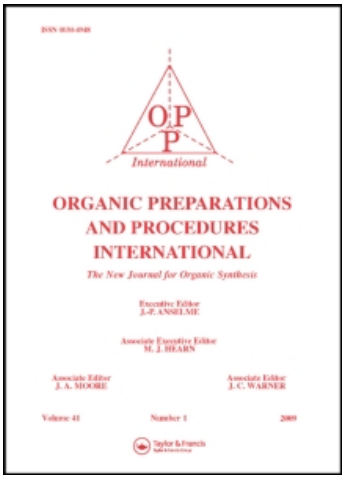

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AN IMPROVED SYNTHESIS OF 3-CYANO-4-FLUOROBENZYL BROMIDE

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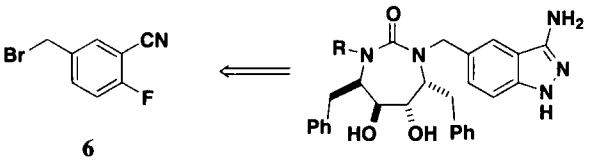
A key feature in the enhanced HIV protease inhibitory activity of our recently reported cyclic ureas,[1-4] such as drug candidates DMP850 (**1**) and DMP851 (**2**),[2] is the presence of a 3-aminoindazole P2 substituent. The 3-aminoindazole groups are introduced into these compounds by

N-alkylation of ureas with 3-cyano-4-fluorobenzyl bromide (**6**), followed by treatment with hydrazine.[1]



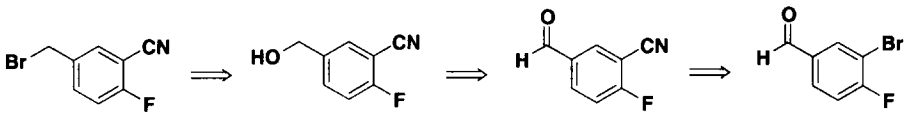
1 R = benzyl K_i = 0.031 nM

2 R = *n*-butyl K_i = 0.021 nM

6

Benzylic bromide **6** was initially prepared by standard radical bromination (NBS, cat. benzoyl peroxide, CCl_4, reflux) of 3-cyano-4-fluorotoluene. As is typically observed for this type of bromination reaction, the desired bromide **6** was produced contaminated by unreacted starting material and the dibrominated product. Isolation of pure bromide **6** required extensive and tedious flash column chromatography followed by recrystallization to provide only ca. 50% yield. Although 3-cyano-4-fluorotoluene is commercially available,[5] it is prohibitively expensive for scale-up work. The literature synthesis[6] reports a two-step preparation. Our in-house synthesis of this starting material proceeded in 80% yield. Thus the overall yield of **6** in this initial synthesis was only 40%.

Our requirement for larger amounts of **6**, coupled with the poor bromination yield and difficult purification process, led us to seek an improved synthesis which would avoid the radical bromination step. Retrosynthetic analysis showed that **6** could be obtained from an alternate and less expensive starting material (**3**).[7] We herein report a much more efficient, scalable three step synthesis of target compound **6** from **3**.



6 **5** **4** **3**

3-Bromo-4-fluorobenzaldehyde (**3**) was treated with a small excess of copper(I) cyanide in hot N-methylpyrrolidinone[8] (NMP) until TLC analysis showed complete consumption of **3**. Filtration through a Celite pad to remove copper salts, extractive work-up, and concentration gave crude nitrile **4** still containing some residual NMP. This nitrile was readily purified by flash chromatography to deliver **4** cleanly in 85% yield. The aldehyde group of **4** was reduced under standard $NaBH_4$ conditions to produce pure benzylic alcohol **5** in excellent yield (96%). Finally, alcohol **5** was converted into the desired benzylic bromide **6** by reaction with slight excesses of NBS and Ph_3P in dichloromethane.[8] Simple flash chromatography provided **6** in 91% yield of excellent purity. The oily product **6** eventually became a solid which melts very slightly above room temperature.

In summary, we have devised a new route to our key reagent **6** which proceeded conveniently on a reasonably large scale in only three steps and an overall yield of 74%.

EXPERIMENTAL SECTION

Commercial reagents were used without further purification. Melting points were determined on a Thomas/Hoover apparatus in open capillary tubes and are uncorrected. TLC analyses were performed on E. Merck silica gel 60 F_{254} plates in EtOAc/hexane solvent systems with UV detection. Flash chromatography was conducted with E. Merck Kieselgel 60 F_{254} silica gel. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR instrument. NMR spectra were recorded using a Varian Unity 300 spectrometer. Mass spectral data were obtained on a Finnigan MAT 8230 or VG 70-VSE with NH_3 chemical ionization. Elemental analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ.

WARNING: Title compound **6** is a ***powerful*** lacrymator and should be handled only by experienced personnel taking all necessary safety precautions.

3-Cyano-4-fluorobenzaldehyde (4).- 3-Bromo-4-fluorobenzaldehyde[7] (150 g, 740 mmol) and CuCN (76 g, 844 mmol) were mixed with NMP (270 mL) in a 3 liter RB flask with efficient mechanical stirring. The mixture was slowly warmed over several hours until the bath temperature reached 170°, then held at that temperature for 24h. The temperature was then reduced to 80° and Celite (ca. 200 g) was added. While the reaction mixture was stirred at 80°, EtOAc (2.5 L) and water (1.5 L) were added *via* an addition funnel. Heating was discontinued and the cooled reaction mixture was filtered through a pad of Celite (ca. 300 g). After rinsing the solids with EtOAc (1.5 L), the two phases of the filtrate were separated. The organic phase was extracted with half-saturated brine (2 x 500 mL), then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was flash chromatographed on silica gel and eluted with a gradient of hexane to 24% EtOAc in hexane; the solution was evaporated *in vacuo* and the residue dried to yield 93.7 g (85%) of **4** as a colorless crystalline solid, mp. 85.5-87.5°. IR (KBr): 2237, 1702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.00 (s, 1H), 8.21-8.15 (m, 2H), 7.43 (t, J = 8 Hz, 1H). ^{19}F NMR ($CDCl_3$): δ -97.02. MS (*m/e*) 150 ($M + H^+$). HRMS (*m/e*) calc'd for $M + H^+$: 150.0355, found: 150.0330.

Anal. Calcd for C_8H_4FNO: C, 64.43; H, 2.70; N, 9.39; F, 12.74
Found: C, 64.36; H, 2.64; N, 9.40; F, 12.59

3-Cyano-4-fluorobenzyl Alcohol (5).- Sodium borohydride (12.7 g, 340 mmol) was added in small portions over 45 min to a stirred solution of aldehyde **4** (50 g, 340 mmol) in MeOH (500 mL) cooled to 0°. After an additional 40 min, the mixture was concentrated *in vacuo*, then extracted with EtOAc (2 L) and water (2 x 1 L), then brine (100 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Drying under high vacuum provided 49.2 g, (96%) of **5** as a pale yellow crystalline solid, mp. 52-53.5°. IR (KBr): 3328, 2234, 1499 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.66-7.60 (m, 2H), 7.21 (t, J = 9 Hz, 1H), 4.72 (s, 2H), 2.21 (br s, 1H). ^{19}F NMR ($CDCl_3$): δ -109.00. ^{13}C NMR ($CDCl_3$): δ 162.32 (d, J = 258 Hz), 138.70 (d, J = 3 Hz), 133.54 (d, J = 8 Hz), 131.41, 116.41 (d, J = 19 Hz), 114.03, 100.93 (d, J = 15 Hz), 62.99. MS (*m/e*) 152 ($M + H^+$). HRMS (*m/e*) calc'd for M^+: 151.0433, found: 151.0436.

Anal. Calcd for C_8H_6FNO: C, 63.58; H, 4.00; N, 9.28; F, 12.57
Found: C, 63.58; H, 4.10; N, 9.22; F, 12.46

3-Cyano-4-fluorobenzyl Bromide (6).- N-Bromosuccinimide (56.7 g, 319 mmol) was added to a stirred 0° solution of alcohol **5** (45.8 g, 303 mmol) and Ph_3P (83.5 g, 318 mmol) in CH_2Cl_2 (1 L). The mixture was allowed to slowly warm to RT overnight. The entire mixture was absorbed onto silica gel (500 g) by evaporation *in vacuo*, then it was chromatographed on silica gel and eluted with a gradient of hexane to 20% EtOAc in hexane. Concentration *in vacuo* and drying under high vacuum yielded 58.7 g (91%) of **6** as a pale yellow oil. IR (KBr): 2238, 1614, 1502 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.68-7.61 (m, 2H), 7.21 (t, J = 9 Hz, 1H), 4.45 (s, 2H). ^{19}F NMR ($CDCl_3$): δ -106.85. ^{13}C NMR ($CDCl_3$): δ 162.65 (d, J = 260 Hz), 135.86 (d, J = 8 Hz), 135.23 (d, J = 4 Hz), 133.88, 117.06 (d, J = 20 Hz), 113.42, 101.85 (d, J = 16 Hz), 30.50. MS (*m/e*) 214 ($M + H^+$).

Anal. Calcd for C_8H_5BrFN: C, 44.89; H, 2.35; N, 6.54; Br, 37.33; F, 8.89

Found: C, 44.55; H, 2.31; N, 6.39; Br, 37.38; F, 9.00

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