Pergamon

Tetrahedron Letters, Vol. 37, No. 27, pp. 4643-4646, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00923-9

Approaches to Combinatorial Synthesis of Heterocycles: Solid Phase Synthesis of Pyridines and Pyrido[2,3-d]pyrimidines

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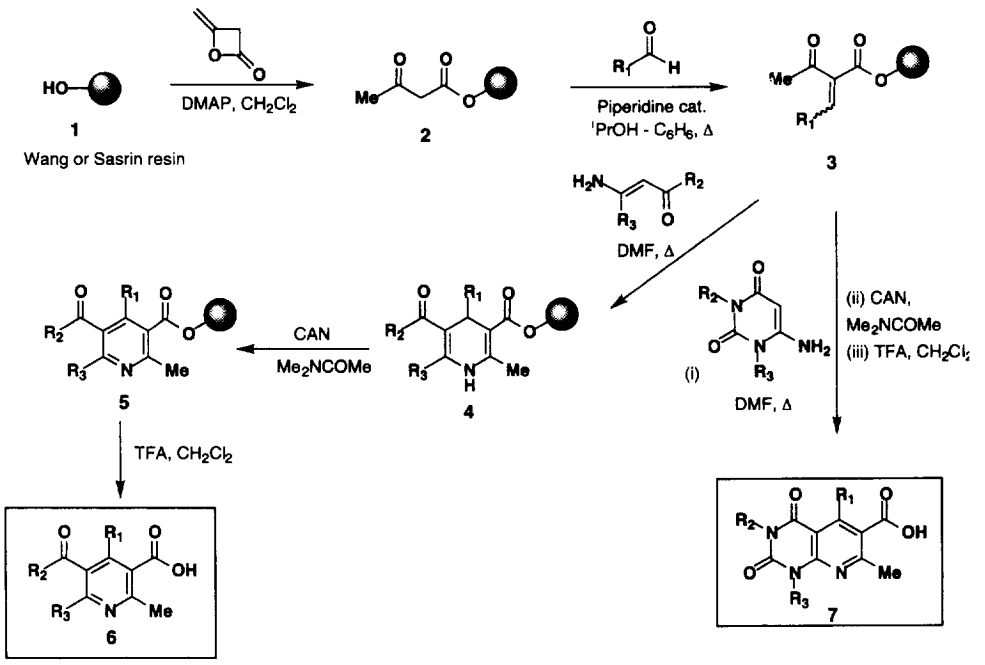
Abstract: *An efficient solid phase synthesis of diverse pyridines and pyrido[2,3-d]pyrimidines is described. O-Immobilized keto esters* **2** *react with aldehydes to afford Knoevenagel derivatives* **3**. *These undergo Hantzsch-condensation with α-oxo enamines to generate 1,4-dihydropyridines* **4** *that are oxidized with CAN to produce immobilized pyridines* **5**. *The method has been extended to synthesis of fused pyrido[2,3-d]pyrimidines employing 6-aminouracils as the α-oxo enamine component. The course of the reaction on solid phase was studied by gel-phase ^{13}C NMR spectrosopy. The synthesis is designed to be amenable for combinatorial libraries preparation.* Copyright © 1996 Elsevier Science Ltd

Drug discovery and development is an extremely laborious and costly process involving synthesis and screening of miriads of diverse organic compounds. Combinatorial chemistry has recently emerged as a promising tool to dramatically accelerate the process of drug discovery.[1] While methods for generation of combinatorial libraries of peptides and oligonucleotides are already well established, design and synthesis of libraries of small organic molecules remains a relatively new and rapidly evolving area of research.[1,2] Significantly, it is this latter aspect of combinatorial chemistry which may hold greatest promise for the efficient discovery of viable drug leads and candidates. In order to utilize the "split and pool"[3] protocol for combinatorial synthesis, it becomes necessary to develop a synthesis of molecular entities of interest on solid supports.[1-3]

Among small organic molecules, nitrogen heterocycles hold a special place as historical pharmacophores.[1-3] For example, pyridine derivatives were amongst the most frequently cited heterocyclic compounds in a sample study of 1000 commercial pharmaceutical agents.[4] The pyridine nucleus is a key feature of various drugs, including numerous antihistamines, as well as antiseptic, antiarrhytmic, antirheumatic, and other pharmaceuticals. Notably, the MDDR data base lists in excess of 7000 pyridine derivatives.[5] As an extension of our studies toward combinatorial syntheses of pharmacophoric azine derivatives,[2f] we now report a general method for SPS of pyridines and pyrido[2,3-d]pyrimidines.

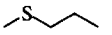
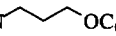
Scheme 1



The SPS of pyridines is based on Knoevenagel and Hantzsch condensation chemistry and commences from preparation of immobilized β-keto esters **2** as shown in Scheme 1. Simple acetoacetylation can be performed by treatment of hydroxyl functionalized polymers **1** such as Wang or Sasrin resin with diketene (cat. DMAP, CH_2Cl_2, -50 °C to rt). The resulting β-keto ester **2** can be conveniently analyzed by cleavage/heterocyclization into 3-methyl-3-pyrazoline-5-one (5% hydrazine in EtOH, 30 min, rt) followed by gravimetric or spectrophotometric analysis of the cleaved product. Nearly quantitative conversion of **1** to **2** was typically observed by this method. Initially, a model study was performed employing ^{13}C labelled benzaldehyde to monitor the course of reaction on solid support by fast gel phase ^{13}C NMR spectroscopy.[6] Thus, Knoevenagel condensation of **2** with $Ph^{13}CHO$ (i-PrOH/C_6H_6, 60 °C, MS 4°A or $HC(OMe)_3$) gave rise to corresponding ^{13}C - labeled benzylidene resin **3** (R_1 = Ph; δ ^{13}CH ca. 140 ppm). Next, a Hantzsch-type heterocyclization with methyl aminocrotonate (DMF, 80 °C, MS 4A° or $HC(OMe)_3$, 10h) proceeded quantitatively by ^{13}C NMR to generate the corresponding 1,4-dihydropyridine derivative **4** as evident by the shift of the signal from olefinic to benzylic region (R_1 = Ph; R_2 = R_3 = Me; δ ^{13}CH-4 ca. 40 ppm). The penultimate intermediate **4** was oxidized with cerric ammonium nitrate (CAN) in dimethylacetamide (rt, 15 min) to afford the expected immobilized pyridine **5**. The latter conversion on solid support resulted in a downfield shift of the ^{13}C label to the aromatic region (R_1 = Ph; R_2 = R_3 = Me; δ ^{13}C -4 ca. 145 ppm). Essentially similar sequence of events was repeated utilizing different aldehyde and α-oxo enamine building blocks to generate a diverse collection of pyridines (Table 1). A completion of the Knoevenagel condensation step is ensured when negative pyrazoline test is observed with ethanolic

hydrazine (by TLC). The resulting heterocycles are cleaved cleanly from the polymeric support with 95% aq. TFA or 3% TFA in CH_2Cl_2 (for Wang or Sasrin resin, respectively). Cyclocondensation of immobilized 2-alkylidene or arylidene keto esters **3** with cyclic enamino ketones leads to fused pyridines such as tetrahydroquinoline derivative **6n**. Employing 6-amino uracils as the enamino component provides a facile entry into yet another class of biologically important bicyclic azine heterocyles, namely the pyrido[2,3-d]pyrimidines **7** (Scheme 1, Table 1).[7]

Table I. Solid Phase Synthesis of Pyridines **6** and Pyrido[2,3-d]pyrimidines **7**

Compound #	R_1	R_2	R_3	HPLC purity,[a] %
6a	$Ph(^{13}C)$[b]	MeO	Me	80 (91[c])
6b	$Ph(^{13}C)$[b]	i-PrO	Me	95
6c	p-$HOOCC_6H_4$	MeO	Me	99
6d	o-FC_6H_4	MeO	Me	98
6e	2-naphthyl	MeO	Me	98
6f	4-Py	iPrO	Me	81
6g	m-$O_2NC_6H_4$	MeO	Me	95
6h	p-$MeOC_6H_4$	i-PrO	Me	90
6i	n-Hexyl	MeO	Me	90
6j		MeO	Me	70
6k	Ph	MeO	Me	90
6l	Me_2N  OC_6H_4-p	MeO	Me	70
6m	Ph	Me	Me	90
6n	Ph	$CH_2CMe_2CH_2$		90
6o	H[d]	Me	Me	80
6p	$Ph(^{13}C)$[b]	Me	PhCONH	95
7a	$Ph(^{13}C)$[b]	H	H	91
7b	$Ph(^{13}C)$[b]	Me	Me	90 (93[c])
7c	Ph	Et	Et	98
7d	Ph	H	All	100

[a]HPLC data for crude products, detection at 220 nm.[10] Essentially quantitative yields for all crude products were observed. [b]Prepared using $Ph^{13}CHO$. Reaction followed by gel-phase ^{13}C NMR. [c]Yields for products made on Sasrin resin. All other compounds were obtained on Wang resin. [d]Made with i-PrCHO on Wang resin.

As seen from Table 1, this SPS route well tolerates variations around the pyridine or pyrido[2,3-d]pyrimidine scaffold, and enables for preparation of diverse heterocyclic derivatives. A noteworthy feature is that both

aromatic and aliphatic aldehydes can be successfully employed. With an α-branched aliphatic aldehyde such as i-PrCHO, 4-unsubstituted pyridine **6o** (R_1 = H) was obtained, resulting from an apparent CAN or TFA-induced dealkylation of the corresponding 4-isopropyl group.[8] Amongst suitable α-oxo enamine reagents, acyclic enamino esters and enamino ketones, as well as cyclic enamino ketones and 6-aminouracil derivatives were succesfully utilized in this study. In addition, ketene aminals may also be employed to produce 2-aminopyridines as exemplified by the SPS of compound **6p.** In general, the crude compounds **6a-p** and **7a-d** were isolated in essentially quantitative yields with HPLC purity of 70-100% (Table 1).[9] These results demonstrate the versatility of the solid phase route for preparation of these types of nitrogen heterocycles. Also evident in these results is an inherent advantage of the ability to drive difficult reactions to completion on solid support by using an excess of solution reagents, and the ease of isolation of immobilized intermediates from solution reagents. For example, while a solution phase route did not allow for preparation of pyrido[2,3-d]pyrimidines with N^1, N^2-unsubstituted 6-aminouracil which was characterized as lacking the reactivity of enamines,[10] such compounds can be conveniently synthesized by the SPS method (cf. Table 1, compound **7a**; Hantzsch condensation performed at 95 °C; 91% purity by HPLC for the crude product).

In conclusion, an efficient and general solid phase synthesis of pyridines and pyrido[2,3-d]pyrimidines has been developed. The method is amenable to the construction of heterocyclic combinatorial libraries. These studies, along with further extension of the methods to preparation of structurally novel pyridines and pyrimidines are currently in progress, and will be reported in due course.

Notes and References:

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2. Some recent examples are listed below: (a) Kick, E. K.; Ellman, J. A. *J. Med Chem.* **1995**, *38*, 1427; (b) Holmes, C. P.; Jones, D. G. *J. Org Chem.* **1995**, *60*, 2318; (c) Campbell, D. A.; Bermak, J. C.; Burkoth, T. S.; Patel, D. V. *J. Am. Chem. Soc.* **1995**,*117*, 5381; (d) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**,*117*, 5381; (e) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253; (f) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem.* **1996**, *61*, 924.
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6. Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588-7510.
7. Gel-phase ^{13}C NMR data (C_6D_6) for a representative SPS of the compound **7b** on Wang resin are given below. Immobilized 1,4-dihydropyrido[2,3-d]pyrimidine (R_1 = Ph; R_2 = R_3 = Me): δ ^{13}CH-4 ca. 40 ppm. Immobilized pyrido[2,3-d]pyrimidine **7b** (R_1 = Ph; R_2 = R_3 = Me): δ ^{13}C-4 ca. 147 ppm.
8. Similar oxidative dealkylation of 1,4-dihydropyridines with nitric acid has been reported. See, Boecker, R. H.; Guengerich, F. P. *J. Med. Chem.* **1986**, *29*, 1596.
9. Column: Microsorb 5 mM C18, 4.6 x 250 mm. A: 0.1% TFA in water; B: 0.1% TFA in MeCN. Gradient (B%) 0-60% (amino acids) or 0-30% (peptides) over 40 min; 1.5 ml/min, UV detection at 220 nm. Compounds **6** and **7** were characterized by 400 MHz ^1H NMR and ESI MS data.
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(*Received in USA* 15 *April* 1996; *revised* 30 *April* 1996; *accepted* 7 *May* 1996)