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Synthesis of Functionalized Furo[2,3-b]pyridines via the Pd-catalyzed Coupling of Acetylenes to Iodopyridones. Preparation of a Key Intermediate to a New HIV Protease Inhibitor L-754, 394.

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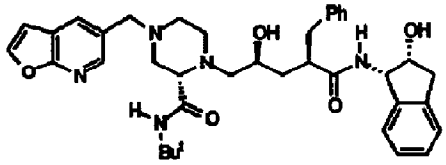
Summary: The synthesis of 1 was accomplished in 55% overall yield via the Pd-catalyzed coupling of 3 and 4 followed by Cu-catalyzed cyclization of the resulting intermediate 2.

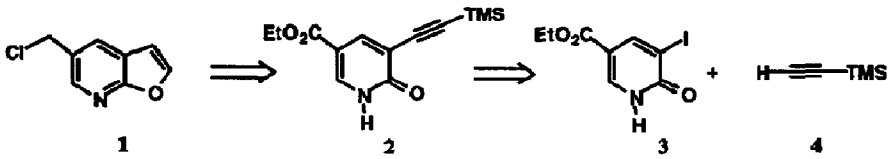
The furopyridine functionality has emerged as a useful pharmacophore in a variety of therapeutic areas including the treatment of skin disease and relief of intraoccular pressure among others.[1] More recently this structural unit has been incorporated into the HIV protease inhibitor candidate L-754,394.



L-754,394

The synthesis of L-754,394 involved appendage of the chlorinated furopyridine **1** to the piperazine right hand portion of the molecule as described previously for the synthesis of the current HIV-Protease clinical candidate L-735,524.[2,3]

We report here a 5-step procedure for the synthesis of **1** (~55% overall), from readily available ethyl 2-hydroxy nicotinate, via a Pd-catalyzed coupling of **3** and **4** followed by cyclization of the resulting intermediate alkynyl pyridone **2** as shown in the retrosynthetic analysis. In addition, this process also allows the construction of a wide variety of substituted furopyridines.



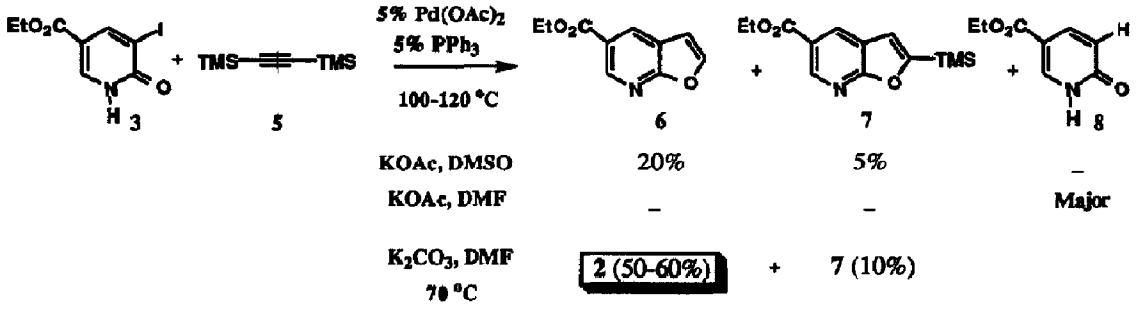
1 **2** **3** **4**

Pd-Catalyzed syntheses of heterocyclic compounds can be found in abundance in the literature with benzofurans, indoles, tryptophan derivatives, heterocondensed pyrroles and nucleoside derivatives having been synthesized using such processes.[4] However, only few examples in the literature make use of Pd chemistry in the synthesis of furopyridines.[5]

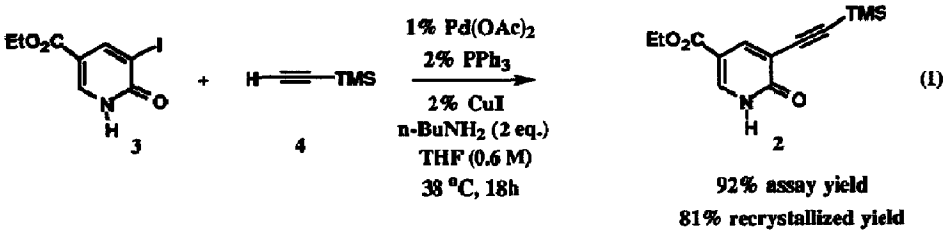
In an attempt to expand Larock's methodology[6] for the synthesis of substituted indoles and benzofurans to the synthesis of **1** and its analogues, iodide **3**[7] was treated with bis-trimethylsilylacetylene **5** under a variety of conditions. However, following the standard coupling protocol, only low yields of the cyclized products **6** and **7** were obtained when the condensation was done in DMSO with KOAc as the base (Scheme I) while only **8** was formed in DMF. After considerable experimentation (varying the solvent, the catalyst precursor, the

stoichiometry of the reagents, the addition of external halide (eg. LiCl), the phosphine ligand and the base) it was found that **3** could be condensed with 5 equiv of **5** to give the head-on coupling product **2** in 50-60% yield along with ca. 10% of **7** (Scheme I). It would thus appear that formation of **6** proceeds via the intermediates **2** and **7** instead of a migratory insertion of an intermediate aryl Pd^{II} compound into the triple bond as observed by Larock.[8] However, when that reaction mixture, containing **2** and **7**, was heated to 100°C the yields of these compounds decreased indicating decomposition of **2** under more severe reaction conditions. Consequently a procedure was sought that would produce **2** in high yield under milder conditions followed by a separate cyclization step.

Scheme I

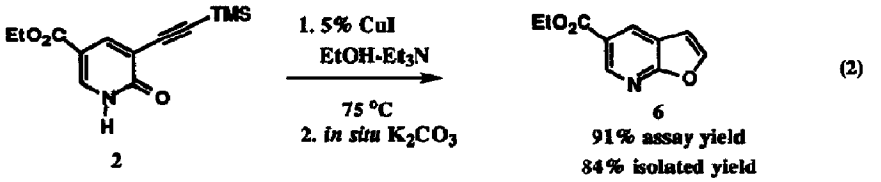


Condensation of terminal acetylenes with aryl and vinyl halides under Pd(0), Cu(I) catalysis is well known in the literature; however, in our hands, the catalyst combination that gave high yields in the coupling of iodouracil derivatives with acetylenes [4% $Pd(PPh_3)_4$, 8% CuI, Et_3N, THF or DMF] was only modestly successful.[9] The isolated yield of **2** was 53% in THF, and substantial amounts of **8** were formed in DMF. Further investigation revealed that although the reaction proceeded in good yield (as determined by quantitative HPLC assay) the isolation was problematic due to the relatively large excess of reagents present in the reaction medium. In addition, due to the high catalyst load required, the cost of the Pd reagent would be prohibitive for large scale work. In the ensuing investigation it was discovered that the amount of catalysts (both Pd and Cu) could be reduced to acceptable levels if n-$BuNH_2$ was used as the base under the conditions shown in eq. 1. A short study of the effect of the base on the rate showed that in THF the rate of the reaction decreased in the order n-$BuNH_2$ > Et_3N > iPr_2NEt > K_2CO_3.[10]



Extractive workup with disodium EDTA, to remove the Cu salts, followed by sequential acid and base extraction and an unoptimized crystallization gave **2** in 81% isolated yield (92% assay yield).

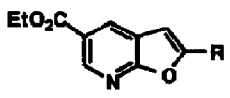
The cyclization of 2 to the furopyridine could now be investigated. Analogous cyclizations of 1-alkynyl phenols and anilines with stoichiometric CuI in DMF to give benzofurans and indoles have been pioneered by Castro.[11] To avoid the use of stoichiomeric CuI, a modified procedure[9] was used involving 5 mole % of CuI in EtOH-Et_3N at 75°C to give a 4.5:1 ratio of 6 and 7.[12] Addition of 1 equiv of finely powdered K_2CO_3 converts 7 to 6 in situ and the latter can be isolated in 84% yield (91% assay) after extractive workup. However, when this cyclization protocol was implemented on the crude mixture after the coupling (in an attempt to avoid the isolation step) only 23% of 7 and traces of 6 could be isolated along with several unidentified impurities.



(2)

Interestingly, when the generality of this two-step procedure was investigated with a variety of other acetylenes, it was discovered that the initial coupling products cyclized directly, and in high yield, under the reaction conditions used for the coupling upon heating of the initial mixture to 40-60°C. Scheme II shows these results.

Scheme II



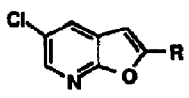
R= Ph, 78%

R= CH_2OMe, 76%

R= pyridyl, 81%

R= cyclopropyl, 79%

R= Bu, 70%



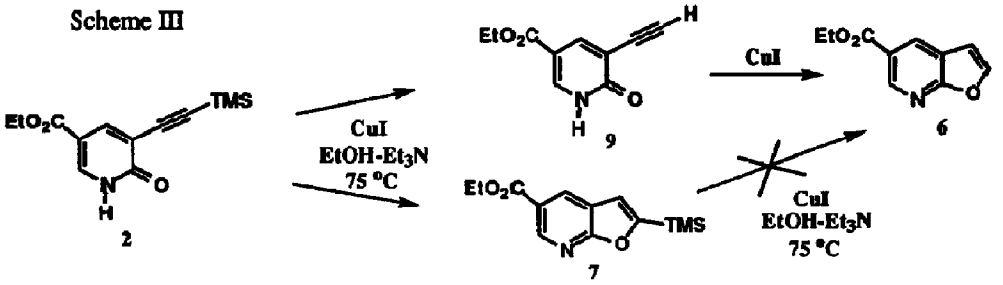
R= Ph, 75%

R= CH_2OMe, 83%

R= cyclopropyl, 79%

The failure of 2 to cyclize directly in the reaction mixture, was quite puzzling in light of the results in Scheme II. A number of control experiments established that PPh_3 and $Ph_3P{=}O$ did not inhibit the cyclization and that $Pd(OAc)_2$ in THF, in the absence of base, gave ca. 70% of 7. Careful monitoring of the reaction by HPLC revealed that the cyclization of 2 proceeded via two pathways one giving 7 directly while the second involved initial desilylation of 2 to give 9, under the basic conditions of the reaction, followed by cyclization to 6. Under the reaction conditions 7 does not get converted to 6. Control experiments also revealed that traces of

Scheme III



Pd (as low as 0.4% by atomic absorption) from the coupling step caused decomposition of **9** and thus must be removed from the reaction medium. In practice, these difficulties were circumvented by crystallizaton of **2** from the reaction mixture (see eq 1) to obtain Pd-free material which cyclized in high yield to give **6** under the conditions described in eq 2. The latter was converted to **1** in 83% overall yield following standard protocols (DIBAL then $SOCl_2$). In conclusion, the synthesis of a number of functionalized furopyridine derivatives was accomplished in 68-83% overall yield.

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7. The iodopyridone **3** was synthesized by reacting the parent ester with N-iodosuccinamide in MeOH at 50 °C for 10 hours. Under those conditions 10-15% of starting material still remained. Complete conversion was effected by the addition of 10 mole % of conc. HCl to the mixture and heating for an additional 3 hours. The product was isolated in 95% yield by addition of water and filtration of the resulting precipitate.

8. (a) This mechanistic hypothesis is supported by the results obtained in the synthesis of indoles (see ref. 6a and 4g). We do not believe this mechanism is operating in this case since none of the 2,3-bis-silyl furopyridine adduct was found by NMR in the crude reaction mixture. (b) Tao, W.; Silverberg, L.J.; Rheingold, A.L.; Hede, R.F. *Organometallics*, **1989**, *8*, 2550.

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