Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5633-5636, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01219-1

Application Of The Pictet-Spengler Reaction In Combinatorial Chemistry.

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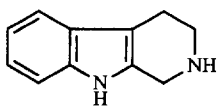
Abstract. Reaction of polymer bound tryptophan with a variety of aldehydes and ketones under Pictet-Spengler like conditions was found to produce 1,2,3,4-tetrahydro-β-carbolines in excellent yield. The straightforward, easily automated chemistry and the availability of numerous commercial aldehydes and ketones makes this approach ideal for combinatorial chemistry application. Copyright © 1996 Elsevier Science Ltd

Combinatorial technology, initially focused on peptides and peptide-like structures,[1a-e] has recently begun to emphasize low molecular weight compounds for use in basic drug discovery. Renewed interest in polymer based synthetic methodology has dramatically expanded application of the original solid phase concept.[2] As a result, a number of pharmaceutically useful heterocyclic structures can now be prepared by solid phase methodology, including the benzodiazepines,[3a,b] hydantoins,[3b] lactones,[3c] tetrahydrofurans,[3d] thiazolidines[3e] and pyrrolidines.[3f] This repertoire continues to expand rapidly.



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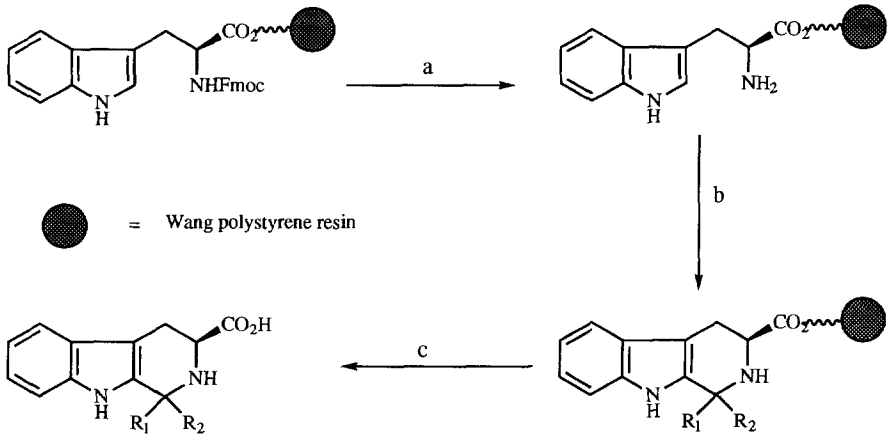
The β-carboline **1** is a key structural motif common to a large class of tryptophan derived natural product alkaloids. This class includes the simple tricyclic eleagnines and harmines as well as a number of structurally more complex examples such as yohimbine, ajmalicine, and the medicinally important reserpine.[4] In addition to the diverse biological activity of the naturally occuring compounds, synthetically derived β-carbolines also exhibit significant bioactivity, particularly in the central nervous system, where several are known to interact at benzodiazepine,[5a] serotonin,[5b] and dopamine[5c] receptor sites. The broad spectrum of biological activity and the rigid, heterocyclic skeleton of this unique pharmacophore presented an excellent opportunity for combinatorial application.

We and others[6] have reasoned that access to this class of compounds could be realized through the Pictet-Spengler cyclization reaction[7] in a solid phase protocol (Scheme 1). Due to the commmercial

availability of a wide variety of aldehydes and ketones as well as a number of substituted tryptophan derivatives, a large number of β-carbolines could be realistically proposed.

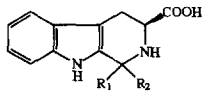
A key aspect of the methodology is the condensation of a polymer bound tryptophan and an aldehyde or ketone component at room temparature under acidic conditions. Use of 1% trifluoroacetic acid/methylene chloride reaction mixture was an ideal choice for several reasons: polystyrene based supports exhibit excellent swelling properties in both solvents; the Wang[8] resin linker utilized in this procedure is stable to low (<5%) TFA concentrations; these conditions are also compatible with existing automated synthesis instruments.



Scheme 1. Generalized synthetic procedure. a) 2 x 20% piperidine/ DMF. b) 4 eq. aldehyde or ketone in 1% TFA/CH_2Cl_2, r.t. c) 95% TFA/H_2O 2hrs.

The following is a description of the general procedure: a 1g portion of Fmoc-L-Tryptophan-Wang resin (available from a number of commercial sources) with a typical loading range of 0.5 to 0.7 mmol/g was treated with two portions of 20% piperidine in DMF to remove the Fmoc protecting group. The resin was then washed several more times with DMF followed by CH_2Cl_2 before introduction of four equivalents of an aldehyde or ketone in a 1% solution of TFA in CH_2Cl_2. The reaction vessel was then agitated at room temperature for two to four hours in the case of the aldehydes and from 48 to 72 hours when utilizing ketone synthons. Reaction progress could be conveniently monitored by the Kaiser method.[9] Cleavage from the support was accomplished by suspending and stirring the resin in neat trifluoroacetic acid for a period of two hours at room temperature and the product was recovered by filtering the suspension and concentrating the filtrate. Selected examples are summarized in Table 1. Analytical high performance liquid chromatography was used to analyze the crude samples and revealed the presence of both diastereomers in a majority of the aldehyde derived products, although no attempt was made to assign absolute stereochemistries. Purities of the crude compounds were typically in excess of 85% based on HPLC analysis; however, a number of methyl ketones (entries **5**, **6** and **7** in Table 1) exhibited purities of only around 50%. In these cases the sole contaminant was identified as unreacted tryptophan. Preparative scale, liquid chromatography (0.1% HCl in

water/ acetonitrile, Vydac C-18 preparative column) was utilized for purification of representative samples. Characterization consisted of ^{1}H-NMR and electrospray mass spectroscopy.[10]



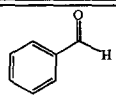
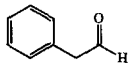
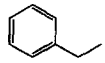
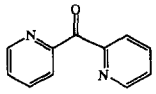
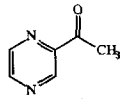
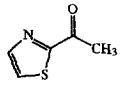
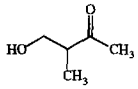
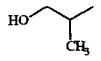
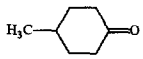
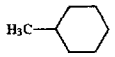
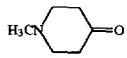
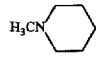
entry	aldehyde/ ketone	R_1	R_2	% HPLC [11a] purity	% mass [11b] recovery
2			H	90	85
3			H	92	89
4				87	98
5			CH_3	56	97
6			CH_3	46	91
7			CH_3	53	99
8		spiro 		84	94
9		spiro 		97	95

Table 1. Structures of representative β-Carbolines.

Our results demonstrate the Pictet-Spengler reaction to be an efficient method for the solid phase synthesis of β-carbolines from tryptophan based substrates[12], a chemistry that is also compatible with our current methods of automation. We anticipate that this reaction will be an important tool for the construction of diverse arrays of small molecules based on β-carbolines and other related heterocycles.

Acknowledgement

We thank Doug Lenz of Amgen Boulder Inc. for carrying out mass spectral analysis and Dr. Theodore Jones and Dr. Lawrence Melvin for their support as well as helpful comments regarding the manuscript.

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10) Spectral data for cmpd **3** : ^{1}H NMR (CD_3OD, 300MHz) δ 7.0-7.6 (m, 9H), 4.9, 5.1 (m, 1H), 3.6-3.9 (m, 1H), 2.9-3.2 (m, 4H). ^{13}C NMR exhibited bridgehead (C-1) diastereomeric signals at 53.5ppm and 55.8ppm. Electrospray mass spectral characterization : 307 [MH^+], calc. : 306.

11) a) Analysis was carried out by HPLC (Vydac C18 column, 4.6 x 250mm, 0-50% acetonitrile/water containing 0.1% TFA) with integration of peak areas at 220nm. b) Mass recoveries were calculated from the weight of crude material and the initial loading level of Fmoc-Trp-Wang resin.

12) In preliminary experiments we have tried to increase diversity within the carboline scaffold through alkylation of the position 2 nitrogen. While activated alkylating reagents such as α-bromomethyl acetate efficiently alkylated some carbolines, this reaction was not reproducible over a wide series of substrates. This chemistry is under investigation.

(*Received in USA* 11 *April* 1996; *accepted* 14 *June* 1996)