

AROMATIC ANNELATION. I. SYNTHESIS OF PYRIDINES.

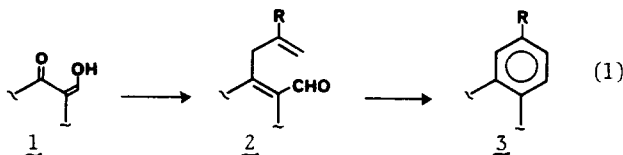
Marcus A. Tius,* Andrew Thurkauf and Joel W. Truesdell

Department of Chemistry, University of Hawaii
Honolulu, Hawaii, 96822, U.S.A.

Summary: The preparation of substituted pyridines from cycloalkanones by elaboration of an aromatic ring is described.

Renewed interest in the area of aromatic annelations has resulted in some progress in the synthesis of phenols, pyridines and benzene rings from non-aromatic precursors.¹ Most of the known methods rely upon one of two strategies. In the first a Diels-Alder reaction produces a cyclohexadiene which undergoes an elimination or oxidation to introduce the last unit of unsaturation.^{1a-d} The alternate strategy relies upon a Robinson annelation which is followed by ejection of a β leaving group to form a phenol.^{1e,f} In our approach to the total synthesis of dihydrophenanthrene natural products juncunol and juncusol² we were faced with the problem of elaborating a specifically substituted phenol from a non-aromatic precursor. Our solution to this problem has resulted in a mild and general synthesis of pyridines and phenols.³

In earlier work we demonstrated the ease with which an intramolecular Prins reaction leads to benzoannulated products (equation 1).⁴ The preparation of unsaturated aldehydes 2



was accomplished in a single operation from addition of allylic Grignard reagents to the O-trimethylsilyl derivative of 1, followed by hydrolysis with dilute aqueous acid. If ketoaldehyde 4 could also be prepared from 1 it could serve as a common precursor both to phenol 5 and pyridine 6 (equation 2).

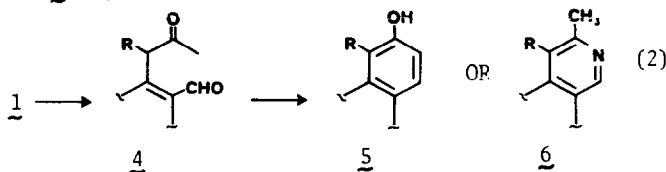
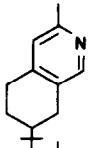
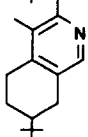
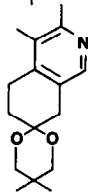
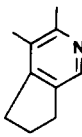
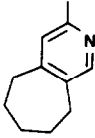
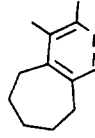
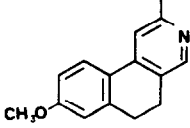


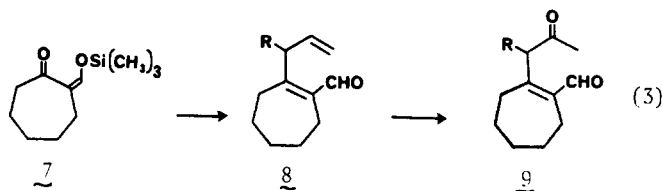
Table 1

Pyridine ^a		¹ H 100-MHz nmr (CDCl ₃ , δ)	ir (ν _{max} , cm ⁻¹)	mass spectrum (m/e)
1. 	91%	8.19 (br s, 1H, Ar-H) 6.82 (br s, 1H, Ar-H) 2.43 (s, 3H, CH ₃)	2960, 1605, 1470, 1365, 1240.	203 (p), 188 (p-CH ₃), 146 (p-tBu), 132, 131, 119.
2. 	50%	8.06 (br s, 1H, Ar-H) 2.44 (s, 3H, CH ₃) 2.10 (s, 3H, CH ₃)	2960, 1590, 1470, 1365, 1240.	217 (p), 202 (p-CH ₃), 160 (p-tBu), 146, 145.
3. 	98% mp 87-88°C	8.02 (br s, 1H, Ar-H) 3.52 (s, 4H, OCH ₂) 2.43 (s, 3H, CH ₃) 2.11 (s, 3H, CH ₃) 0.98 (s, 3H, CH ₃) 0.96 (s, 3H, CH ₃)	2930, 2880, 1590, 1460, 1440, 1380, 1365, 1115, 850.	261 (p), 246 (p-CH ₃ , very weak), 193, 192, 175, 162, 160, 148, 147, 146, 133.
4. 	87%	8.18 (br s, 1H, Ar-H) 2.47 (s, 3H, CH ₃) 2.19 (s, 3H, CH ₃)	2950, 1605, 1440, 1410, 1195.	147 (p), 146, 132 (p-CH ₃), 131, 117, 91.
5. 	49% ^b	8.17 (br s, 1H, Ar-H) 6.88 (br s, 1H, Ar-H) 2.47 (s, 3H, CH ₃)	2920, 2850, 1605, 1445.	161 (p), 160, 146 (p-CH ₃), 132, 120, 119, 91.
6. 	95% ^b	8.02 (br s, 1H, Ar-H) 2.49 (s, 3H, CH ₃) 2.23 (s, 3H, CH ₃)	2920, 1590, 1445, 1400.	175 (p), 174, 160 (p-CH ₃), 146.
7. 	90%	8.28 (br s, 1H, pyr-H) 7.34 (br s, 1H, pyr-H) 3.81 (s, 3H, OCH ₃) 2.80 (s, 4H, (CH ₂) ₂) 2.53 (s, 3H, CH ₃)	2950, 1600, 1490, 1260, 1050, 910.	225 (p), 210 (p-CH ₃), 194, 180, 96, 94.

(a) Yields refer to materials purified by flash chromatography.

(b) Overall yield for the oxidation and the cyclization.

The attenuated electrophilicity⁵ of the carbonyl group in vinylogous silyl esters such as 7 limited our choice of nucleophile (equation 3). Since the addition of allylic Grignard reagents to 7 and the subsequent hydrolysis to 8 was successful, (R = H 76%, R = CH₃ 87%), we reasoned that selective, palladium catalyzed oxygenation of the non-conjugated double bond of 8 would provide access to the desired intermediate 9.⁵ The oxidation was performed through a



modification of Tsuji's procedure.⁶ In aqueous *N,N*-dimethylformamide (DMF) containing 3 equiv of cuprous chloride⁷ and 0.1 equiv of palladous chloride, oxidation was complete within 2.5h when a slow stream of oxygen was bubbled through the solution at 45°C. The ketoaldehydes thus obtained were surprisingly labile and underwent appreciable decomposition both during storage and during column chromatography on silica gel. Best results were obtained when the crude materials were cyclized.⁸

The conversion of the dicarbonyl precursors to the substituted pyridines was accomplished by treatment at 23°C with a solution of gaseous ammonia in anhydrous ethanol. A milder and more convenient method was found when ethanolic ammonium acetate was used instead. Under these (neutral) conditions conversion to the pyridine was complete within 15 to 30 min. Representative examples are listed in Table 1.⁹

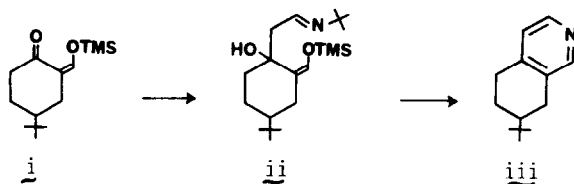
The scope of this mild, new method will be demonstrated through its application to the total synthesis of polyfunctional natural products. Experimental details follow.

Cyclization of 8 (R = CH₃) to the pyridine: A solution of 110 mg of 8 in 770 μ l of DMF containing 183 μ l of water was treated with 11 mg (0.1 equiv) of palladous chloride and 183 mg (3 equiv) of cuprous chloride⁶ at 45°C. A stream of oxygen was introduced through a capillary for 2.5h. The reaction mixture was treated with 3 ml of acetonitrile, was stirred with half-saturated aqueous sodium bicarbonate for 2h and was filtered. Partitioning between methylene chloride and water furnished crude ketoaldehyde 9 (R = CH₃; 136 mg) which was immediately dissolved in 6 ml of absolute ethanol and treated with 237 mg (ca. 5 equiv) of ammonium acetate. After 0.5h the solution was diluted with two volumes of water and was concentrated. The concentrate was basified by addition of 1N aqueous sodium hydroxide and was extracted with methylene chloride. Drying (K₂CO₃) followed by concentration furnished the crude product. Flash chromatography gave 103 mg (95% overall) of the pyridine as an oil: ν_{\max} 2920, 1590, 1445 cm⁻¹; ¹H nmr (CDCl₃) δ 8.02 (br s, 1H, Ar-H), 2.49 (s, 3H, CH₃), 2.23 (s, 3H, CH₃); mass spectrum m/e 175 (p), 174, 160 (p-CH₃), 146.

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References and Notes

- (a) A. G. Schultz, M. Shen and R. Ravindranathan, *Tetrahedron Lett.*, 1767 (1981); (b) D. L. Boger and J. S. Panek, *J. Org. Chem.*, **46**, 2179 (1981); (c) L. A. Paquette, R. E. Moerck, B. Harirchian and P. D. Magnus, *J. Am. Chem. Soc.*, **100**, 1597 (1978); (d) S. Danishefsky, T. Kitahara, C. F. Yan and J. Morris, *J. Am. Chem. Soc.*, **101**, 6996 (1979); (e) K. Takaki, M. Okada, M. Yamada and K. Negoro, *J. Chem. Soc., Chem. Commun.*, 1183 (1980); (f) D. L. Boger and M. D. Mullican, *J. Org. Chem.*, **45**, 5002 (1980); (g) T. H. Chan and P. Brownbridge, *Tetrahedron*, **37**, Supp. 1, 387 (1981), and references cited therein.
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- The synthesis of phenols is described in the accompanying paper.
- M. A. Tius and S. Ali, *J. Org. Chem.*, in press.
- The addition of the lithium anion of acetaldehyde *tert*-butylimine to enone **i** took place in modest yield. Subsequent treatment of adduct **ii** with a solution of ammonia in anhydrous ethanol or ethanolic ammonium acetate resulted in a low (19%) overall conversion to pyridine **iii**. Substrates other than **i** gave similar results. Use of the



α -trimethylsilyl imine anion or ketone N,N-dimethylhydrazone anions led to no improvement. The low yields may be due in part to competing conjugate addition to the vinylogous silyl ester **i**. E. J. Corey, D. Enders and M. G. Bock, *Tetrahedron Lett.*, 7 (1976).

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- Cuprous chloride was purified: J. Österlöf, *Acta Chem. Scand.*, **4**, 374 (1950).
- The isolated yields for the oxidation step varied from 33% to 59%. The overall yields for the two steps, oxidation to the ketoaldehyde and cyclization to the pyridine, were much higher. See Table 1.
- None of the compounds in Table 1 have been described in the literature. With the exception of entry 3, all compounds were obtained following column chromatography on silica gel as clear oils which darkened upon standing.

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