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PALLADIUM ASSISTED SYNTHESIS OF 1-AZASPIROCYCLES

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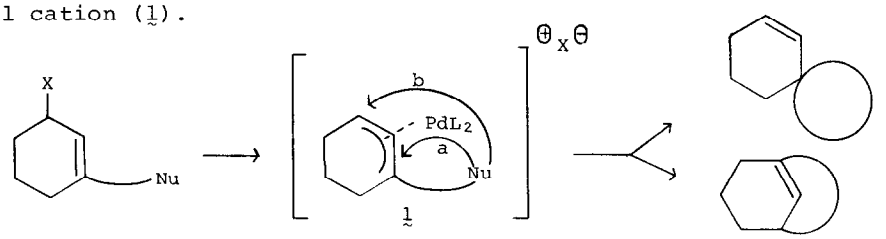
SUMMARY: A facile, general route to 1-azaspirocycles utilizing a π-allyl palladium complex in the key cyclization step has been developed.

INTRODUCTION

An examination of the stereochemical and functional diversity contained in natural products possessing a 1-azaspirocyclic ring structure[1] indicates that any general methodology devoted to the preparation of such spirocycles must have the following features: 1) facile entry to the key spirocyclization step from readily available starting materials; 2) complete stereospecificity in the formation of the spiro center; 3) toleration of a variety of unprotected functionality in the cyclization substrate; 4) potential asymmetric induction in the spirocyclization. The existing methodologies[2,3,4] for the construction of these ring systems typically do not fulfill all of these requirements. We would like to report the development of a new procedure for the preparation of 1-azaspirocycles based on π-allyl palladium chemistry which potentially meets all the stated criteria.[5,6,7,8]

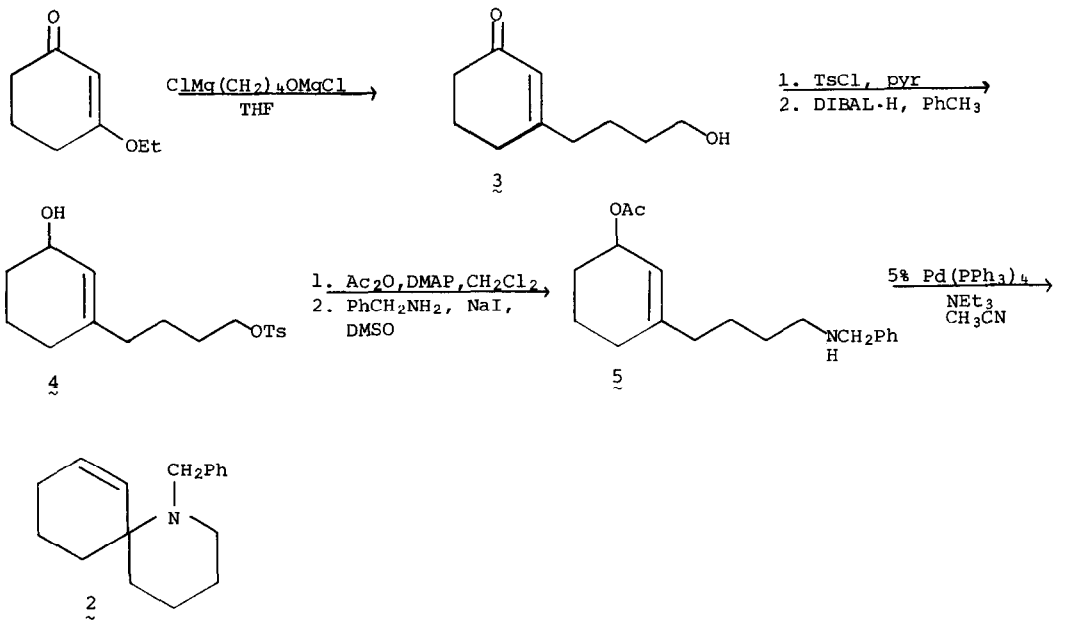
The key intermediate in the palladium catalyzed spirocyclization can be depicted in general as shown below (1). Reaction of an allylic ester (e.g., X = OAc) with tetrakistriphenylphosphine palladium(0) yields the bisphosphine allyl cation (1).



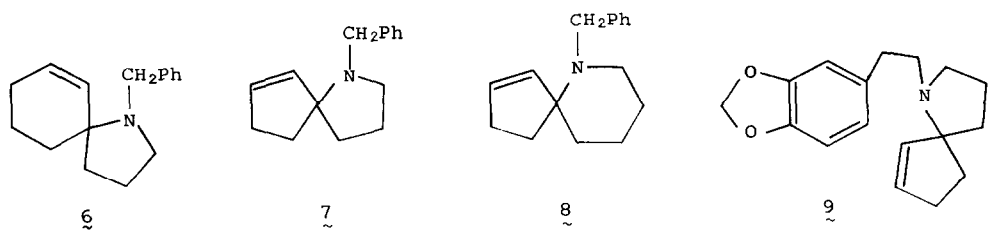
Cyclization of this compound could in principle take place on either terminus of the allyl unit. Cyclization path (a) leads to the desired spirocycle, while b yields a trans-cycloalkenyl system, which for the ring sizes of most interest for spirocyclic natural products ([5,5],[5,4],[4,4] would be an anti-Bredt olefin.[9]

RESULTS

Based on this rationale, the preparation of a variety of 1-azaspirocycles (Nu = NHR) has been accomplished. As the sequences are closely related and the yields in each are comparable, a detailed description of the preparation of only N-benzyl-1-azaspiro[5,5]undec-7-ene (2) will be given.



The addition of the Normant Grignard reagent[10] derived from 4-chloro-1-butanol to the vinylogous ester, 3-ethoxy-2-cyclohexen-1-one, followed by an acidic workup yielded α,β-unsaturated ketoalcohol (3) in 85% yield. Tosylation of 3 (TsCl, pyr, 0°C, 8 h) followed by DIBAL-H reduction (toluene, -78°C, 7 h) provided the desired allylic alcohol (4) in an overall yield for the two steps of 75%. Acetylation of 4 (Ac_2O, dimethylaminopyridine, CH_2Cl_2, 0°C, 2h) followed by a NaI catalyzed displacement of the tosylate by benzyl amine (2 equiv. $PhCH_2NH_2$, cat. NaI, DMSO, rt, 5h) gave the desired precursor for cyclization (5) (65% yield for two steps).[11] Treatment of 5 with 5 mole % of tetrakistriphenyl phosphine palladium(0) in CH_3CN and one equiv. of NEt_3 at 70°C yielded the azaspirocycle (2) in quantitative yield (≥ 95%) in two hours. This general procedure has been utilized to prepare the azaspirocycles (6, 7, 8, 9).[12] The yields in the key cyclization step are uniformly quantitative.



Performance of the necessary control experiments clearly indicates the intimate involvement of the metal in these reactions.

Compounds 2 and 9 serve as models for perhydrohistrionotoxin and cephalotaxine, respectively; total syntheses of which are currently under active investigation in our laboratories. In addition, the use of a variety of carbon and oxygen nucleophiles is currently being pursued by us. We feel that this metal assisted route will provide a general means of entry into a wide variety of spirocyclic systems which is by virtue of the π-allyl palladium intermediate particularly suited to application to natural product syntheses.

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References

1. Devon, T. K.; Scott, A. I."Handbook of Naturally Occurring Compounds," Vol. I, II, Academic Press, New York (1975).
2. Krapcho, A. P. Synthesis, 1976, 383.
3. ibid., 1976, 425.
4. For a recent metal assisted route to spirocycles see: Pearson, A. J. Accts. Chem. Res. 1980, 13, 463; Pearson, A. J.; Ong, C. W. Tetrahedron Lett. 1980, 4041; Pearson, A. J. J.C.S. Perkin I 1980, 400; ibid., 1979, 1255.
5. Stereospecificity; i.e., complete retention of configuration with respect to allylic C—X bond in nucleophilic addition, Trost, B. M.; Weber, L. J. Am. Chem. Soc. 1975, 97, 1611.
6. Chemospecificity, Trost, B. M.; Dietsche, T. J.; Fullerton, T. J. J. Org. Chem. 1974, 39, 737.
7. Asymmetric induction via the use of chiral phosphines on Pd, Trost, B.M.; Dietsche, T. J. J. Am. Chem. Soc. 1973, 95, 8200.
8. Accounts of this work have been presented at the following meetings: 179th National ACS Meeting, Houston, Texas, March 1980, "Palladium Catalyzed Preparations of 1-Azaspirocycles"; 180th ACS National Meeting, Las Vegas, Nevada, August 1980,"Studies in the Synthesis of Cephalotaxine."
9. Although there is the intriguing possibility of stabilization of such an intermediate via synergistic interaction with the metal, this mode of cyclization has not been observed. We are currently pursuing the preparation of such complexes.
10. Cahiel, G.; Alexakis, A.; Normant, J. F. Tetrahedron Lett. 1978, 3013.
11. Typically the crude amino-allylic acetate (5) was subjected to medium pressure liquid chromatographic purification before cyclization.
12. Spectral data for 6, 7, 2, 8, 9 are as follows.

6 ^{1}H NMR (100 MHz) ($CDCl_3$) δ7.36 (br s, 5H); 5.92 (m, 1H); 5.68 (br, d, 1H, J = 10 Hz); 3.74 and 3.54 (AB quartet, 2H, J = 13 Hz); 2.72 (m, 2H); 2.2-1.4 (m, 10H).

^{13}C NMR ($CDCl_3$) {^{1}H} (off resonance decoupling used to provide multiplicities) 141.2 (s); 133.9 (d); 128.9 (d), 128.3 (d); 128.0 (d); 126.3 (d); 63.4 (s); 53.6 (t); 50.4 (t); 38.4 (t); 29.0 (t); 25.3 (t), 21.3 (t); degeneracy of peak at 21.3 reflected in its relative intensity and peak width.

IR (CCl_4) 2915, 1495, 1455, 1365, 1350, 1240, 1190, 1160, 1105, 1025, 915, 695 cm^{-1}.

MS (75 eV) 227 (M^+) 212, 198, 184, 170, 108, 91 (Base).

7 ~ ^{1}H NMR (100 MHz) ($CDCl_3$) δ7.28 (br s, 5H); 5.88 (m, 1H); 5.68 (br d, 1H, J ≅ 7 Hz); 3.56 and 3.36 (AB quartet, 2H, J = 14 Hz); 2.56 (m, 2H); 2.50 (m, 2H); 2.0-1.5 (m, 6H).

^{13}C NMR ($CDCl_3$) {^{1}H} (off resonance decoupling used to provide multiplicities) 140.6 (s); 135.0 (d); 132.2 (d); 128.5 (d); 128.0 (d); 126.4 (d); 77.5 (s); 53.4 (t); 51.0 (t); 38.2 (t); 31.6 (t); 29.8 (t); 21.3 (t) ppm.

IR (CCl_4) 2915, 1495, 1450, 1355, 1250, 1200, 1185, 690 cm^{-1}.

MS (75 eV) 213 (M^+) 198, 184, 172, 170, 122, 120, 118, 91 (Base).

2 ~ ^{1}H NMR (100 MHz) ($CDCl_3$) δ7.32 (br s, 5H); 5.88-5.32 (m, 2H); 3.88 and 3.08 (AB quartet, 2H, J = 14 Hz); 2.72 (m, 2H); 2.0-1.0 (m, 2H).

^{13}C NMR ($CDCl_3$) {H} (off resonance decoupling used to provide multiplicities) 140.7 (s); 136.2 (d); 127.2 (d); 126.9 (d); 125.3 (d); 55.7 (s); 54.4 (t); 44.8 (t), 35.2 (t); 25.3 (t); 24.4 (t) 21.7 (t); 19.3 (t) ppm. Resonance at 127.2 degenerate (2C), as indicated by relative intensity of peak.

IR (CCl_4) 2930, 1500, 1450, 1365, 1265, 1215, 1190, 1130, 1065, 695 cm^{-1}.

MS (75 eV) 241 (M^+) 226, 213, 212, 198, 184, 150, 91 (Base).

8 ~ ^{1}H NMR (100 MHz) ($CDCl_3$) δ7.26 (br s, 5H); 5.70 (m, 1H); 5.65 (m, 1H); 3.75 and 3.15 (AB quartet, 2H, J = 14 Hz); 2.38 (m, 2H); 2.0-1.0 (m, 10H).

^{13}C NMR ($CDCl_3$) {^{1}H} 141.2; 139.0; 130.6; 129.4; 128.0; 126.3; 72.6; 55.2; 48.4; 37.9; 31.8; 26.3; 25.7; 21.9.

IR (CCl_4) 2930, 1495, 1450, 1355, 1060, 905, 690 cm^{-1}.

MS (75 eV) 227 (M^+) 212, 198, 185, 170, 162, 148, 136, 91 (Base).

9 ~ ^{1}H NMR (100 MHz) ($CDCl_3$) δ6.64 (br s, 3H); 5.95 (s, 2H); 5.80 (m, 1H); 5.50 (m, 1H); 2.70 (br m, 2H); 1.9 (br m, 6H).

^{13}C NMR ($CDCl_3$) {H} 147.3; 145.6; 134.5; 132.2; 121.3; 109.0; 107.9; 100.6; 77.5; 51.4; 51.1; 38.1; 35.8; 31.4; 29.3; 21.3 (one degeneracy).

IR (CCl_4) 2950, 1505, 1495, 1445, 1250, 1045, 720 cm^{-1}.

MS (20 eV) 271 (M^+) 247, 178, 149, 135, 112 (Base), 106.

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