylene intermediate 15.

A further extension of this new indolization method was used to synthesize the important carbazole derivative 20.

### Table 1  Indolization of Imines 1, 3–5

<table>
<thead>
<tr>
<th>Imine</th>
<th>Indole</th>
<th>Yield (%)</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>97</td>
<td>LDA (2.5 equiv) reflux 5 h</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>93</td>
<td>LDA (2.5 equiv) reflux 5 h</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>90</td>
<td>LDA (3 equiv) reflux 5 h</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>42</td>
<td>LDA (2.5 equiv) reflux 16 h</td>
</tr>
</tbody>
</table>

**Scheme 2**  *Reagents and conditions:*  
- a) n-BuLi/t-BuOK, THF –78 °C, 1 h;  
- b) CO$_2$ (s);  
- c) SOCl$_2$, reflux 1.5 h;  
- d) NH$_3$, CH$_2$Cl$_2$, 0 to 20 °C;  
- e) aq NaOH, Br$_2$, reflux 1.5 h, steam distill.

**Scheme 3**  *Reagents and conditions:*  
- a) 13, toluene, p-TsOH, reflux, separate H$_2$O, 4 h;  
- b) 2.5 equiv LDA, THF, reflux 16 h;  
- c) H$_2$O
from the 2-fluorophenyl enaminone 17 (Scheme 4). The
enaminone 17 was prepared from 1,3-cyclohexanedione
and 2-fluoroaniline by heating them neat at 120 °C in a
manner analogous to that described by Kibayashi and
treated with 3 equivalents of LDA in THF. In contrast to
the previous cases, 17 required a minimum of 3 equiv-
ulents of LDA for indolization to occur. If only 2 equiv-
ulents were used, even prolonged heating at 75 °C did not
result in any indolization. With 3 equivalents of LDA, in-
dolization proceeded in the normal manner giving the de-
sired carbazole dianion 18. The dianion 18 was partially
quenched with one equivalent of acetic acid, followed by
in situ alkylation with methyl iodide to give the desired
methyl carbazole 20. This one-pot lithiation, indolization,
partial quench, alkylation protocol was found to be a very
convenient route to 20, a pivotal intermediate in the syn-
thesis of the antiemetic drug ondansetron and related
compounds.

Alternatively, the reaction mixture containing dianion 18
can be quenched with excess acetic acid, protected from
exposure to air, and quickly purified by flash chromato-
graphy to give the carbazole 21.11 It is noteworthy that
when this reaction was quenched with excess water, the
alkaline crude reaction mixture containing 18 was very
sensitive to oxidative decomposition. If an N-alkyl carba-
zole is the ultimate goal, it is best to perform the alkylation
in situ as described for 20.

In conclusion, the indolization method described in this
paper is generally applicable for the synthesis of a variety of
2- or 2,3-disubstituted indoles and provides a new effi-
cient route to diverse indole derivatives.

Reagents and solvents were used as received from commercial ven-
dors without further purification. Anhyd THF, 1.8 M LDA in hept-
ane/THF/ethylbenzene, 1.5 M lithium diisopropylamide
mono(tetrahydrofuran) in cyclohexane and 2.5 M n-butyllithium
in hexanes were obtained in Sure/Seal bottles from Aldrich Chemi-
ical Co., Milwaukee, WI and transferred via syringe under dry nitro-
gen and the organic layer was separated, dried over anhyd Na2SO4

Flash chromatography was on Silica 60 (230–400 mesh) from EM Science.
Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison NJ.

(1-Benzylpiperidin-4-ylidene)-(2-fluorophenyl)amine (1)
N-Benzyl-4-piperidone (5.55 g, 29.3 mmol), 2-fluoroaniline (2.85 g, 25.7 mmol) and catalytic p-TsOH (65 mg) were combined in tol-
ue (100 mL) and heated at reflux with removal of H2O using a
Dean–Stark trap. After 15 h the reaction was cooled to r.t. and con-
centrated in vacuo. The crude reaction mixture was then vacuum
distilled bulb-to-bulb, using a Buchi Kugelhrapp apparatus (250 °C, 2
mmHg), to give 1 as a bright yellow oil which solidified upon
cooling; yield: 6.68 g (92%). This material was sufficiently pure to
be used in the next step without further purification. An analytical sample was crys-
tallized from hexane; mp 70–72 °C; Rf 0.40 (EtOAc–hexanes, 1:2).

1H NMR (CDCl3): δ = 7.34–7.25 (complex m, 5 H), 7.03 (m, 3 H),
6.82 (m, 1 H), 3.58 (s, 2 H), 2.72 (m, 2 H), 2.66 (m, 2 H), 2.55 (t, J = 5.8 Hz, 2 H), 2.29 (t, J = 5.8 Hz, 2 H).

13C NMR (CDCl3): δ = 175.33, 153.36, 150.63, 138.35, 137.93,
137.75, 129.31, 128.33, 127.21, 124.51, 124.42, 124.28, 124.23,
122.82, 122.79, 115.95, 115.68, 62.24, 53.94, 53.25, 38.35, 31.82.

Anal. Calcd for C14H12FN, 213.0954; found, 213.0974.

(2-Fluorophenyl)-(1-phenylethylidene)amine (4)
Acetophenone (6.0 g, 50 mmol), 2-fluoroaniline (5.6 g, 50 mmol)
and p-TsOH (cat., 25 mg) were combined in toluene (150 mL) and
heated at reflux with removal of H2O using a Dean–Stark trap.
After 4 h the reaction was cooled to r.t. and washed with 5% aq Na2CO3
(50 mL). The organic layer was separated, dried over anhyd Na2SO4
and filtered. Silica gel (15 g) was added and the toluene solution
was evaporated to adsorb the product onto silica, which was then
applied to a silica column and purified by flash chromatography,
(EtOAc–hexanes, 1:10) to give 4 as an orange oil; yield: 4.66 g
(44%); Rf 0.56 (EtOAc–hexanes, 1:10).

1H NMR (CDCl3): δ = 7.99 (complex m, 2 H), 7.42 (complex m, 3 H),
7.12–7.05 (complex m, 3 H), 6.89 (m, 1 H), 2.23, 2.22 (2 s, total 3 H).

13C NMR (CDCl3): δ = 168.35, 153.67, 150.44, 139.29, 139.11,
130.89, 128.49, 127.52, 124.61, 124.54, 124.49, 122.42,
122.39, 116.19, 115.92, 17.95, 17.92.

HRMS: m/z calcd for C19H14F2N, 213.0954; found, 213.0974.
(2-Fluorophenyl)-N-(1-thien-2-yl)ethylidene)amine (5)
2-Acetyltiophene (2.5 g, 19.9 mmol), 2-fluoroaniline (2.2 g, 20.0 mmol) and p-TsOH (cat., 25 mg) were combined in toluene (50 mL) and heated at reflux with removal of H₂O using a Dean–Stark trap. After 4 h the reaction was cooled to r.t., diluted with of toluene (50 mL) and washed with 5% aq. Na₂CO₃ (25 mL). The organic layer was separated, dried over anhyd Na₂SO₄ and filtered. Silica gel (10 g) was added and the toluene solution evaporated to adsorb the product on to the silica, which was then applied to a silica column and purified by flash chromatography (EtOAc–hexanes, 1:20) to give 5 as a yellow glass, which solidified to a waxy solid upon refrigeration; yield: 2.28 g (52%); mp 51 °C; Rₚ 0.50 (EtOAc–hexanes, 1:20).

1H NMR (CDCl₃): δ = 7.47–7.43 (m, 2 H), 7.09–7.03 (complex m, 4 H), 6.90 (m, 1 H), 2.20, 2.21 (2 s, total 3 H).
13C NMR (CDCl₃): δ = 136.07, 135.93, 150.69, 145.87, 138.08, 137.91, 130.51, 129.10, 127.57, 124.84, 124.74, 124.37, 124.32, 122.90, 122.86, 116.08, 115.81, 18.04, 18.01. Anal. Calcd for C₁₈H₁₈N₂ (262.35): C, 82.41; H, 6.92; N, 10.68. Found: C, 82.06; H, 6.94; N, 10.64.

2-Benzyl-2,3,4,5-tetrahydro-1-{[(pyridin-4-yl)amino]-2H-indole (2)
2-Benzyl-2,3,4,5-tetrahydro-1H-indole (2) was cooled to r.t., quenched with H₂O (10 mL) and partitioned between H₂O (3 mL) and cyclohexane (10 mL). The organic layer was separated, dried over anhyd Na₂SO₄, and filtered. Silica gel (10 g) was added and the toluene solution evaporated to adsorb the product on to the silica, which was then applied to a silica column and purified by flash chromatography (EtOAc–hexanes, 1:10) to give 2 as a yellow solid; yield: 0.92 g (97%). An analytical sample was crystallized from EtOAc–hexane; mp 160–161 °C; Rₚ 0.40 (EtOAc–hexanes, 1:1).

1H NMR (CDCl₃): δ = 7.80 (br s, 1 H), 7.44–7.25 (complex m, 7 H), 7.07 (m, 2 H), 3.80 (s, 2 H), 3.73 (br s, 2 H), 2.87 (m, 4 H).
13C NMR (CDCl₃): δ = 138.71, 136.09, 132.19, 129.16, 128.36, 127.15, 126.21, 121.13, 119.26, 117.56, 110.61, 108.80, 62.40, 50.14, 49.81, 23.73. Anal. Calcd for C₂₅H₂₃NS (326.35): C, 72.82; H, 6.73; N, 10.64. Found: C, 72.82; H, 6.73; N, 10.64.

5,6-Dihydro-1H-benz[a]carbazole (6)
α-Tetralone (3.30 g, 22.6 mmol), 2-fluoroaniline (2.51 g, 22.6 mmol), and p-TsOH (cat., 25 mg) were combined in toluene (100 mL) and heated at reflux with removal of H₂O using a Dean–Stark trap. After 15 h the reaction was cooled to r.t., diluted with of toluene (100 mL) and washed with 5% aq. Na₂CO₃ (25 mL). The organic layer was separated, dried over anhyd Na₂SO₄, and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc–hexanes, 1:1) to give 6 as a yellow solid; yield: 253 mg (42%). An analytical sample was crystallized from EtOAc–hexane; mp 167–168 °C; Rₚ 0.40 (hexanes–CH₂Cl₂, 1:1).

1H NMR (CDCl₃): δ = 8.20 (br s, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.37 (d, J = 7.8 Hz, 1 H), 7.29–7.08 (complex m, 5 H), 6.74 (dd, J = 0.85, 2.1 Hz, 1 H).
13C NMR (CDCl₃): δ = 135.50, 134.60, 131.31, 128.08, 126.85, 123.55, 121.89, 121.52, 119.52, 119.43, 109.74, 99.43. Anal. Calcd for C₂₅H₁₉NS (309.35): C, 72.27; H, 4.55; N, 7.03. Found: C, 72.16; H, 4.37; N, 6.94.

2-Fluorobenzoic Acid-d₄ (11)
2-Benzyl-2,3,4,5-tetrahydro-1H-indole (3) was dissolved in anhyd THF (30 mL) under N₂ in an oven dried flask equipped with a reflux condenser. The solution was cooled to −78 °C and LDA·THF (1.5 M, 11 mL, 16.5 mmol) in cyclohexane was added via syringe. The reaction was stirred at −78 °C for 15 min, then warmed to r.t. and heated to reflux under an atmosphere of N₂. After 5 h at reflux the reaction was cooled to r.t., quenched with H₂O (3 mL) and concentrated in vacuo. The residue was partitioned between H₂O (30 mL) and CH₂Cl₂ (100 mL). The organic layer was separated, dried over anhyd Na₂SO₄, and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc–hexanes, 1:1) to give 7 as a tan solid; yield: 0.95 g (90%). An analytical sample was crystallized from EtOAc–hexane; mp 190 °C (lit. 186–188 °C); Rₚ 0.25 (EtOAc–hexanes, 1:10), blue-fluorescent spot.

1H NMR (CDCl₃): δ = 137.57, 137.08, 132.18, 128.83, 128.58, 127.33, 124.94, 121.49, 119.97, 119.30, 111.24, 98.61.
2-Fluorobenzamide-\(\text{NH}_3\) (20 mL) was added to the stirring solution by condensation (53%).

The title compound was prepared from 2-acetylthiophene and 2-fluoroaniline-\(\text{H}_2\) (3.05 g, 21.16 mmol) was treated with neat excess SOCl\(_2\) (16 g, 134 mmol) at reflux for 1.5 h and the SOCl\(_2\) evaporated in vacuo to give a greenish-brown oil. This oil was dissolved in CH\(_2\)Cl\(_2\) (50 mL) and the solution cooled in an ice bath while liquid NH\(_3\) (20 mL) was added to the stirring solution by condensation and the mixture was heated at reflux for 1.5 h. Distillation of approximately half of the reaction volume gave the desired product as a separate layer in the distillate, which was extracted with CH\(_2\)Cl\(_2\) (25 mL). The organic layer was separated and concentrated in vacuo leaving the desired aniline 13 as an orange liquid; yield: 0.94 g (53%).

2-Thien-2-yl-1H-indole-\(d_1\) (16)

The compound was prepared from 2-acetyliophene and 2-fluoroaniline-\(d_1\) (13) by the procedure described for indole 8 to give 16 as a tan solid.

3-(2-Fluorophenyl)amino)cyclohex-2-en-1-one (17)

1,2,3,9-Tetrahydro-9-methyl-4H-carbazole-4-one (20)

The title compound was prepared from 2-acetylthiophene and 2-fluoroaniline-\(\text{H}_2\) (3.05 g, 21.16 mmol) was treated with neat excess SOCl\(_2\) (16 g, 134 mmol) at reflux for 1.5 h and the SOCl\(_2\) evaporated in vacuo to give a greenish-brown oil. This oil was dissolved in CH\(_2\)Cl\(_2\) (50 mL) and the solution cooled in an ice bath while liquid NH\(_3\) (20 mL) was added to the stirring solution by condensation and the mixture was heated at reflux for 1.5 h. Distillation of approximately half of the reaction volume gave the desired product as a separate layer in the distillate, which was extracted with CH\(_2\)Cl\(_2\) (25 mL). The organic layer was separated and concentrated in vacuo leaving the desired aniline 13 as an orange liquid; yield: 0.94 g (53%).
2.43 (t, $J = 6.2$ Hz, 2 H), 2.12 (m, 2 H). $^{13}$C NMR (DMSO-$d_6$): $\delta =$ 192.78, 152.17, 135.80, 124.49, 122.35, 121.43, 120.14, 111.72, 111.45, 37.77, 23.38, 22.68.

(12) Longer reflux gives increasing amounts of the benzazepine side product discussed in the text.

(13) If desired the crude imine 3 can be distilled under reduced pressure to give a colorless oil; bp 170–172 °C (0.25 mmHg).
