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Solid-Phase Syntheses of Furopyridine and Furoquinoline Systems

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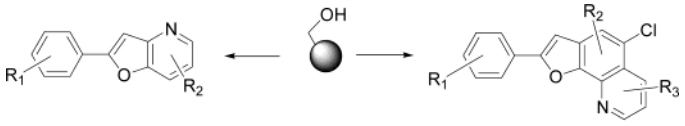
ABSTRACT



Syntheses of 2-substituted furo[3,2-*b*]pyridines and furo[3,2-*h*]quinolines have been achieved for the first time in the solid-phase mode. The central enabling steps involved concomitant deprotection/cyclization promoted by the mild base K_2CO_3. Reactions were monitored "in situ" in real time by a variety of spectroscopic techniques, which allowed full and accurate control of progress in these syntheses.

Completion of the Human Genome Program (HGP) in April 2003, along with accumulating DNA sequence information from the genomes of an exponentially increasing number of microbial, plant, or animal species, has led to a correspondingly large number of protein targets that must be matched with effective and selective organic molecule ligands identified through high-throughput screening.[1] The demand for potential ligands may best be met by combinatorial synthesis onto diverse scaffolds, as expedited by a solid-phase mode (SPOS) that has the advantages of being amenable to automation and potentially giving products suitable for further testing without going through time-consuming intermediate purification steps.[2]

The focus of this report is to describe solid-phase syntheses of furo[3,2-*b*]pyridines and furo[3,2-*h*]quinolines. The former heterocycle is rarely found in nature,[3] yet its heteroaromatic unit is the nucleus of the pharmacophores of potent HIV protease inhibitors such as L-754,394[4] and PNU-142721.[5] The latter tricyclic system has been encountered even fewer times.[6] Precedents for solution syntheses in these families are relatively sparse,[7] and to the best of our knowledge, their

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(1) Current logic of the drug discovery field was reviewed by: Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2878−2890 and references therein.

(2) For examples of relatively complex natural products that can be prepared efficiently by SPOS, see: (a) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268−272. (b) Myers, A. G.; Lanman, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 12969−12971. (c) Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959−2962.

(3) (a) Grundon, M. F. *The Alkaloids*; Academic Press: New York, 1979; Vol. 17, pp 105−198. (b) Arruda, M. S. P.; Fernandes, J. B.; Vieira, P. C.; Da Silva, M. F. D. G. F.; Pirani, J. R. *Biochem. Syst. Ecol.* **1992**, *20*, 173−178.

(4) (a) Houpis, I. N.; Choi, W. B.; Reider, P. J.; Molina, A.; Churchill, H.; Lynch, J.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 9355−9358. (b) Bhupathy, M.; Conlon, D. A.; Wells, K. M.; Nelson, J. R.; Reider, P. J.; Rossen, K.; Sager, J. W.; Volante, R. P.; Dorsey, B. D.; Hoffman, J. M.; Joseph, S. A.; McDaniel, S. L. *J. Heterocycl. Chem.* **1995**, *32*, 1283−1287.

(5) (a) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. *J. Org. Chem.* **1998**, *63*, 7851−7859. (b) Wishka, D. G.; Graber, D. R.; Kopta, L. A.; Olmsted, R. A.; Friis, J. M.; Hosley, J. D.; Adams, W. J.; Seest, E. P.; Castle, T. M.; Dolak, L. A.; Keiser, B. J.; Yagi, Y.; Jeganathan, A.; Schlachter, S. T.; Murphy, M. J.; Cleek, G. J.; Nugent, R. A.; Poppe, S. M.; Swaney, S. M.; Han, F.; Watt, W.; White, W. L.; Poel, T. J.; Thomas, R. C.; Voorman, R. L.; Stephanski, K. J.; Stehle, R. G.; Tarpley, W. G.; Morris, J. *J. Med. Chem.* **1998**, *41*, 1357−1360. (c) Uenishi, J.; Takagi, T.; Ueno, T.; Hiraoka, T.; Yonemitsu, O.; Tsukube, H. *Synlett* **1999**, *1*, 41−44.

(6) For examples, see: (a) Beugelmans, R.; Bois-Choussy, M. *Heterocycles* **1987**, *26*, 1863−1871 and references therein. (b) Yavari, I.; Anary-Abbasinejad, M.; Alizadeh, A. *Tetrahedron Lett.* **2002**, *43*, 4503−4505.

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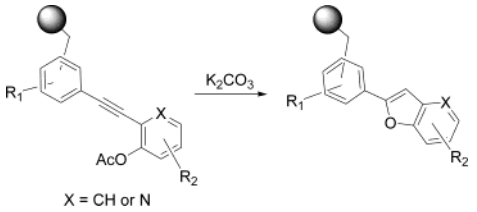
solid-phase syntheses have not been described previously.[8] A further feature of the present study is the monitoring of all reactions "in situ" in real time, using FT-IR (KBr pellets), ^{13}C gel-phase NMR, and ^{13}C MAS NMR; this allowed full and accurate control of progress in these syntheses.[9]

The enabling step of our overall process involves smooth base-promoted deprotection, which is followed directly by cyclization without a requirement for further catalysis (Scheme 1). Cyclization is favored with electron-withdrawing

Scheme 1. Deprotection/Cyclization Step



substituents in the aromatic ring that includes the nucleophilic phenoxide moiety.

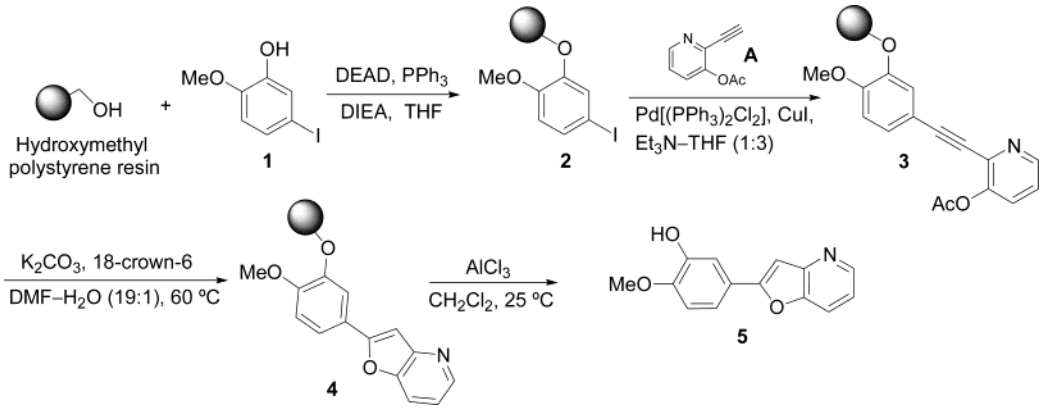
In the first stage of this research, hydroxymethyl polystyrene resin (Merrifield-OH; 0.98 mmol/g) was used as the solid support, due to its stability and robustness under different conditions. The first synthetic step (Scheme 2) involved incorporation of 5-iodo-2-methoxyphenol **1** onto the resin under classic Mitsunobu conditions,[10] which were monitored by IR with the reaction endpoint indicated by disappearance of hydroxyl stretches (3450 and 3580 cm^{-1}). Loading of the first building block was quantitative, within the limit of detection of IR.

Next, a Sonogashira cross-coupling reaction[11] between the anchored iodophenol **2** and 3-acetoxy-2-ethynylpyridine **A**[12,13] established an aryl-pyridine acetylene **3**.[14] IR monitoring revealed two intense signals (1765 and 2200 cm^{-1}), corresponding to the appearance, respectively, of resin-bound acetoxy and acetylene functions. Gel-phase ^{13}C NMR spectra showed the expected chemical shifts corresponding to the entire molecule being anchored to the resin. No additional signals of any consequence were observed, suggesting that within the limits of the monitoring technique, the reaction had produced predominantly the desired product without significant side reactions. In particular, premature loss of an *O*-acetoxy protecting group in the presence of Pd(0) has been mentioned elsewhere[15] but does not appear to be occurring in the present reactions.

Given our objective to establish the central furan ring by addition of a phenol (or phenoxide) moiety to a triple bond (Scheme 1), several trials were initiated to optimize deacetylation. Acidic conditions were avoided, due to the known lability of alkynes. Of a number of bases tried under a variety of conditions (solvent, temperatures, time), LiOH was abandoned due to a complex pattern of products noted upon gel-phase ^{13}C NMR, whereas $NaHCO_3$ was found to be ineffective [only starting material was detected by the same technique]. Instead, we treated the resin with 0.5 M 18-crown-6 in DMF$-H_2O$ (19:1), in the presence of an excess (saturating amount) of K_2CO_3, at 60 °C for 48 h.[16] The absence of IR stretches at 1765 and 2200 cm^{-1}, and the disappearance of methyl and carbonyl signals in the gel-phase ^{13}C NMR, confirmed the loss of the acetate group. In addition, triple-bond signals at 94.9 and 82.9 ppm had disappeared, and a new signal at 101.0 ppm was attributed to the formation of a resin-bound furan ring. Finally, treatment of the resin intermediate **4** with the Lewis acid $AlCl_3$ (10 equiv) in dry CH_2Cl_2 gave rather high-quality crude product (Figure 1); after semipreparative HPLC, pure 2-(3-hydroxy-4-methoxyphenyl)furo[3,2-*b*]pyridine (**5**) was obtained in 45% overall yield based on the original loading of the starting Merrifield-OH resin.

In a second stage of this research, we prepared on a parallel synthesizer a pilot library, to gain a better appreciation of the scope and limitations of this substituted furan-preparing solid-phase methodology. In one dimension, activated as well as deactivated iodophenols were tried, and the second dimension explored acetylenes[17] linked to three different aromatic nuclei (pyridine, quinoline, aniline) [see Table 1]. While the hydroxyl substituents in the pyridine and quinoline series **A** and **B** were protected as their *O*-acetoxy derivatives as with the earlier work (Scheme 2), the aromatic *ortho*-

Scheme 2



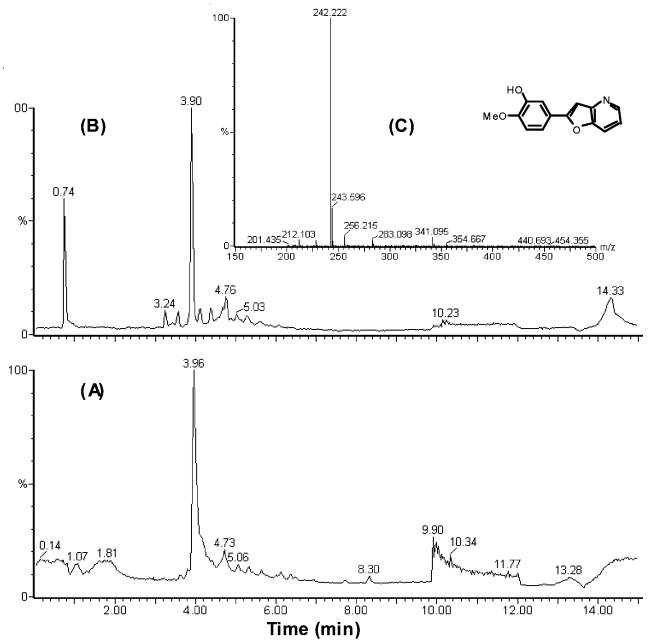
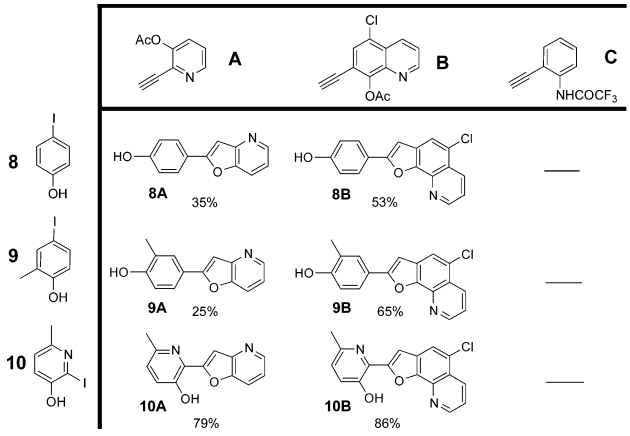


Figure 1. HPLC-MS of crude 2-(3-hydroxy-4-methoxyphenyl) furo[3,2-*b*]pyridine **5**. (A) Total ion current. (B) UV (318 nm) trace. (C) APCI-MS spectrum of the main component (t_R = 3.9 min)

amino group in series **C** was blocked by treatment with trifluoroacetic anhydride in anticipation of a later base-promoted deprotection step.

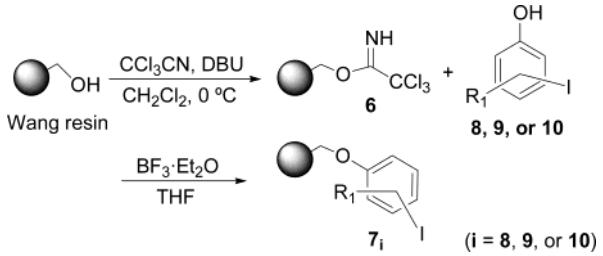
Table 1. Exploratory Library to Generalize Chemistry of Scheme 2[a]



[a] Building blocks are on the top row and left column, outside of the bold solid rules. Isolated yields after purification are indicated, along with the structures of each product for which the chemistry was successful. All results, including those relating to a ring C-alkylation side reaction as described in the text and ref 19, were confirmed by both HPLC-MS and ^{1}H NMR analyses [sometimes adding heterocorreletion analysis (gHSQC and gHMBC)]. The failures of the right column are discussed in the text.

Another aspect of this second-stage research was to replace the Merrifield-OH resin by *p*-alkoxybenzyl alcohol (Wang) resin, in anticipation of more facile final cleavage. Wang

Scheme 3



trichloroacetimidate[18] resin **6** (maximum loading 0.82 mmol/g) was readily loaded, in quantitative fashion, with each of the three iodophenol building blocks (Scheme 3). Completion of reactions was verified by disappearance of strong stretches at 3339 cm^{-1} (N−H) and 1662 cm^{-1} (C═N). Sonogashira cross-coupling reactions using each of three protected acetylene derivatives provided the anticipated resin-bound

(7) Furopyridine synthesis has been reviewed by: (a) Shiotani, S. *Heterocycles* **1997**, *45*, 975−1011. See also: (b) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, 453−457. (c) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409−2412. (d) Mathes, B. M.; Filla, S. A. *Tetrahedron Lett.* **2003**, *44*, 725−728.

(8) Even for the most common benzofuran system, there are few published solid-phase methods. See: Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem.* **2003**, *68*, 387−401 and references therein.

(9) Cironi, P.; Álvarez, M.; Albericio, F. *QSAR Comb. Sci.* **2004**, *23*, 61−68.

(10) (a) Review: Mitsunobu, O. *Synthesis* **1981**, 1−28. See also: (b) Richter, L. S.; Gadek, T. R.; *Tetrahedron Lett.* **1994**, *35*, 4705−4706. (c) Krchňák, V.; Flegelová, Z.; Weichsel, A. S.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6193−6196.

(11) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467−4470. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions;* Diederich, F., Stang, P. J., Eds; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998, pp 203−229. (c) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; pp 493−529.

(12) This known building block was made in three steps and 74% overall yield from commercially available 3-hydroxy-2-bromopyridine, following the procedure in: Lindström, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291−2293. The starting pyridinol was acetylated by treatment with acetic anhydride (Ac_2O), following which Pd(0)-catalyzed coupling with trimethylsilylacetylene established the carbon-arene bond, and final deprotection with tetrabutylammonium fluoride (TBAF) in THF completed the process. See Supporting Information for experimental details.

(13) Requirement for protection of a phenol group for successful coupling was suggested by a literature precedent that reported formation of significant levels of 2,3-disubstituted byproducts when this is not performed: Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280−9288.

(14) When carried out in solution, Sonogashira cross-coupling could be accompanied by a homocoupling side reaction. For a precedent, see: (a) Siemenes, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2634−2657 and references therein. (b) Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett.* **2001**, *42*, 1815−1818. In the methodology of the present study, the iodophenol component is anchored on the solid phase, so homocoupled byproducts remain in solution and can be washed away.

(15) Ajana, W.; Feliu, L.; Álvarez, M.; Joule, J. A. *Tetrahedron* **1998**, *54*, 4405−4412.

(16) As previously reported for a related reaction, KO^{t}Bu-promoted cyclization gave low yields of nitrobenzo[*b*]furans, presumably due to instability of the products under the basic conditions. Dai, W.-D.; Lai, K. W. *Tetrahedron Lett.* **2002**, *43*, 9377−9380

(17) Similar to ref 12, the required building blocks were made in three steps and 74−83% overall yields from commercially available 2-bromo-3-hydroxypyridine, 5-chloro-8-hydroxy-7-iodoquinoline, and *o*-iodoaniline. See Supporting Information for experimental details.

(18) Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 733−736.

bis(aryl)acetylenes, as evidenced by IR. The deprotection/cyclization steps that followed were monitored by IR and allowed to proceed until the characteristic bands (1765 and 2200 cm^{-1}) were entirely abolished. Organic products were released by treatments of the resins with TFA−CH_2Cl_2 (1:9) (2 × 2 h). The combined filtrates were combined with 5% (v/v) H_2O and concentrated to dryness in vacuo.

Several of the library results were as hoped for, with very respectable crude purities and final yields (Table 1). However, the chemistry did not work efficiently in series **C**, which used *ortho*-ethynyltrifluoroacetanilide as a building block; crude material obtained after cleavage was in each case a complicated mixture. We attribute the differential results to the fact that the aniline substituent donates electrons into the triple bond, whereas the π-deficient pyridine or chloroquinoline rings withdraw electrons.

One class of byproducts was observed by HPLC-MS of the crude materials[19] and represents the principal yield-diminishing alternative to formation of desired products in series **A** and **B**. The undesired structures incorporate an extra *p*-hydroxybenzyl moiety (mass 106) derived from the Wang resin linker. Intramolecular rearrangement of a benzylic carbocation with resultant C-ortho-alkylation of aromatic rings that are activated as phenols is a well-known side reaction from peptide chemistry[20] and, in the present context, relates to our recently described "linker leakage" problem.[21]

In summary, we have described an easy and efficient methodology for synthesis of substituted furan-condensed derivatives on hydroxypolystyrene-type solid supports. The protocol should be readily generalizable for the rapid synthesis of large libraries of related compounds, especially in view of the relatively mild conditions for cyclization that make it possible to accommodate a greater range of otherwise labile diversity elements.

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Supporting Information Available: General procedures, description of syntheses, characterization of building blocks, on-resin intermediates, final products, and byproducts, as well as representative spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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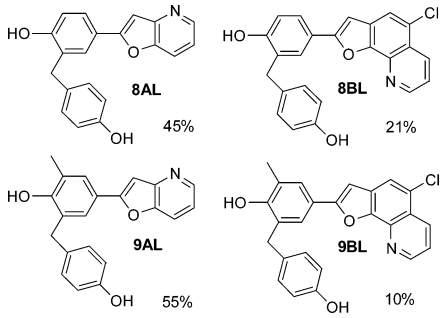
(19) The following C-alkylated derivatives were isolated and characterized by ^1H NMR after purification (overall yields are next to the structures). Further evidence for the structures was provided by masses 106 units higher than anticipated for the desired products shown in Table 1.



(20) Erickson, B. W.; Merrifield, R. B. *J. Am. Chem. Soc.* **1973**, *95*, 3750−3755.

(21) Yraola, F.; Ventura, R.; Vendrell, M.; Colombo, A.; Fernàndez, J.-C.; de la Figuera, N.; Fernández-Forner, D.; Royo, M.; Forns, P.; Albericio, F. *QSAR Comb. Sci*. **2004**, *23*, in press.