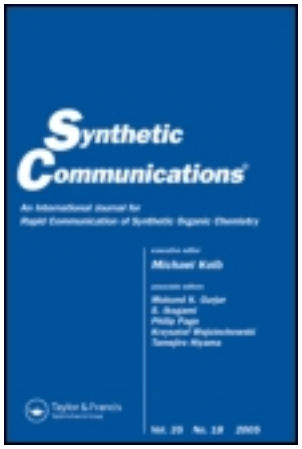

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Synthesis of Novel 4-Fluoro-2H-pyrazol-3-ylamines

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SYNTHESIS OF NOVEL 4-FLUORO-2H-PYRAZOL-3-YLAMINES

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A new and efficient synthesis for the preparation of novel 4-fluoro-2H-pyrazol-3-ylamines is described. It involves the reaction of an acyl chloride with fluoroacetonitrile and sequential ring closure of the α-fluoro-β-ketonitrile with hydrazine. Utilizing this synthetic protocol, we have synthesized a variety of 4-fluoro-2H-pyrazol-3-ylamines with different steric and electronic demands.

Keywords: Aminopyrazole; fluoro; 4-fluoro-2H-pyrazol-3-ylamines

The pyrazole ring continues to attract wide interest in medicinal chemistry. Compounds containing this heterocycle show a broad range of biological activities, including analgesic,[1] antimicrobial,[2] anti-inflammatory,[3] hypoglycemic,[4] and antihypertensive[5] activities. In particular, 3-aminopyrazole derivatives (3-AP, Fig. 1) have been reported as protein β-sheet stabilizers[6] and are largely used as building blocks for the preparation of molecules with potential biological activity.[7,8] 3-AP and their syntheses are widely described in the literature.[9–11]

These aminopyrazoles are usually prepared according to Scheme 1, in which the β-ketonitriles, obtained by the treatment of esters with CH_3CN and NaH/toluene or n-BuLi/tetrahydrofuran (THF), are cyclized with hydrazine in ethanol.

Recently, we have been interested in replacing the hydrogen in position 4 of these derivatives (3-AP) with fluorine (Fig. 1). The substitution of hydrogen atoms with fluorine is a very common strategy in medicinal chemistry and is widely used to improve the profile of a drug candidate.[12]

However, although the introduction of other halogens into the amino pyrazole core has been described in the literature,[13,14] very few examples have been reported on the synthesis of 4-fluoro-2H-pyrazol-3-ylamines (4-F-3-AP, Fig. 1). In these examples, fluorine has been introduced on the pyrazole ring using fluorinating agents

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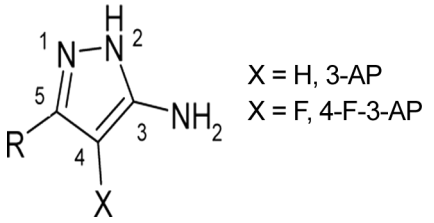
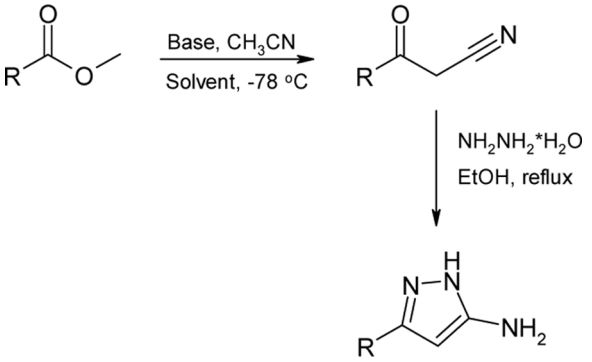


Figure 1. Generic structure of 3-AP and 4-F-3-AP.

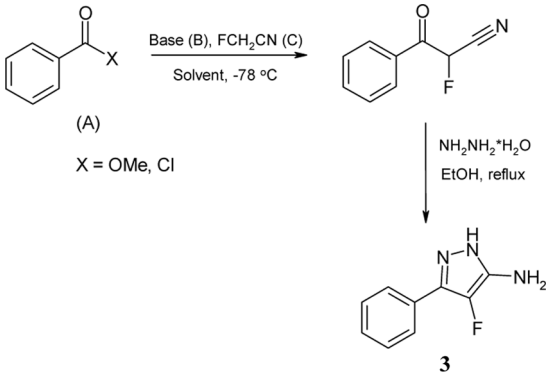
such as Selectfluor.[15] These reactions suffer from low general applicability, formation of a series of potential side products, and poor yields.

We investigated different synthetic approaches to prepare 4-F-3-AP, avoiding the use of fluorinating agents and their related drawbacks.

We initially explored the synthesis by applying the procedure reported for 3-AP, utilizing FCH_2CN instead of CH_3CN (Scheme 2). As a model compound, and to validate the approach, we utilized methyl benzoate as the starting material.



Scheme 1. Generic procedure for the synthesis of 3-AP.



Scheme 2. Validation for the synthesis of 4-F-3-AP.

Table 1. Validation of the synthesis of α-fluoro-β-ketonitrile

Entry	X	Base	Sequence addition	Result[a]
1	−OMe	n-BuLi	C-B-A	No conversion
2	−OMe	LDA	C-B-A	No conversion
3	−OMe	LDA	C-A-B	Product in traces
4	−Cl	LDA	C-A-B	50% conversion
5	−Cl	BTPP	C-A-B	No conversion
6	−Cl	LHMDS	C-A-B	95% conversion

[a]Evaluated by LCMS of the crude solution.

The effect of different addition conditions on the reaction outcome was investigated (Scheme 2, Table 1).

After the initial attempt with n-BuLi failed (entry 1), we examined the use of lithium diisopropylamide (LDA) as a less nucleophilic base (entry 2), to avoid the possible side reaction of n-BuLi with methyl benzoate. Both experiments failed, possibly because of the lower reactivity of the anion of FCH_2CN compared to the anion of CH_3CN.

Knowing that the possibility for FCH_2CN to polymerize in the presence of a base was likely, we decided to reverse the addition of reagents to limit the concentration of anion formed in the reaction (entry 3). With this change, traces of the desired β-ketonitrile were detected in the liquid chromatography–mass spectrometry (LCMS) chromatogram of this reaction, confirming the approach.

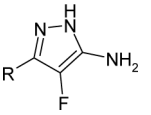
We believed that the nucleophilicity of the anion of FCH_2CN was not sufficient for the reaction with a moderately electrophilic ester, so the acyl chloride was chosen in an attempt to increase the reactivity (entry 4). The 50% conversion confirmed the need for more reactive acyl chlorides. A simple screen for alternative bases allowed optimization of the reaction approach. The use of phosphazene base tert-butyliminotri(pyrrolidino)phosphorane (BTPP, entry 5) was unsuccessful, while lithium bis(trimethylsilyl)amide (LHMDS, entry 6) afforded near quantitative yield of the desired penultimate intermediate. The subsequent ring closure to 4-F-3-AP was achieved by refluxing the α-fluoro-β-ketonitrile with $NH_2NH_2 \cdot H_2O$ in ethanol. These conditions were applied to a small set of molecules, selecting commercially available acyl chlorides with different electronic and steric demands to evaluate the scope of the reaction (Table 2).

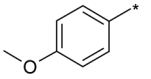
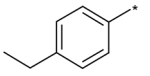
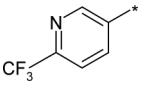
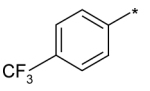
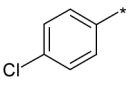
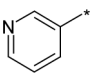
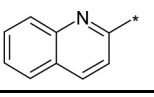
All products were isolated and characterized by NMR and high-performance liquid chromatography (HPLC). Both aromatic and aliphatic acyl chlorides gave the desired products in moderate to good yields, demonstrating the extendibility and reliability of the reaction conditions.

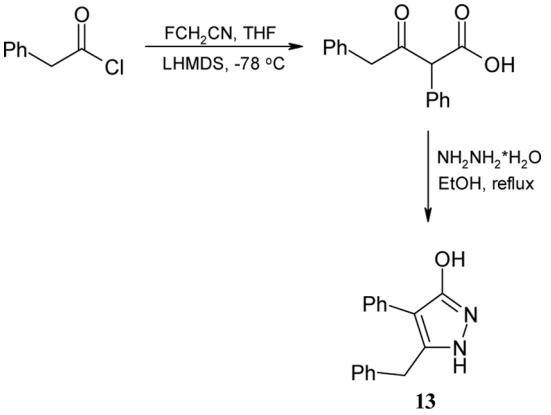
In an attempt to broaden the scope of this reaction, we examined the application of the same conditions to phenacetyl chlorides. To our dismay, this resulted in a drastic change in the reaction profile. In this case, the competitive reaction between two phenacetyl chloride molecules was predominant, and total conversion to 5-benzyl-4-phenyl-1H-pyrazol-3-ol was observed (**13**, Scheme 3).

In summary, a new and efficient synthesis of novel 4-fluoro-3-aminopyrazoles was developed, and its utility was showcased in the preparation of a small set of molecules obtained in fair to good yields.

Table 2. Yields of 4-F-3-AP (isolated yields over two steps)



Compound	R	Yield (%)
1		52
2		37
3		55
4		39
5		54
6		40
7		74
8		45
9		74
10		41
11		68
12		37



Scheme 3. Application of the conditions described to phenacetyl chloride.

The order of addition of the reagents and the choice of base were fundamental factors contributing to the success of the approach. This reaction is applicable to both aromatic and aliphatic acyl chlorides, with the exception of phenacetylchloride (and probably analog molecules).

EXPERIMENTAL

General Experimental Method

All solvents and reagents were used as supplied, unless otherwise stated. Reactions using air/moisture-sensitive reagents were run under a nitrogen atmosphere. Purifications were performed with flash silica-gel cartridges from Merck. All thin-layer chromatographic (TLC) analyses were performed on silica gel, and spots were revealed by ultraviolet (UV) visualization at 254 nm and $KMnO_4$ stain. Characterization of the compounds **1**–**13** was determined by HRMS; NMR spectra were recorded using a 400-MHz spectrometer. Chemical shifts are reported in parts per million referred to the solvent (s: singlet, d: doublet, t: triplet, dd: double doublet, m: multiplet). LCMS 5- and 10-min methods were run with 0.1% formic acid/water and 0.1% formic acid/acetonitrile with gradients 5/95 to 95/5 using C18, 3-μm, 2.0- × 50.0-mm column. Electrospray ionization (ESI) and photodiode array (PDA) detection were used.

Generic Procedure for 4-Fluoro-2H-Pyrazol-3-ylamines

A 1 M solution of LHMDS in THF (10 mL, 10.0 mmol, 2.0 eq) was added dropwise to a solution of acyl chloride (5.0 mmol, 1.0 eq) and FCH_2CN (278 μL, 5.0 mmol, 1.0 eq) in dry THF (15 mL) cooled to −78 °C under nitrogen. The mixture was allowed to reach room temperature, and 1N HCl was added dropwise at pH 2. The mixture was concentrated under reduced pressure to afford the desired α-fluoro-β-ketonitrile in a form pure enough for the next step.

Hydrazine monohydrate (582 μL, 12.0 mmol, 2.4 eq) was added to a solution of the α-fluoro-β-ketonitrile (5.0 mmol) in EtOH (15 mL), and the reaction was heated at reflux for 18 h. The reaction mixture was allowed to cool to room temperature, and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (DCM) and washed with water. The organic phase was concentrated to give a crude product that was purified by SiO_2 column. Yields were between 37% and 74%.

Spectroscopic and Analytical Data

4-Fluoro-5-(4-methyoxy-phenyl)-2H-pyrazol-3-ylamine (1). Following the general procedure described previously, 538 mg of title compound were obtained as a light brown powder (52% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm): 3.83 (s, 3H), 4.34 (s, 2H), 7.02 (d, $J = 8.98$ Hz, 2H), 7.65 (d, $J = 8.48$ Hz, 2H), 10.99 (s, 1H). ^{19}F NMR (376 MHz, acetone-d_6) δ (ppm): −190.55 (s, 1F). MS (ESI): m/z 208 $[M + H^+]^+$; LC Rt = 2.00 min (10-min method). HRMS calcd. for $C_{10}H_{11}FN_3O$ 208.08807; found 208.08823.

5-Cyclopropyl-4-fluoro-2H-pyrazol-3-ylamine (2). Following the general procedure described previously, 261 mg of title compound were obtained as a light brown powder (37% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.66–0.70 (m, 2H), 0.79–0.84 (m, 2H), 1.67–1.74 (m, 1H), 4.50 (s, 2H), 11.11 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): −193.076 (s, 1F). MS (ESI): m/z 142 $[M + H^+]^+$; LC Rt = 0.53 min (10-min method). HRMS calcd. for $C_6H_9FN_3$ 142.07750; found 142.07730.

4-Fluoro-5-phenyl-2H-pyrazol-3-ylamine (3). Following the general procedure described, 563 mg of title compound were obtained as a light brown powder (55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.80 (s, 2H), 7.28–7.32 (m, 1H), 7.41–7.45 (m, 2H), 7.62–7.64 (m, 2H), 11.88 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): −186.91 (s, 1F). MS (ESI): m/z 178 $[M + H^+]^+$; LC Rt = 1.92 min (10-min method). HRMS calcd. for $C_9H_9FN_3$ 178.07750; found 178.07728.

5-(4-Ethyl-phenyl)-4-fluoro-2H-pyrazol-3-ylamine (4). Following the general procedure described, 399 mg of title compound were obtained as a light brown powder (39% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm): 1.23 (t, $J = 7.60$ Hz, 3H), 2.66 (q, $J = 7.60$ Hz, 2H), 4.36 (s, 2H), 7.64 (d, $J = 8.19$ Hz, 2H), 7.30 (d, $J = 8.24$ Hz, 2H), 11.01 (s, 1H). ^{19}F NMR (376 MHz, acetone-d_6) δ (ppm): 189.71 (s, 1F). MS (ESI): m/z 206 $[M + H^+]^+$; LC Rt = 2.73 min (10-min method). HRMS calcd. for $C_{11}H_{13}FN_3$ 206.10880; found 206.10865.

4-Fluoro-5-(6-trifluoromethyl-pyridin-3-yl)-2H-pyrazol-3-ylamine (5). Following the general procedure described, 246 mg of title compound were obtained as a light brown powder (54% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm): 7.95 (d, 1H, $J = 8.24$ Hz), 8.42 (d, 1H, $J = 8.24$ Hz), 9.17 (s, 1H). ^{19}F NMR (376 MHz, acetone-d_6) δ (ppm): −68.77 (s, 3 F), −178.84 (s, 1F). MS (ESI): m/z 247 $[M + H^+]^+$; LC Rt = 2.28 min (10 min method). HRMS calcd. for $C_9H_7F_4N_4$ 247.06014; found 247.06003.

4-Fluoro-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine (6). Following the general procedure described, 490 mg of title compound were obtained as a light brown powder (40% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.96 (s, 2H), 7.79 (d, 2H, $J = 8.47$ Hz), 7.86 (d, 2H, $J = 8.26$ Hz), 12.14 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): −61.96 (s, 4 F), −191.70 (s, 1F). MS (ESI): m/z 246 $[M + H^+]^+$; LC Rt = 1.97 min (5-min method). HRMS calcd. for $C_{10}H_8F_4N_3$ 246.06489; found 246.06472.

5-(4-Chloro-phenyl)-4-fluoro-2H-pyrazol-3-ylamine (7). Following the general procedure described, 780 mg of title compound were obtained as a light brown powder (74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.88 (s, 2H), 7.50 (d, 2H, $J = 8.4$ Hz), 7.65 (d, 2H, $J = 8.4$ Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): −189.06 (s, 1F). MS (ESI): m/z 212 $[M + H^+]^+$; LC Rt = 2.61 min (10-min method). HRMS calcd. for $C_9H_8ClFN_3$ 212.03853; found 212.03837.

5-*tert*-butyl-4-fluoro-2H-pyrazol-3-ylamine (8). Following the general procedure described, 353 mg of title compound were obtained as a light brown powder (45% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm): 1.32 (s, 9H), 4.07 (s, 2H), 10.35 (s, 1H). ^{19}F NMR (376 MHz, acetone-d_6): δ (ppm): −189.83 (s, 1F). MS (ESI): m/z 158 $[M + H^+]^+$; LC Rt = 1.20 min (5-min method). HRMS calcd. for $C_7H_{13}FN_3$ 158.10880; found 158.10867.

4-Fluoro-5-thiophen-2-yl-2H-pyrazol-3-ylamine (9). Following the general procedure described, 677 mg of title compound were obtained as a light brown powder (74% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm): 4.56 (s, 2H), 7.14–7.17 (m, 1H), 7.40–7.42 (m, 1H), 7.49–7.52 (m, 1H), 11.18 (s, 1H). ^{19}F NMR (376 MHz, acetone-d_6) δ (ppm): −180.37 (s, 1F). MS (ESI): m/z 184 $[M + H^+]^+$; LC Rt = 1.78 min (10-min method). HRMS calcd. for $C_7H_7FN_3S$ 184.03392; found 184.03380.

5-Cyclopentyl-4-fluoro-2H-pyrazol-3-ylamine (10). Following the general procedure described, 346 mg of title compound were obtained as a light brown powder (41% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm): 1.61–1.79 (m, 6H), 1.96 – 2.06 (m, 2H), 2.95–3.06 (m, 1H), 4.09 (s, 1H), 10.40 (s, 1H). ^{19}F NMR (376 MHz, acetone-d_6) δ (ppm): −193.04 (s, 1F). MS (ESI): m/z 170 $[M + H^+]^+$; LC Rt = 1.63 min (10-min method). HRMS calcd. for $C_8H_{13}FN_3$ 170.10880; found 170.10899.

4-Fluoro-5-pyridin-3-yl-2H-pyrazol-3-ylamine (11). Following the general procedure described, 605 mg of title compound were obtained as a light brown powder (68% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.95 (s, 2H), 7.44–7.49 (m, 1H), 7.97–8.00 (m, 1H), 8.49–8.51 (m, 1H), 8.85–8.87 (m, 1H), 12.03 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): −189.96 (s, 1F). MS (ESI): m/z 178 $[M + H^+]^+$; LC Rt = 0.21 min (10-min method). HRMS calcd. for $C_8H_8FN_4$ 179.07275; found 179.07250.

4-Fluoro-5-quinolin-2-yl-2H-pyrazol-3-ylamine (12). Following the general procedure described, 421 mg of title compound were obtained as a light brown powder (37% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.83 (s, 2H), 7.57–7.62 (m, 1H), 7.76–7.82 (m, 2H), 7.91–8.00 (m, 2H), 8.41–8.46 (m, 1H), 12.26 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): −186.02 (s, 1F). MS (ESI): m/z 229

$[M + H^+]^+$; LC Rt = 2.07 min (10-min method). HRMS calcd. for $C_{12}H_{10}FN_4$ 229.08840; found 229.08825.

5-Benzyl-4-phenyl-1H-pyrazol-3-ol (13). Following the general procedure described, 650 mg of title compound were obtained as a light brown powder (52% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 2H), 4.14 (s, 2H), 7.16–7.35 (m, 8H), 7.50–7.52 (m, 2H), 10.47 (s, 1H, br). MS (ESI): m/z 251 $[M + H^+]^+$; LC Rt = 1.92 min (10-min method). HRMS calcd. for $C_{16}H_{15}N_2O$ 251.11789; found 251.11773.

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