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Efficient synthesis of 2-trihalomethyl-5-cyanopyridines

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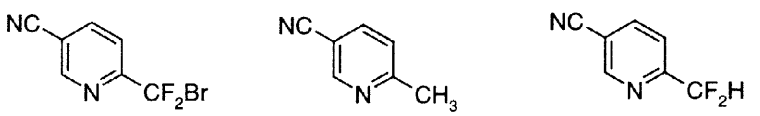
Abstract

Efficient and practicable routes to 2-trifluoromethyl-5-cyanopyridine, 2-bromodifluoromethyl-5-cyanopyridine and 2-chlorodifluoromethyl-5-cyanopyridine have been developed.

To support the pre-clinical investigation of a compound in early development we required an efficient synthesis of 2-bromodifluoromethyl-5-cyanopyridine **1** (Scheme 1).

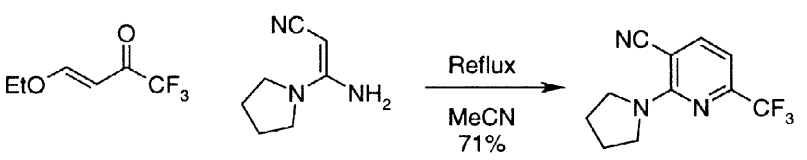
Scheme 1



1 **2** **3**

Early efforts focussed on the elaboration of 2-methyl-5-cyanopyridine **2** via 2-difluoromethyl-5-cyanopyridine **3**. However, in spite of considerable effort, an overall yield of only 4% was achieved in a process which included photolytic bromination and chromatography. Due to the difficulties encountered in halogenating the methyl group we decided to explore a route from acyclic precursors which incorporated a fully halogenated methyl group. A paper by Cocco *et al*[1] alerted us to the possibility of forming pyridines of a similar type from acyclic precursors such as the trifluoromethyl enone **4** and enaminonitrile **5** (see Scheme 2).

Scheme 2



4 **5**

We sought to investigate the applicability of this reaction to our own case which would require only a single activating amino group in the enaminonitrile so as to leave the 6-position unsubstituted. Furthermore, since aminoacrylonitrile is not commercially available we used a 2 stage procedure so as to exploit the readily available dimethylaminoacrylonitrile **6**. As a model system we reacted the dimethylaminoacrylonitrile **6** with enone **4** to give the enaminoenone **7** as an orange solid[2] in 73% yield after crystallisation. To effect cyclisation the enaminoenone **7** was treated with ammonium acetate in DMF[3] to give crude 2-trifluoromethyl-5-

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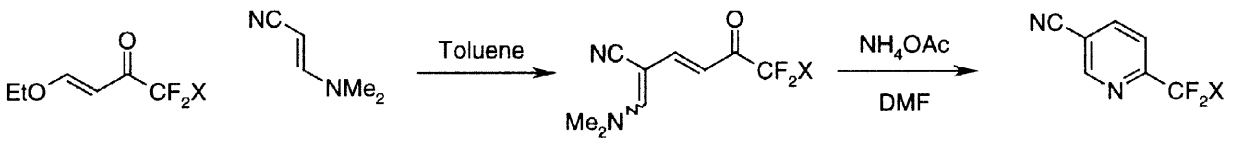
cyanopyridine **8** as a red solid in 82% yield (Scheme 3). Distillation afforded **8** as a white solid with 70% recovery.

Scheme 3



4 X=F
9 X=Br
10 X=Cl

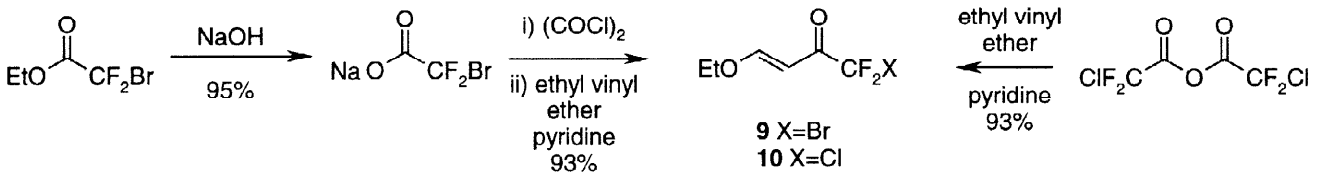
6

7 X=F, 73%
11 X=Br, 60%
12 X=Cl, 79%

8 X=F, 82%
1 X=Br, 80%
13 X=Cl, 84%

To apply this route to the preparation of **1**, the bromodifluoromethyl enone **9** was required. The chloro analogue **13** was also of interest as a potential alkylating agent. Bromodifluoromethyl enone **9** was not commercially available nor was the chlorodifluoromethyl enone **10** but both were prepared by modification of literature procedures[4] from available materials in 3 steps and 1 step respectively (Scheme 4).

Scheme 4



9 X=Br
10 X=Cl

The two enones were readily converted through to the pyridines in good yield (Scheme 3). In the case of the chloro enaminoenone **12**, NOE was used to establish the geometry about the enamine double bond as Z (*ie* as shown). For the enaminoenone **11** it was found that only the Z isomer reacted to give the pyridine **1**. In order to maximise the yield of Z-**11** small amounts (10mol%) of triethylamine were added which had the effect of catalysing double bond isomerisation.

Typical experimental procedure[5]

The enone **4** (23.0g, 0.137mol) was dissolved in toluene (23ml) and treated with the enamine **6** (13.2g, 0.137mol) while stirring at 20°. The red-brown solution was heated at *ca* 100° for *ca* 2h until TLC (silica, ethyl acetate/*i*-hexane 1:1, R_f 0.17 for the product) showed complete consumption of the starting materials. To the hot solution was added *i*-octane (95ml) and the resulting slurry was cooled to *ca* 10° and the solid collected by filtration, washed with toluene/*i*-octane (1:3, 50ml) and dried in vacuum oven at 45° overnight. The enaminoenone **7** was isolated as an orange solid (21.8g, 0.100mol) in 73% yield. Mp 158-160°, MS (ES^+) 219 (MH^+, 100%), ^{1}H NMR (d_6-DMSO): 3.26 (3H, s, Me), 3.38 (3H, s, Me), 6.05 (1H, d, J = 12Hz, α-CH), 7.91 (1H, d, J = 12Hz, β-CH), 8.01 (1H, s, δ-CH). ^{13}C NMR (d_6-DMSO): 37.11 (Me), 46.08 (Me), 76.77 (C), 101.70 (CH), 115.36 (CN), 115.63 (q, J = 292Hz, CF_3), 152.99 (CH), 159.43 (CH), 174.87 (q, J = 32Hz, CO). The enaminoenone **7** (10.0g, 0.0459mol) was dissolved in DMF (50ml), treated with ammonium acetate (5.3g, 0.068mol) and the resulting deep red solution stirred at 20° overnight. The solution was diluted with water (100ml) and extracted with toluene (3 x 150ml). The combined toluene extracts were washed with water (2 x 100ml) and brine (100ml) then concentrated in *vacuo* to give a red oil which crystallised on standing (6.5g, 0.0378mol, 82% yield). The crude material was purified by vacuum distillation (bp 36-41°/0.1-0.2mbar) to give a clear, colourless liquid which crystallised on standing to give 2-trifluoromethyl-5-cyanopyridine **8** as a white, crystalline solid (4.6g, 0.0267mol) in 58% overall yield. Mp 36-37°, MS (CI^-) 172 (M^-, 100%), ^{1}H NMR ($CDCl_3$): 7.90 (1H, d, J = 8Hz), 8.27 (1H, dd, J = 8 and 2Hz), 9.03 (1H, d, J = 2Hz). ^{13}C NMR ($CDCl_3$): 113.32 (C), 115.67 (CN), 120.99 (q, J = 275Hz, CF_3), 121.00 (CH), 141.70 (CH), 151.20 (q, J = 36Hz, C2), 152.83 (CH).

References

[1] Cocco MT, Congiu C and Onnis V. *J. Heterocycl. Chem.* 1995, **32**, 543-545.
[2] Isolated as essentially a single double bond isomer.
[3] Initially this cyclisation was carried out with ammonia in methanol which gave rise to unidentified by-products.
[4] Colla A, Martins MAP, Clar G, Krimmer S and Fischer P. *Synthesis* 1991, 483-486.
[5] We are grateful to Eleanor Wright, a work experience student, for repeating some experiments.