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An improved synthesis of a novel α_{1A} partial agonist including a new two-step synthesis of 4-fluoropyrazole

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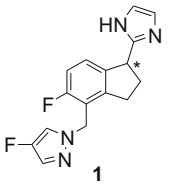
ABSTRACT

This Letter outlines a new two-step process for the synthesis of 4-fluoropyrazole and its application in an improved synthesis of 4-fluoro-1-[5-fluoro-1-(1*H*-imidazol-2-yl)-indan-4-ylmethyl]-1*H*-pyrazole. The original synthesis of 4-fluoro-1-[5-fluoro-1-(1*H*-imidazol-2-yl)-indan-4-ylmethyl]-1*H*-pyrazole is also described.

Compound **1** as a single enantiomer has been identified as a potent, partial agonist of the α_{1A} adrenergic receptor (K_i 5 nM, EC_{50} 9 nM, E_{max} 60%).[1]



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We required compound **1** as a single enantiomer on gram scale to assess its potential use as a treatment for stress urinary incontinence.

In this communication, the original synthesis of **1** and subsequent improvements to the route which enabled the synthesis of **1** to be performed on gram scale are described. The original route to **1** (Scheme 1) was designed to allow the exploration of the structure activity relationship (SAR) of the series. Intermediate **6** contains two synthetic handles (the methyl ester and cyano groups) which were utilised for late-stage functionalisation when exploring the SAR.

Compound **1** was initially synthesised on milligram scale in 17 steps.[1] Commercially available benzoic acid **2** was protected as the methyl ester with MeI and subsequently converted into cinnamic ester **3** via Heck coupling. Hydrogenation of the double bond, acidic cleavage of the *tert*-butyl ester and basic hydrolysis of the methyl ester gave diacid **4**. Intramolecular Friedel–Crafts cyclisation was achieved via conversion into the diacyl chloride in the presence of $AlCl_3$. The resulting indanonyl acyl chloride was treated with MeOH to give **5**. Reduction of the ketone with $NaBH_4$ followed by chlorination and displacement with NaCN gave nitrile **6**. Hydrolysis of the methyl ester to the carboxylic acid, activation with CDI and reduction with $NaBH_4$ gave the benzyl alcohol which was converted into intermediate **8** through chlorination and displacement with 4-fluoropyrazole. Treatment of the nitrile with a saturated solution of ethanolic HCl followed by reaction with aminoacetaldehyde dimethyl acetal and ring closure under acidic conditions furnished the target molecule. The active enantiomer was subsequently separated by chiral HPLC.

A more direct route was required to deliver **1** on gram scale for follow-up studies. Although benzoic acid **2** was protected as the methyl ester in the first step of the original route, the methyl ester was incompatible with intramolecular Friedel–Crafts step (f) and therefore had to be hydrolysed to the acid in step (e) and subsequently re-introduced. It was envisaged that **1** could be synthesised more efficiently by installing the 4-fluoropyrazole moiety early in the synthesis, thus avoiding several functional group interconversions and reducing the overall number of steps.

Retrosynthetically, we anticipated that the imidazole ring could be introduced via Negishi coupling of vinyl triflate **17**, which would be derived from indanone **16** (Scheme 2). We expected that synthesis of the indanone ring could be achieved either by Rh-catalysed cyclocarbonylation[2] of trimethylsilyl acetylene intermediate **15**, or by intramolecular Friedel–Crafts cyclisation of the corresponding propionic acid **14**. In a closely related analogue, where the 4-fluoropyrazole ring had been replaced with a methoxy group, we had successfully formed the indanone ring through Rh-catalysed cyclocarbonylation of a trimethylsilyl acetylene intermediate,[1] however, the Friedel–Crafts approach had proved unsuccessful due to displacement of the methoxy group by chloride.

The key obstacle to this new synthetic strategy was the synthesis of 4-fluoropyrazole in sufficient quantity to enable its introduction at the beginning of the route. Although several routes to 4-fluoropyrazole have been reported in the literature, most suffer from limitations that would preclude their use on large scale (lengthy syntheses

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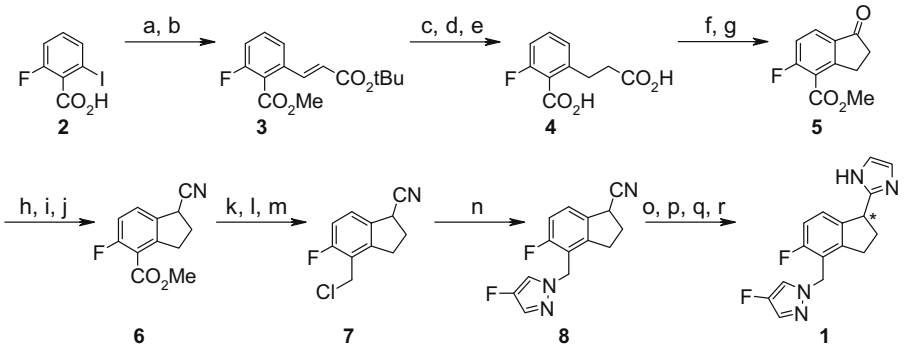


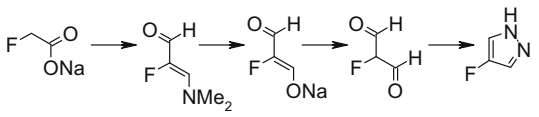
Scheme 1. Original route to **1**. Reagents and conditions: (a) MeI, DBU, acetone, 99%; (b) *tert*-butyl acrylate, $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, MeCN, 45 °C, 98%; (c) 50 psi H_2, Pd/C, EtOH, 89%; (d) TFA, CH_2Cl_2, quant.; (e) LiOH, H_2O, THF, quant.; (f) $(COCl)_2$, $AlCl_3$, cat. DMF, CH_2Cl_2, 15 °C to rt; (g) MeOH, 15 °C to rt, 83% over two steps; (h) $NaBH_4$, MeOH, quant.; (i) $SOCl_2$, CH_2Cl_2, quant.; (j) NaCN, DMSO, 63%; (k) LiOH, H_2O, THF, quant.; (l) CDI, THF, $NaBH_4$, quant.; (m) $SOCl_2$, CH_2Cl_2, 0 °C to rt, quant.; (n) 4-fluoropyrazole, NaH, THF, 5–80 °C, 58%; (o) HCl, EtOH, 5 °C, quant.; (p) aminoacetaldehyde dimethyl acetal, MeOH, quant.; (q) HCl, H_2O, reflux, 80%; (r) chiral HPLC, 81%.

requiring cryogenic conditions or ozone-depleting dichlorofluoromethane).[3–5] The shortest route that does not employ cryogenic conditions is a four-step synthesis from sodium fluoroacetate which provides 4-fluoropyrazole in 19% overall yield (Scheme 3).[6]

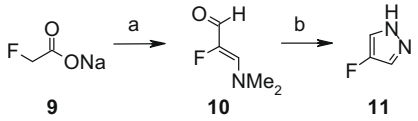
We envisaged that condensation of fluoroaminoacrolein intermediate **10** with hydrazine would deliver 4-fluoropyrazole directly and would provide a shorter alternative to converting **10** into the fluoromalonaldehyde. Pleasingly, the reaction proceeded cleanly and rapidly under acidic conditions, furnishing 4-fluoropyrazole in only two steps and in identical overall yield (Scheme 4).[7]

With this novel, short, scalable route to 4-fluoropyrazole in hand, we then decided to explore the synthesis of the indanone derivative **16** (Scheme 5). Benzylic bromination of 2-fluoro-6-iodotoluene **12** followed by displacement with 4-fluoropyrazole afforded intermediate **13**. This was subsequently converted into trimethylsilyl acetylene **15** by Sonogashira coupling and to propionic acid **14** by a modified one-pot procedure reported by Doucet and Santelli.[8] Heck coupling of intermediate **13** with acrolein ethylene acetal followed by hydrolysis gave the propionic acid **14** in good yield. Our modified procedure used P(*o*-tol)$_3$ as a cheaper alternative to the Tedicyp ligand, and replaced DMF with acetonitrile to facilitate subsequent solvent removal.

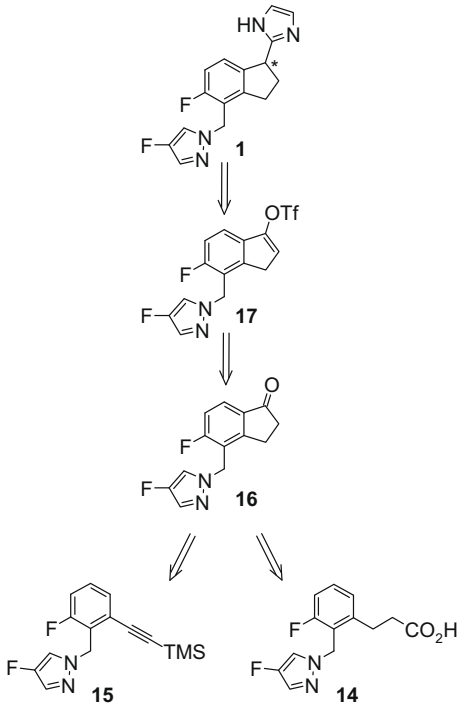
Intermediates **14** and **15** were used to investigate two routes to the indanone in parallel. The first (Rh-catalysed cyclocarbonylation of the trimethylsilyl acetylene **15**)[1,2] was unsuccessful, however,



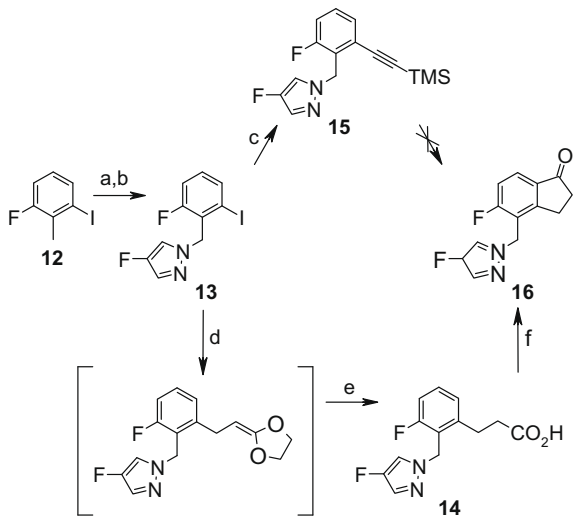
Scheme 3. A reported four-step synthesis of 4-fluoropyrazole.



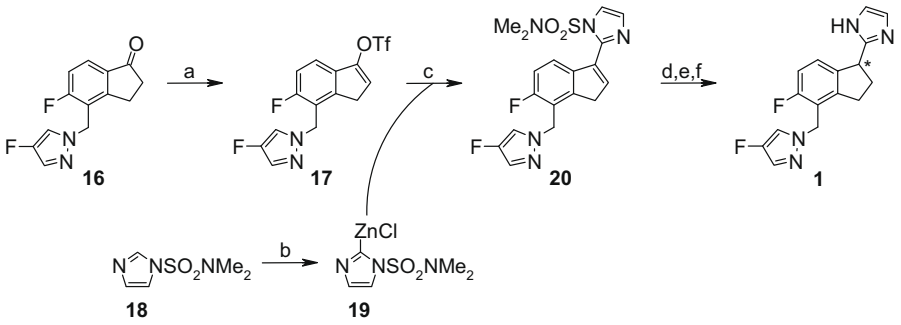
Scheme 4. Improved 4-fluoropyrazole synthesis. Reagents and conditions: (a) (i) $(COCl)_2$, DMF; (ii) Et_3N; (iii) K_2CO_3 (aq), 0–80 °C, 24%; (b) $H_2NNH_2{\cdot}2HCl$, EtOH, 55 °C, 77%.



Scheme 2. Retrosynthetic strategy to a key vinyl triflate intermediate.



Scheme 5. Approaches to indanone intermediate **16**. Reagents and conditions: (a) NBS, benzoyl peroxide, CCl_4, reflux, 75%; (b) 4-fluoropyrazole, NaH, THF, reflux, 95%; (c) trimethylsilyl acetylene, $Pd(PPh_3)_4$, Et_3N, CuI, DMF, 78%; (d) acrolein ethylene acetal, $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, MeCN, 120 °C; (e) NaOH (aq), 80 °C, 79%; (f) (i) $(COCl)_2$, CH_2Cl_2, cat. DMF, 0 °C to rt; (ii) $AlCl_3$, 84%.



Scheme 6. Introduction of the imidazolyl moiety. Reagents and conditions: (a) Tf_2O, DTBMP, CH_2Cl_2, 93%; (b) (i) *n*-BuLi, THF; (ii) $ZnCl_2$; (c) $Pd(PPh_3)_4$, THF, 50 °C, 61% over two steps; (d) HCl (aq), EtOH, reflux, 79%; (e) 50 psi H_2, Pd/C, EtOH, 81%; (f) chiral HPLC, 81%.

the second (intramolecular Friedel–Crafts cyclisation of the propionic acid **14**) proceeded in good yield to afford indanone **16**.

As expected, the indanone was readily converted into the imidazole **1**. Facile conversion of indanone **16** into vinyl triflate **17** followed by formation of the imidazolylzinc intermediate **19** and Negishi coupling, cleavage of the sulfonyl urea unit and hydrogenation of the olefin gave **1** as a racemic mixture. The enantiomers were resolved using chiral HPLC to deliver **1** on gram scale as a single enantiomer for further characterisation (Scheme 6).

Experience with a closely related analogue indicates that asymmetric hydrogenation of the olefin could deliver compound **1** in enantioenriched form.[9] By analogy with the absolute stereochemistry of the active enantiomer of this analogue, we anticipate that the active enantiomer of **1** also has *R* stereochemistry.

In conclusion, we have developed a new, elegant two-step synthesis of 4-fluoropyrazole that enabled its early introduction in the synthesis of **1**, reducing the number of linear steps from 17 to 8 and delivering **1** on gram scale as a single enantiomer.

References and notes

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7. *Representative procedure to* **10**: A suspension of 5.00 g of sodium fluoroacetate (0.05 mol, 1 equiv) (*Caution*: very toxic) in DMF (35 mL) was cooled to 0 °C and 9.62 mL of oxalyl chloride (0.11 mol, 2.2 equiv) was added dropwise over 40 min. The reaction mixture was stirred at room temperature for 30 min, heated to 60 °C for a further 30 min, then cooled to 0 °C. Et_3N (13.9 mL, 0.10 mol, 2 equiv) was added dropwise over 20 min. The reaction mixture was stirred at 0 °C for 30 min then at 50 °C for 30 min. The reaction mixture was cooled to 0 °C and 10 mL of ice water was added followed by 65 mL of saturated K_2CO_3 solution, portion wise. The reaction mixture was heated at 80 °C for 30 min, then cooled to room temperature, diluted with a minimum volume of H_2O to dissolve the precipitate, 350 mL of brine was added and the aqueous extracted with CH_2Cl_2 (3×300 mL). The combined organics were dried over Na_2SO_4 and concentrated in vacuo to give a brown oil that was purified by flash column chromatography (neat EtOAc) to give 1.4 g (24%) of **10** as a brown oil.
   Representative procedure to **11**: 448 mg of hydrazine dihydrochloride (4.3 mmol, 1 equiv) was added to a solution of 500 mg of **10** (4.3 mmol, 1 equiv) in 1 mL of a 40% v/v solution of EtOH in H_2O and the resulting solution heated at 55 °C for 20 min. The reaction mixture was cooled to room temperature, basified to pH 9 with a saturated solution of $NaHCO_3$ and extracted with Et_2O (3×30 mL). The organics were combined, dried over $MgSO_4$ and most of the solvent removed by distillation to give 366 mg of **11** as a yellow oil (77% product by mass).
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9. Asymmetric hydrogenation of a closely related analogue (150 psi H_2, $RuCl_2$[(*S*)-BINAP], MeOH, 80 °C) resulted in an ee of 47%.