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CONVENIENT ACCESS TO 2-PYRIDYLINDOLE CYTOTOXIC ANTICANCER AGENTS

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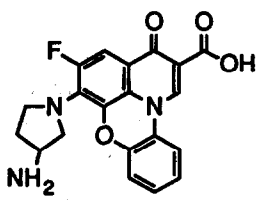
Summary: The regiospecific synthesis of highly substituted 2-pyridylindoles has been accomplished via a three step reaction sequence which involves the unique formation of the synthetically flexible pyridine intermediate 2.

Recently, heterocyclic fused systems containing the 2-pyridylindole skeleton have been claimed to exhibit antitumor,[5] antiviral,[6] and antidepressive[7] activity. During synthetic investigations involving attempts to optimize cytotoxic antitumor activity of quinolone **1**, we discovered a moderately efficient preparation of pyridine **2** which provides ready access to cytotoxic 2-pyridylindole **3**. Herein, we wish to report the unique chemistry that affords convenient access to synthetically useful tetrasubstituted pyridines such as **2**.



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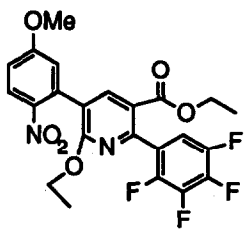

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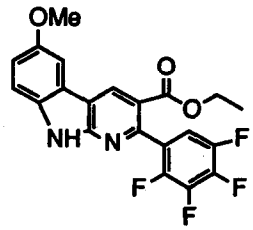
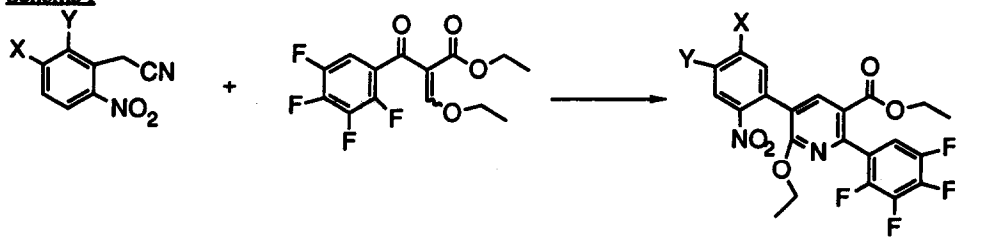


3

5-Methoxy-2-nitrophenyl acetonitrile **4a** was prepared according to established procedures.[8] Treatment of **4** with 2 equivalents[9] of sodium bis (trimethylsilyl) amide in dry THF (0.05M) at -78° C for 30 minutes, followed by the dropwise addition of 1.1 equivalents of enol ether **5**,[10] led after warming to -20° C (1.5 hours) to the direct formation of tetrasubstituted pyridine **2** (Scheme I). Isolated yields of **2** were generally 35-45%, and the product was purified by column chromatography (silica gel, CH_2Cl_2/ hexanes 3:7). The corresponding 4,5-dimethoxy-2-nitrophenyl acetonitrile[11] **4b** and 5-fluoro-2-nitrophenyl acetonitrile **4c** gave similar results. Although the ^{1}H NMR spectrum at 300 MHz, and the mass and IR spectra supported the assigned structure, the assignment was unambiguously confirmed by X-ray crystallographic determination.[12] An ORTEP projection of **2a** is shown in Figure 1.

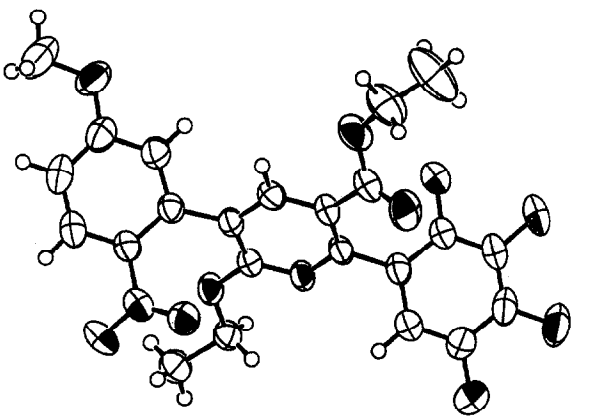
Scheme I



4 5 2

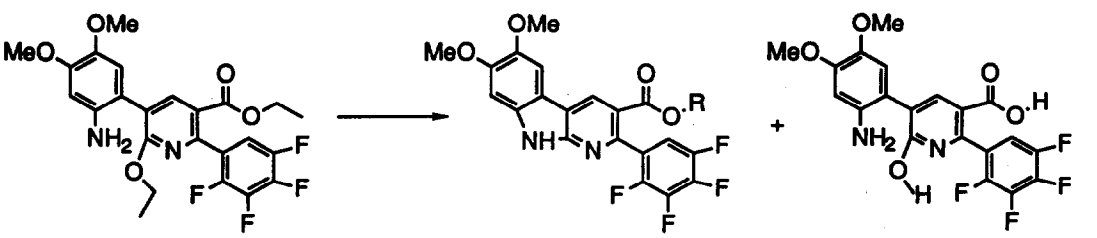
a X= OMe, Y= H
b X= OMe, Y= OMe
c X= F, Y= H

Figure I



The 4,5-dimethoxy-2-nitro analog **2b** was reduced in high yields (90%) by catalytic hydrogenation (10% Pd(C), ethyl acetate, r.t.) to amino pyridine **6**. There is certainly much precedent for the amination of 2-hydroxy pyridines via their corresponding chloro derivatives,[13] trimethylsilyl ethers,[14] or by direct acid catalyzed dehydration.[15] We found that simply heating amino pyridine **6** in a 1:2 mixture of dioxane and 10% aqueous solution of HCl at 90° C for 2.5 days provided an easy separable mixture of indole ester **7**,[16] indole acid **8**, and hydroxy pyridine **9** in 75% yield in a ratio of 3:6:1 (Scheme II).[17]

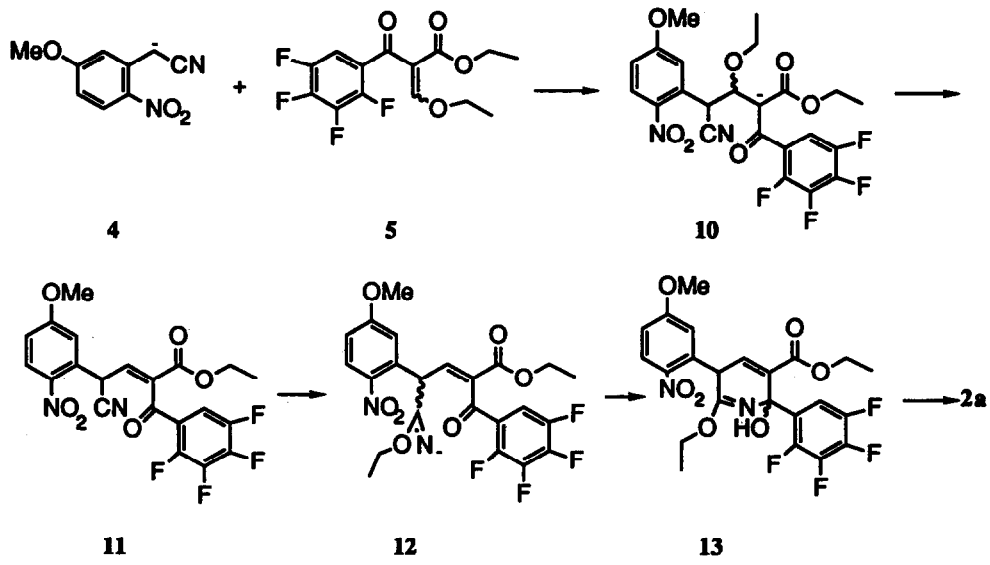
Scheme II



6 **7** R= Ethyl, **8** R= H **9**

It seems reasonable to propose that the key pyridine intermediate **2** isolated directly from the reaction of acetonitrile **4** and enol ether **5** is formed via the following sequence of events (Scheme III). Nitrile anion (derived from **4**) addition to enol ether **5** provides the corresponding keto-ester anion **10**, which undergoes slower elimination of ethoxide to afford unsaturated keto-ester **11**. Eventually, ethoxide addition to the cyano group of **11** gives the imino anion **12** which subsequently condenses with the neighboring keto group to provide dihydropyridine **13**. Dehydration gives the product pyridine **2**.

Scheme III

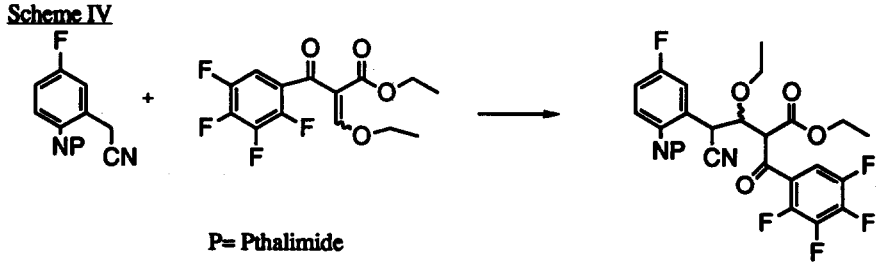


4 **5** **10**

11 **12** **13**

Some evidence for the proposed reaction sequence described in Scheme III comes from earlier studies. For example: the condensation of nitrile **14** with enol ether **5** at -78° C followed by quenching after five minutes affords almost exclusively a mixture of diastereoisomers of **15** in good yield (55-65%) (Scheme IV).

Scheme IV



P= Pthalimide

14 **15**

Further studies and efforts to delineate the scope of this chemistry for the preparation of novel antitumor compounds are in progress.

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References and Notes:

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2. Anti-infective Research Division.
3. Catalytic hydrogenation Services.
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9. Use of 2 equivalents of base gave more consistently chemical yields of 35-45%. Use of 1.2 equivalents of base resulted in slightly lower yields (20-30%). Further studies regarding base, solvent, and reaction temperature are ongoing.
10. Enol ether 5 was prepared by heating the parent keto-ester in the presence of 6 equivalents of acetic anhydride and 2.5 equivalents of triethyl orthoformate for 2 hours with elimination of ethyl acetate via a Dean Stark trap. The crude enol ether was subjected to rotary evaporation at 80° C for 2 hours, and then used directly.
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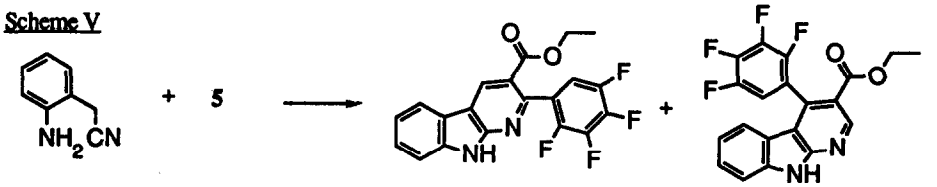
16. Satisfactory spectral data (IR, ^{1}H NMR at 300 MHz, and MS) were obtained for all new compounds. Selected physical data:

    2a: ^{1}H NMR ($CDCl_3$): 1.25 (6H, overlapping t), 3.95 (3H, s), 4.26 (2H, q, J= 6 Hz), 4.38 (2H, broadened q), 6.9 (1H, d, J= 1-2 Hz), 7.02 (1H, dd, J= 8 Hz, J= 1-2 Hz), 7.24 (1H, m), 8.14 (1H, d, J= 8 Hz), 8.21 (1H, s). MS: M+1= 495. IR: 1720, 1520, 1260. CHN: Calc.: C: 55.87, H: 3.66, N: 5.66. Found: C: 55.98, H: 3.66, N: 5.51.
    2b: ^{1}H NMR ($CDCl_3$): 1.23 (3H, t, J= 6 Hz), 1.26 (3H, t, J= 6 Hz), 4.01 (3H, s), 4.03 (3H, s), 4.26 (2H, q, J=6 Hz), 4.37 (2H, q, J= 6 Hz), 6.80 (1H, s), 7.25 (1H, m), 7.70 (1H, s), 8.18 (1H, s). MS: M+1= 525.
    6: ^{1}H NMR ($CDCl_3$): 1.22 (3H, t, J= 6 Hz), 1.35 (3H, t, J= 6 Hz), 3.84 (3H, s), 3.9 (3H, s), 4.23 (2H, q, J= 6 Hz), 4.50 (2H, q, J= 6 Hz), 6.52 (2H, br s), 6.72 (1H, s), 7.18 (1H, m), 7.27 (1H, s), 8.21 (1H, s). MS: M+1= 495.
    7: ^{1}H NMR (DMSO): 1.19 (3H, t, J= 6 Hz), 3.88 (3H, s), 4.00 (3H, s), 4.22 (2H, q, J= 6 Hz), 7.08 (1H, s), 7.63 (1H, m), 7.97 (1H, s), 9.04 (1H, s), 12.04 (1H, br s). MS: M+ = 448.
    8: ^{1}H NMR (DMSO): 3.88 (3H, s), 3.92 (3H, s), 7.08 (1H, m), 7.11 (1H, s), 8.08 (1H, s), 9.29 (1H, s). MS: M+ = 420.

17. The structures of pyridylindoles 3 and 7 have been additionally confirmed by comparison of their ^{1}H NMR spectra to that of **16**. Both regioisomers **16** and **17** were isolated (10% yield, in a ratio of 1:1) from the condensation of nitrile **18** with enol ether **5** under different reaction conditions (Scheme V). Request X-ray structure report 358-JP-37954-141B for indole **16**. IC_{50} values for **16** against B16F10, HT29, A549, and P388 were 1.32, 3.91, 2.15, and 82.6 ug/ml, respectively.

Scheme V



18 **16** **17**

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