



Solid Phase Synthesis of 2,3-Dihydro-4-pyridones: Reaction of Danishefsky's Diene with Polymer-Bound Imines

Yihan Wang and Stephen R. Wilson*

Department of Chemistry, New York University,

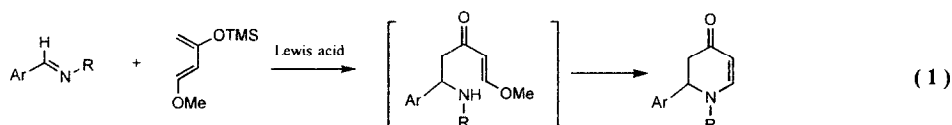
Washington Square, New York, NY 10003

Abstract: An efficient method for the construction of 2,3-dihydro-4-pyridones on solid support has been developed, which utilized the Lewis-acid catalyzed tandem Mannich-Michael reaction of Danishefsky's diene with polymer-bound aldimines. © 1997 Elsevier Science Ltd.

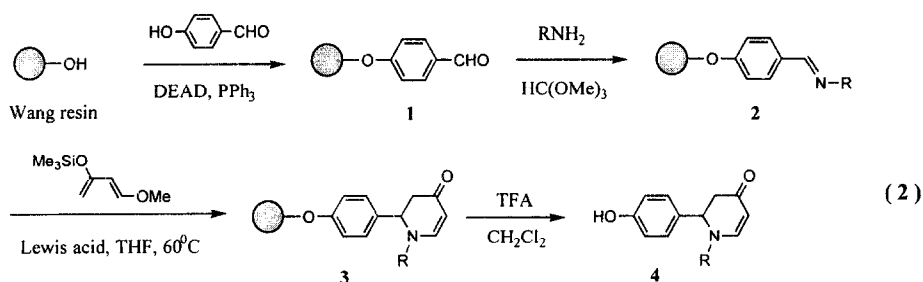
Combinatorial chemistry has recently emerged as a promising tool to dramatically accelerate the process of drug discovery. While methods for generation of combinatorial libraries of peptides and oligonucleotides are already well established, design and synthesis of libraries of small organic molecules remains a relatively new area and become the current focus of research.^{1,2} Solid phase synthesis techniques have been successfully applied to the preparation of a variety of heterocyclic structures, including benzodiazepines, hydantoins, pyrrolidines, thiazolidinones, diketopiperazines and several other compound classes.

Among small organic molecules, nitrogen heterocycles hold a special place as historical pharmacophores, and imine is one of the most common precursors leading to these compounds.³ Polymer-bound imines have been utilized in the synthesis of pyrrolidines,⁴ β -lactams,⁵ thiazolidinones⁶, etc. We report herein the solid phase synthesis of 2,3-dihydro-4-pyridone by the reaction of Danishefsky's diene with polymer-bound imines.

The reaction of Danishefsky's diene with imines has been reported in solution and is catalyzed by different Lewis acids (equation 1).⁷ The reaction is postulated to proceed by a tandem Mannich-Michael reaction mechanism.^{7c-f}



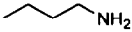


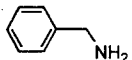
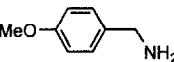
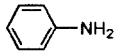
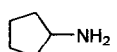
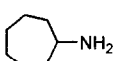
To study the reaction on solid support, we prepared a polymer bound benzaldehyde **1**, which was obtained by Mitsunobu reaction of *p*-hydroxybenzaldehyde with Wang resin (equation 2), and has been advantageously applied to several studies on solid phase synthesis.⁸ The formation of imine **2** was implemented using a protocol developed by the Affymax group, in which trimethyl orthoformate was used as dehydrating agent.⁹ In most cases (Table: entry a-h), the imine formation was complete in a single overnight reaction. Only in entry f where the nucleophilicity of amine is reduced due to the connection to a phenyl ring, the imine formation was repeated several times to drive the reaction to completion. Then the polymer bound imine **2** was treated with Danishefsky's diene in dry THF solution, in the presence of a Lewis acid, to achieve the formation of 2,3-dihydro-4-pyridone **3** on solid support (equation 2). Several different Lewis acids were used, including ZnCl₂, AlCl₃, Et₂AlCl, TiCl₄, BF₃·OEt₂ and Yb(OTf)₃.¹⁰ The water tolerant Lewis acid Yb(OTf)₃¹² gave the highest yield. Yb(OTf)₃ is one of the lanthanide Lewis acid catalysts developed recently, and has been successfully used as catalyst for solution phase studies in aza-Diels-Alder reaction^{7h} as well as other organic transformations.¹³



The final products **4** were obtained after cleavage with TFA/CH₂Cl₂(1:1), in relatively high yields and purities (see table). The spectroscopic data confirmed the structures of desired products.¹⁴

In conclusion, we reported here a new reaction of Danishefsky's diene with polymer bound aldimines, an efficient solid phase method for the construction of 2,3-dihydro-4-pyridones. The polymer bound 2,3-dihydro-4-pyridone provides a scaffold for other useful synthetic transformations,¹⁵ and could be used to prepare libraries of analogs of a variety of alkaloids by the solid phase method.¹⁶ Research along that line will be reported in due course.

Table. Yield and mass spectrometric data for 2,3-dihydro-4-pyridones.

Entry	RNH ₂	Yield ^a	Calculated Mass	APCI-MS	Purity ^b
a		90%	245.1	246.0	88%
b		82%	245.1	246.0	93%
c		85%	231.1	231.9	90%
d		80%	279.1	280.0	85%
e		65%	309.1	310.0	90%
f		60%	265.1	265.9	70%
g		75%	257.1	258.0	78%
h		63%	285.2	285.8	75%

^a Isolated yield based upon the capacity of starting Wang resin (0.95mmol/g, Advanced ChemTech)

^b Purity was determined by C18 RP HPLC at 215nm, 5-80% CH₃CN in H₂O containing 0.1% TFA.

References and notes:

- Wilson, S. R.; Czarnik, A. W. *Combinatorial Chemistry: Synthesis and Application*, John Wiley & Sons, Inc., New York, 1997.
- See reviews: (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233-1251. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1285-1401. (c) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135-8173. (d) Hermkens, P. H. H.; Ottenheijm, H. C.; Rees, D. *Tetrahedron* **1996**, *52*, 4527-4554. (e) Rinnova, M.; Lebl, M. *Collect. Czech. Chem. Commun.* **1996**, *61*, 171-231. (f) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17-42. (g) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600. (h) Balkenhohl, F.; Bussche-Hunnefeld, C. Von dem; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288-2337.
- See review, Govindachari, T. R.; Chirnasamy, P.; Rajeswari, S.; Chandrasekaran, S.; Premila, M. S.; Natarajan, S.; Nagarajan, K.; Pai, B. R. *Heterocycles* **1984**, *22*, 585-655.
- Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029-7030.
- Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253-254.
- Holms, C. P.; Chinn, J. P.; Look, G. C.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328-7333.

7. (a) Danishefsky, S.; Kervin, J., Jr. *Tetrahedron Lett.* **1982**, *23*, 3739-3742. (b) Vacca, J. P. *Tetrahedron Lett.* **1985**, *26*, 1277-1280. (c) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067-1068. (d) Kunz, H.; Pfrengle, W. *J. Org. Chem.* **1989**, *54*, 4261-4263. (e) Waldmann, H.; Braun, M.; Drager, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1468-1471. (f) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444-4451. (g) Yamamoto, H.; Hattori, K. *J. Org. Chem.* **1992**, *57*, 3264-3265. (h) Yamamoto, H.; Hattori, K. *Tetrahedron* **1993**, *49*, 1749-1760. (i) Kobayashi, S.; Ishitami, H.; Nagayama, S. *Synthesis* **1995**, 1195-1202.
8. (a) Sarshar, S.; Siev, D.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 835-838. (b) Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671-3674.
9. Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937-2940.
10. Yb(OTf)₃¹¹ gave the highest yield and thus was chosen to obtain the data reported in this paper. The other catalysts were either less efficient or caused premature cleavage, leading to poor results.
11. Zhang, C.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 5457-5460.
12. Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590-3596.
13. Marshman, R. W. *Aldrichim. Acta* **1995**, *28*, 77-84.
14. General procedure for the synthesis of 2,3-dihydro-4-pyridones: Wang resin bound benzaldehyde **1** (100mg, loading 0.85 mmol/g) was treated with 5 equiv of amine in 5 ml trimethyl orthoformate at room temperature overnight, then the resin was filtered, washed with CH₂Cl₂ (3x), then dried *in vacuo*. To the resin was added dry THF 5 ml, Danishefsky's diene 4.3 mmol (5 equiv), and Yb(OTf)₃ (5 mg, 0.1 equiv) under N₂. The reaction was heated at 60°C for 3 hours. Water was added, and the resin was filtered, washed consecutively with CH₂Cl₂ (3x), MeOH (3x), DMF (3x), CH₂Cl₂ (3x), dried *in vacuo*. Final cleavage of the products was effected with TFA/CH₂Cl₂ (1:1) (3 ml 2x) and washed with CH₂Cl₂ (3mlx2). All compounds listed have ¹H-NMR data consistent with the proposed structure. Selected proton NMR data for compound **4d** and **4e** are as follows: compound **4d**, ¹H-NMR (300MHz, CDCl₃/TFA): 8.11(s, 1H), 7.48-7.46(m, 5H), 7.19(d, *J*=8.7Hz, 2H), 7.17(d, *J*=7.7Hz, 1H), 7.00(d, *J*=8.7Hz, 2H), 4.92(dd, *J*₁=5.7Hz, *J*₂=9.9Hz, 1H), 4.75(d, *J*=14.7Hz, 2H), 4.49(d, *J*=14.7Hz, 2H), 4.03(d, *J*=7.7Hz, 1H), 3.36(dd, *J*₁=18.9Hz, *J*₂=9.9Hz, 1H), 3.02(dd, *J*₁=18.9Hz, *J*₂=5.7Hz, 1H); compound **4e**, ¹H-NMR(300MHz, CDCl₃/TFA): 8.12(s, 1H), 7.24(d, *J*=8.7Hz, 2H), 7.17(d, *J*=8.7Hz, 2H), 7.08(d, *J*=8.7Hz, 2H), 7.07(d, *J*=7.6Hz, 1H), 7.05(d, *J*=8.7Hz, 2H), 4.97(dd, *J*₁=5.7Hz, *J*₂=9.9Hz, 1H), 4.73(d, *J*=14.7Hz, 2H), 4.56(d, *J*=14.7Hz, 2H), 4.06(d, *J*=7.6Hz, 1H), 3.98(s, 3H), 3.40(dd, *J*₁=18.9Hz, *J*₂=9.9Hz, 1H), 3.05(dd, *J*₁=18.9Hz, *J*₂=5.7Hz, 1H).
15. Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719-4728. References cited therein.
16. See reviews, (a) Waldmann, H. *Synthesis* **1994**, 535-551. (b) Waldmann, H. *Synlett.* **1995**, 133-141.

(Received in USA 25 March 1997; accepted 22 April 1997)