

Diels–Alder Reactions of 5-Vinyl-1-acyl-2-aryl-2,3-dihydro-4-pyridones: Regio- and Stereoselective Synthesis of Octahydroquinolines

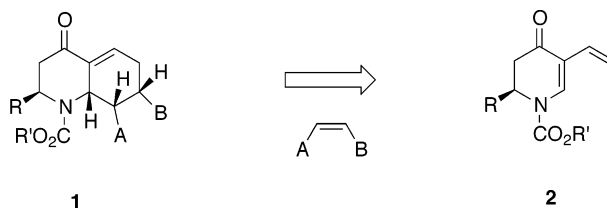
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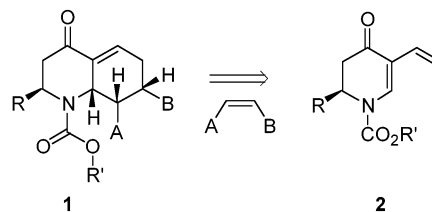
ABSTRACT



Readily available 5-vinyldihydropyridones **2** undergo Diels–Alder cyclization with various dienophiles to afford novel octahydroquinolines. The process is highly stereoselective and provides heterocyclic products containing synthetically useful functionality.

The Diels–Alder reaction provides an efficient and rapid means of constructing highly functionalized heterocyclic ring systems with control of the regio-, diastereo-, and enantioselectivity.¹ In particular, the Diels–Alder reaction of amino-substituted dienes has emerged as a powerful method for the preparation of complex piperidines.² While reactions of 1-*N*-acylamino-1,3-dienes and *N,N*-dialkylaminodienes are plentiful,^{3,4} to our knowledge no reports have surfaced regarding the Diels–Alder reactions of substituted 5-vinyl-

1-acyl-2,3-dihydro-4-pyridones of type **2**. *N*-Acyl-2-alkyl-(aryl)-2,3-dihydro-4-pyridones have proven to be valuable building blocks for alkaloid synthesis.⁵ As part of a program to expand the synthetic utility of these versatile building blocks, we have investigated the Diels–Alder reactions of diene **2** with various dienophiles as a method of preparing novel octahydroquinoline derivatives of general type **1**. In this Letter we disclose our initial findings in this area.




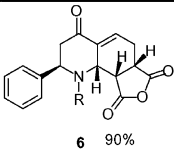
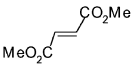
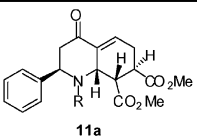
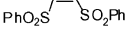
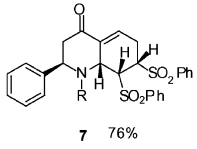
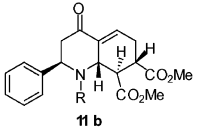

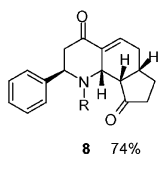

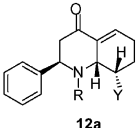
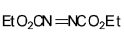
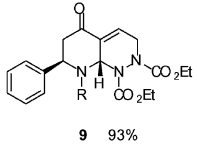
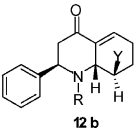
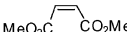
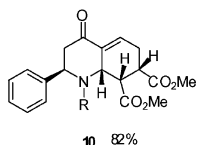
The study began with racemic **3**, prepared by addition of phenylmagnesium chloride to 1-((phenoxy)carbonyl)-4-methoxy-pyridinium chloride. Iodination of **3** with NIS/cat.-[hydroxy(tosyloxy)iodo]benzene (HTIB) followed by Stille coupling with tributyl(vinyl) tin afforded **4** in good overall

(1) For leading references, see: (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (b) Nicolau, K. C.; Snyder, S. A.; Montagnon, T.; Vassiliogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (c) Tietze, L. F.; Kettischau, G. In *Topics in Current Chemistry*; Metz, P., Ed.; Springer-Verlag: Berlin, 1997; Vol. 189, pp 1–120 and references therein. (d) Waldmann, H. *Synthesis* **1994**, 535.

(2) For reviews on the Diels–Alder reaction of amino-substituted dienes, see: (a) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023. (b) Barluenga, J.; Suarez-Sobrinio, A.; Lopez, L. A. *Aldrichim. Acta* **1997**, *32*, 4.

(3) (a) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352. (b) Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, 3089. (c) Overman, L. E.; Yaylor, G. F.; Houk, K. N.; Domelsmith, L. S. *J. Am. Chem. Soc.* **1978**, *100*, 3182. (d) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 4537. (e) Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816.

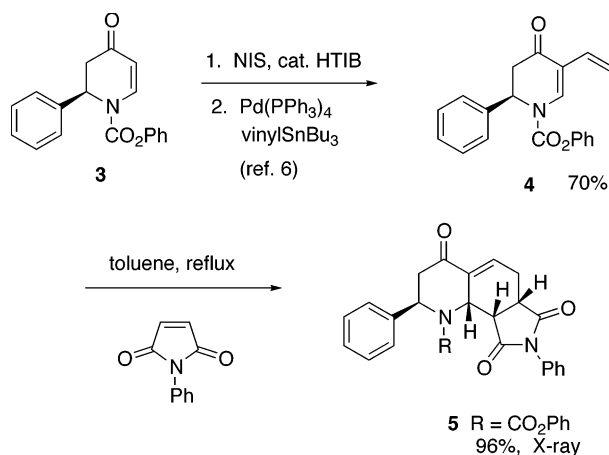
Table 1. Diels–Alder Reactions of **4** with Various Dienophiles

entry ^a	dienophile	cycloadduct ^{b,c}	entry ^a	dienophile	cycloadduct ^{b,c}
1		 6 90%	6		 11a 11a : 11b = 1 : 1
2		 7 76%			 11b
3		 8 74%	7		 12a
4		 9 93%			 12b 12a : 12b = 25 : 1, Y = CO₂Me 86% 12a : 12b = 2 : 1, Y = CN, 91% 12a : 12b = 2 : 1, Y = SO₂Ph, 66%
5		 10 82%			

^a Scale 0.1–0.2 mmol. ^b Isolated yields. ^c Ratio determined by ¹H NMR or HPLC.

yield.⁶ Reaction of **4** with *N*-phenylmaleimide in refluxing toluene afforded cycloadduct **5** as a single diastereomer in 96% isolated yield. The relative stereochemistry of **5** was unequivocally established by single-crystal X-ray analysis, which showed the exclusive preference for endo approach of the dienophile.⁷ Since the C-2 phenyl group of diene **4** occupies a pseudoaxial orientation,⁸ excellent diastereofacial control was observed where addition of the dienophile occurred exclusively anti to the phenyl substituent, thus setting the three new contiguous chiral centers with complete

stereocontrol. The Diels–Alder reactions of **4** with various dienophiles are summarized in Table 1. When *cis*-disubstituted dienophiles were employed (entries 1–5), the cycloadducts **6**–**10** were obtained as single diastereomers in good to excellent yields. The structures were determined by ¹H NMR analysis by comparison of coupling constants with those observed for cycloadduct **5**. On the other hand, when dimethyl fumarate served as the dienophile (entry 6), no endo/exo selectivity was observed and cycloadducts **11a** and **11b** were obtained as a 1:1 mixture of diastereomers. Interestingly, reaction of **4** with methyl acrylate, acrylonitrile, and phenyl vinyl sulfone (entry 7) only showed modest preference for the endo adducts **12a**. However, in each case the products were in full accord with that predicted by

Scheme 1

(4) (a) Ha, J. D.; Kang, C. H.; Belmore, K. A.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 3810 and references therein. (b) Aelterman, W.; De Kimpe, N. *Tetrahedron* **1998**, *54*, 2563. (c) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700. (d) Jiang, J.; DeVita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvrat, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593. (e) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Tetrahedron Lett.* **2002**, *43*, 8159 and references therein.

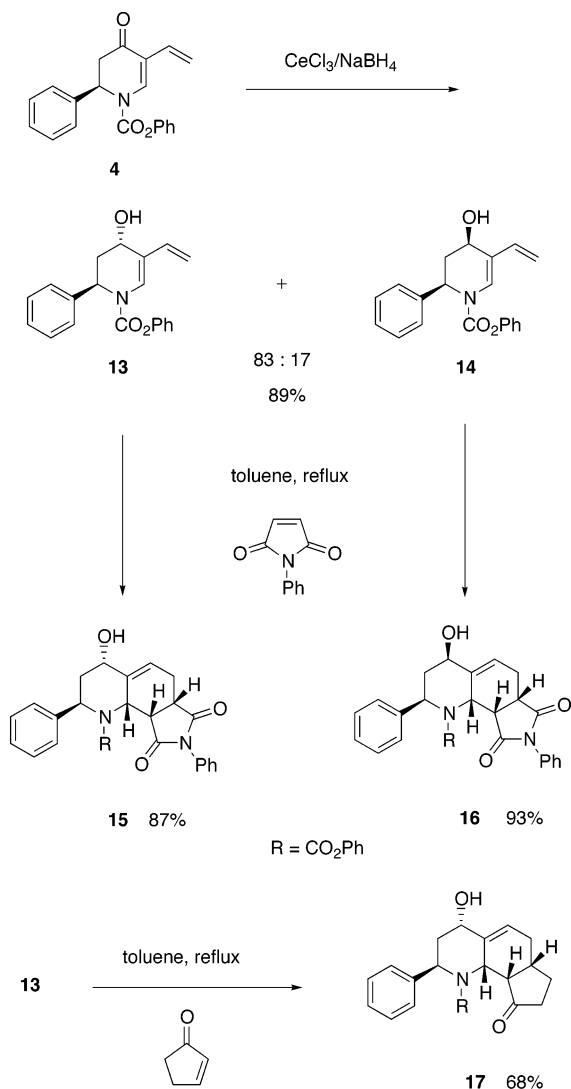
(5) For leading references, see: (a) Comins, D. L.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184. (b) Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229. (c) Comins, D. L.; Fulp, A. B. *Org. Lett.* **1999**, *1*, 1941. (d) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855. (e) Huang, S.; Comins, D. L. *Chem. Commun.* **2000**, *7*, 569.

(6) Comins, D. L.; Joseph, S. P.; Chen, X. *Tetrahedron Lett.* **1995**, *36*, 9141.

(7) Details can be found in Supporting Information.

(8) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 2, pp 251–294 and references therein.

Scheme 2



HOMO diene-LUMO dienophile interaction. In all cases (entries 1–7), there was no detectable amount of double bond isomerization of the cycloadducts.

To further explore the synthetic utility of the process, the Diels–Alder chemistry of dienes **13** and **14** was also explored. Luche reduction of **4** provided **13** and **14** as a 83:17 mixture (**13**:**14**) in a combined yield of 89%. The isomers were easily separated by silica gel chromatography. Individual reaction of **13** and **14** with *N*-phenylmaleimide in refluxing toluene for 30 min gave cycloadducts **15** and **16** as single diastereomers in 87% and 93% yield, respectively. In similar fashion, reaction of **13** with cyclopentenone provided **17** in 68% isolated yield. In conclusion, the Diels–Alder reaction of 5-vinyl-1-acyl-2-aryl-2,3-dihydro-4-pyridones provides a highly diastereoselective means of preparing octahydroquinolines containing various functionalities. By taking advantage of the C-2 axial substituent, three contiguous centers can be set in a single synthetic operation. Although this study used racemic starting material, the methodology can lead to enantiopure products by starting with readily available nonracemic dihydropyridones.⁹ Application of this chemistry to the synthesis of natural products is underway in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental and spectral data for compounds **5**–**17**. ORTEP plot and X-ray crystal data for **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1994**, *35*, 7343. (c) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807.