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Solid Phase Synthesis of Tetrahydroisoquinolines & Tetrahydroimidazopyridines

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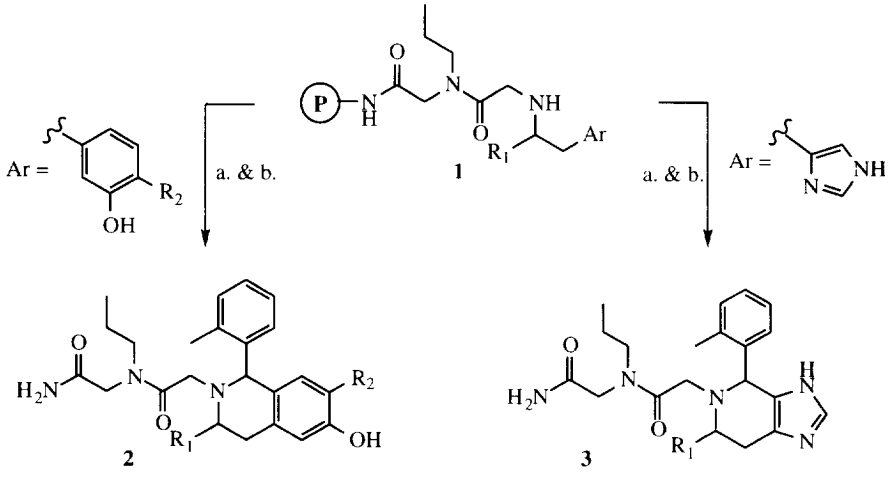
Abstract: *The preparation of 1,2,3,4-tetrahydroisoquinolines and 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridines on a solid support has been developed. The route utilizes substituted m-tyramines, histamines and various aromatic, aliphatic and heterocyclic aldehydes.* Copyright © 1996 Elsevier Science Ltd

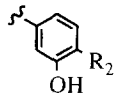
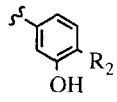
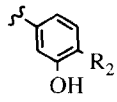
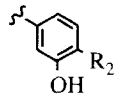
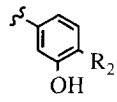
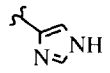
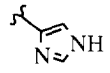
Isoquinoline alkaloids are an important and rather large (>1000 members)[1a] family of natural products. They possess many diverse types of biological activities (i.e. bronchodilators,[1b] skeletal muscle relaxants,[1c] and antiseptics[1d]) and have been extensively studied over the past hundred years.[1a] The related tetrahydroimidazopyridine core has also exhibited biological activity in the form of central nervous system (CNS) activity.[2] Combinatorial libraries which contain biologically interesting compounds such as the ones described above are an extremely valuable source for new leads. Recently Meutermans reported the solid phase synthesis of tetrahydroisoquinolines utilizing the Bischler-Napieralski reaction.[3] Concurrently we have developed a general synthetic strategy which allows for the preparation of tetrahydroisoquinolines as well as tetrahydroimidazopyridines *via* cyclization[1a,4] of a resin-bound imine intermediate under very mild conditions.

Scheme:



a. *o*-tolualdehyde, pyridine, 100°C b. 90:10 trifluoroacetic acid / water

Table 1:

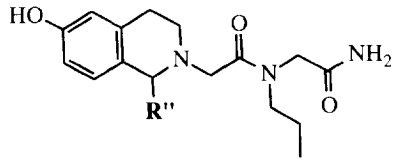
Entry	R_1 Group	R_2 Group	Ar Group	HPLC Purity[7]	Mass Spec[8]
2a	CH_3	H		94%	410
2b	CH_2CH_3	CH_3		94%	438
2c	CO_2CH_3	OH		81%	470
2d	H	OH		90%	412
2e	H	OCH_3		81%	426
3a	H	-		93%	370
3b	CO_2CH_3	-		82%	428

Our starting point was the cyclo-condensation of resin-bound[5] **1** with aldehydes. Compound **1** was chosen as a convenient scaffold and was prepared according to a procedure similar to that developed by Zuckermann.[6] Heating compound **1** with aldehydes leads to the formation of resin bound tetrahydroisoquinolines. Kametani has reported solution-phase conditions for similar cyclizations employing ethanol[1a] and pyridine[4] as solvents. Solvent and temperature effects on this reaction were examined. Optimized conditions for cyclization on the solid-support were identified to be pyridine at 100°C. Products can be cleaved from the solid support using standard cleavage conditions (90:10 trifluoroacetic acid - water) to yield compounds of structure **2** & **3**.

This reaction scheme can also utilize substituted *m*-tyramine derivatives (see Table **1**). Substituents at R_1 range from a small methyl group (**2a**) to a methyl ester (**2c**). The ester could also be further elaborated to introduce another dimension. The addition of another hydroxy (**2c** & **2d**) or methoxy (**2e**) to the aromatic ring also does not diminish the purity of the cleaved compounds.

The cyclization of resin bound substitued histamines to yield 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-c]pyridines (**3**) was also examined.[2] The cyclization proceeds under the same conditions as described above. The final compounds can be cleaved from the solid support yielding compounds with high chemical purity.

Table 2:



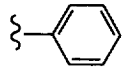
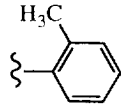
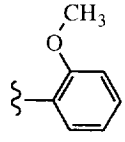
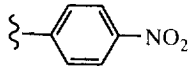
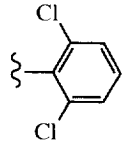
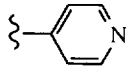
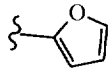
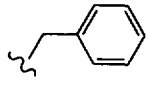
Entry	R" Group	HPLC Purity [7]	Mass Spec[8] ([M+H]+ peak)
4a		96%	382
4b		96%	396
4c		92%	412
4d		96%	427
4e		85%	451
4f		77%	383
4g		94%	372
4h		88%	396
4i		74%	362

Table 2 illustrates the wide range of 1,2,3,4-tetrahydroisoquinolines that can be prepared utilizing this scheme. Benzaldehyde yielded the desired product (**4a**) in high purity. Ortho substitution on the phenyl ring

including methyl (**4b**) and an electron donating methoxy (**4c**) also yielded products with high purity. Sterically hindered 2,6-dichlorobenzaldehyde yielded the desired compound (**4e**) with moderate to high purity. Heterocyclic aldehydes also worked well yielding final products with moderate (**4f**, 4-pyridyl) to high (**4g**, 2-furyl) purities. Even aliphatic aldehydes which in solution suffer from polymerization problems yielded products (**4h** & **i**) with reasonable purities.

In summary, we have demonstrated that the preparation of substituted 1,2,3,4-tetrahydroisoquinolines and 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-c]pyridines on a solid support is viable and yields products that can be cleaved from the solid support in moderate to high chemical purity. This procedure together with the ready commercial availability of amines and aldehydes will allow for the preparation of large non-peptidic combinatorial libraries.

Acknowledgements: Special thanks to Ms. Amy Bernick for performing mass spectral analysis and to Gary Kath and Greg King of the Merck Bioelectronics Department for their design and fabrication of the instrument that allows us to heat and mix the reactions.

General Procedure: The preparation of compound **1** is described in reference 6. The reactions were carried out on 100 mg of resin. The resin was washed with pyridine (4x2mL). Then, 1 mL of the desired aldehyde (0.5 M) in pyridine is added and the reaction heated to 100°C. After mixing for 14 hours at 100°C the resin is allowed to cool to ambient temperature and washed with pyridine (4x2mL), DMA (4x2mL), 1:1 tetrahydrofuran-methylene chloride (4x2mL), methylene chloride (4x2mL) and glacial acetic acid (4x2mL). A double cleavage is then performed with 1 mL of 90:10 trifluoroacetic acid - water for 20 minutes each time. The solution is concentrated to dryness and analyzed by HPLC and mass spec.

References and Notes:

1. (a) Kametani, T. and Fukumoto, K. *Heterocycles* **1975**, *3(4)*, 311-341. (b) Fogelman, F. and Grundy, H. F. *Br. J. Pharmac.* **1970**, *38*, 416-432. (c) Winter, C. A. and Lehman, J. T. *J. Pharm. Exp. Ther.* **1950**, *100*, 489-501. (d) Hope, E.; Pyman, F. L.; Remfry, F. G. P. and Robinson, R. *J. Chem. Soc.* **1931**, 236-247.
2. Kametani, T.; Koizumi, M.; Okui, K.; Nishii, Y and Ono, M. *J. Med. Chem.* **1972**, *15(2)*, 203-204
3. Meutermans, W. D. F. and Alewood, P. F. *Tetrahedron Lett.* **1995**, *36(42)*, 7709-7712.
4. Kametani, T.; Kigasawa, K.; Hiiragi, M. and Ishimaru, H. *J. Chem. Soc. (C)* **1971**, 2632.
5. The resin used was purchased from Rapp Polymere (Polyethyleneglycol spacer on a polystyrene bead (130 micron, 0.23 mmol/g) - TentaGel S RAM Fmoc - cat. # S30023).
6. Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H. and Moos, W. H. *J. Am. Chem. Soc.* **1992**, *114*, 10646-10647.
7. HPLC Conditions: 10 - 100% acetonitrile in water + 0.1% trifluoroacetic acid, linear gradient over 10 minutes, flow rate: 1.5 mL/min, Zorbax SB C8 column (4.6 mm x 7.5 cm), 230 nm.
8. All samples were run on a Finnigan MAT TSQ700 using electrospray ionization.

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