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A Palladium Mediated Spiroketal Synthesis

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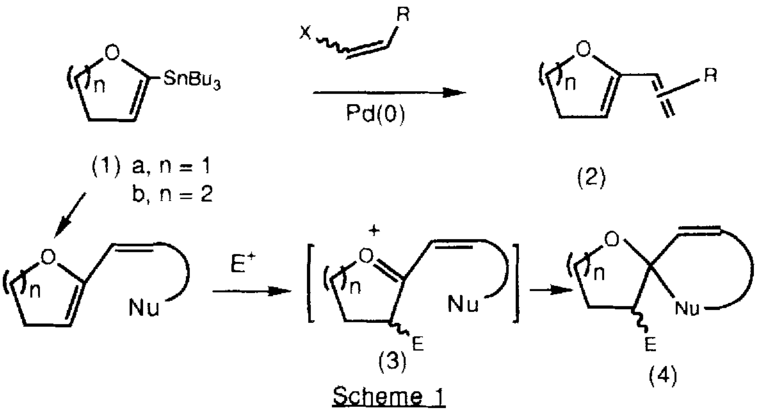
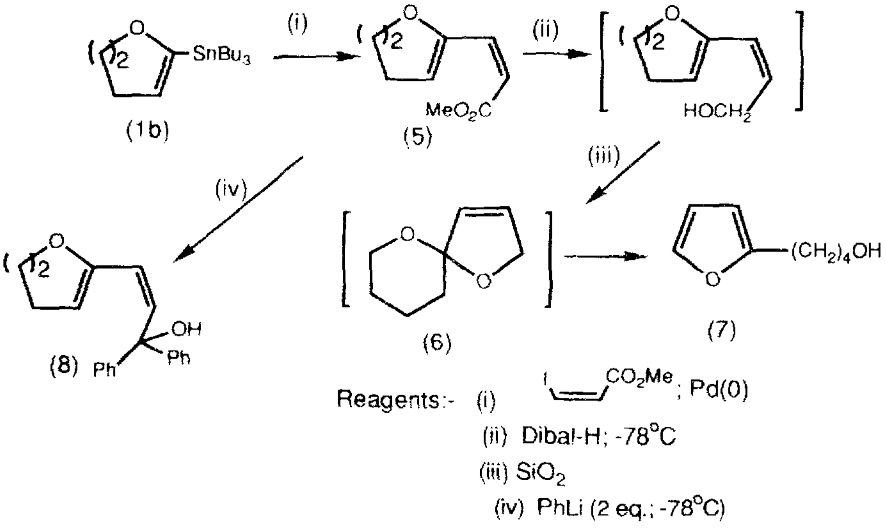
Abstract: *The synthesis of a variety of spiroketal-containing systems is outlined, utilising a palladium catalysed coupling reaction in the pivotal carbon-carbon bond forming step.*

We recently reported[1] that stannanes such as (**1**) undergo clean palladium-mediated cross-coupling reactions with a variety of vinyl(aryl) halides to afford the heterocyclic systems (**2**). Herein we report that addition of a suitable electrophilic trigger generates an oxonium cation (**3**) which undergoes intramolecular capture with a suitably positioned nucleophilic centre affording the functionalised spirocyclic[2] species (**4**), Scheme 1.

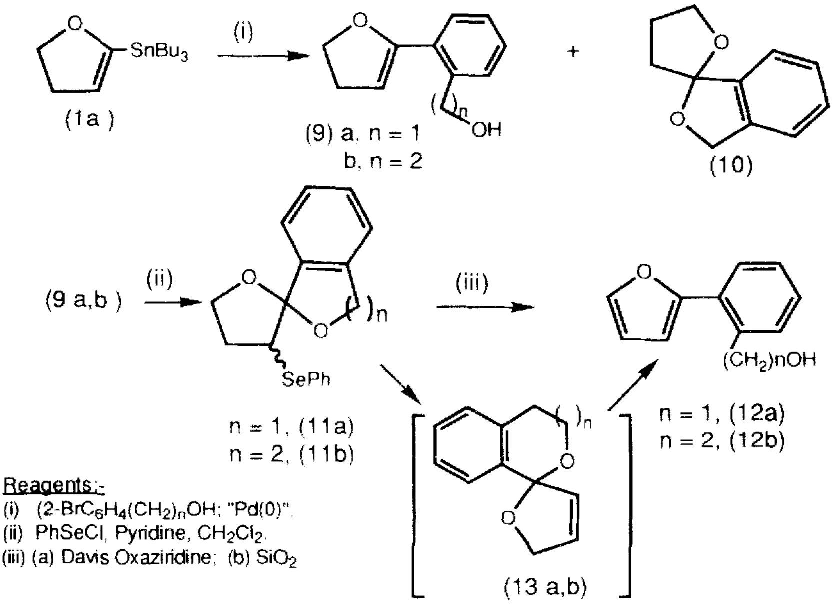


Scheme 1

Our initial attempts to prepare spiroketals by this protocol were disappointing. Reduction of the readily available diene (**5**) (Z:E > 95:1) with Dibal-H (2.2 eq.) at -78°C, followed by an aqueous quench and chromatography (silica) afforded the substituted furan (**7**) in 25% overall yield, presumably via the intermediacy of the "hypersensitive"[3] spiroketal (**6**). All attempts to isolate the spirocycle (**6**) met with failure. Attempted derivatisation of the ester (**5**) by reaction with a variety of organometallic reagents (e.g. with PhMgBr) was hampered by competing[4,5] 1,4-addition reactions. Optimum yields of the carbinol (**8**) (30% yield) were obtained by the reaction with PhLi (2 eq., -78°C to 0°C). However the alcohol (**8**) resisted all attempts to undergo spirocyclisation.

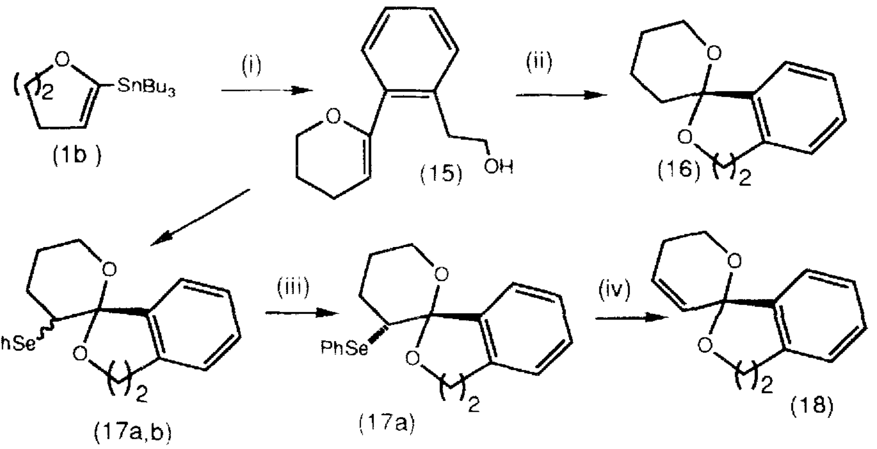


Coupling of the stannane (**1a**) with 2-bromobenzyl alcohol (Pd(OAc)$_2$, 10 mol%; (2-Tol)$_3$P, 20 mol%; Et$_3$N; CH$_3$CN; reflux) afforded a separable mixture of the vinyl ether (**9a**) and the spiroketal (**10**) in 35% and 12% overall yields respectively. Spiroselenocyclisation[6] of the enol ether (**9a**) was readily accomplished (pyridine, 3 eq.; PhSeCl, 2 eq.; CH$_2$Cl$_2$; 25°C, 30 mins.) to afford a diastereoisomeric mixture of spirocycles (**11a**) in excellent yield (82%). However, oxidation[7] ((-)-(2S,8aR)(camphorsulphonyl)oxaziridine, 1.1 eq.; pyridine, 6 eq.; CH$_2$Cl$_2$, 20°C, 1hr) and selenoxide elimination (CH$_2$Cl$_2$, reflux, 16 hrs.) cleanly afforded the rearranged alcohol (**12a**) in good overall yield (75%). The presumed intermediate in this sequence, the unsaturated spirocycle (**13a**) was apparently too unstable to be isolated. Similarly, cyclisation of the enol ether (**9b**), followed by selenide oxidation and elimination afforded the rearranged furan (**12b**) in 60% yield. However, coupling of the stannane (**1b**) with the bromide (**14**) afforded the chromatographically stable enol ether (**15**) in 71% yield. Upon dissolution in "aged" CDCl$_3$ the alcohol (**15**) underwent spontaneous cyclisation to the spirocycle (**16**) in quantitative yield. Alternatively, selenium induced cyclisation (PhSeCl, 2 eq.; pyridine, 3 eq.; CH$_2$Cl$_2$; 20°C, 30 min.) afforded a 1:1 mixture of the selenides (**17 a,b**) (96%), which upon dissolution in "aged" CDCl$_3$ equilibrated (20 min., 20°C) to the diastereomerically pure spiroketal (**17a**) in quantitative yield. As expected, oxidation of the selenide (**17a**) using Davis's[7] reagent proceeded smoothly to affording the stable, unsaturated spirocycle (**18**) (99% yield).



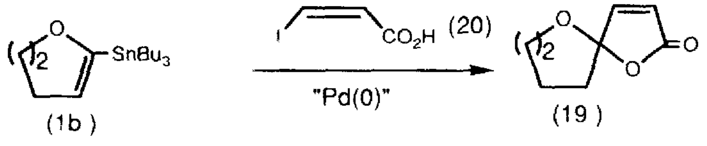
Reagents :-
(i) (2-BrC$_6$H$_4$(CH$_2$)$_n$OH; "Pd(0)".
(ii) PhSeCl, Pyridine, CH$_2$Cl$_2$.
(iii) (a) Davis Oxaziridine; (b) SiO$_2$

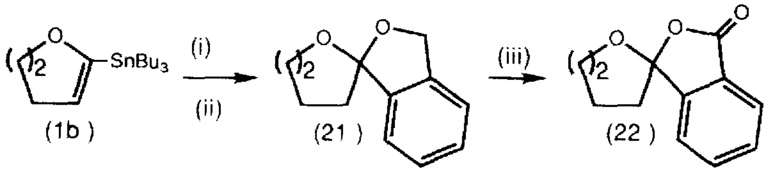
In an attempt to develop a "one-pot" procedure for the synthesis of spirocyclic lactones of type (**19**), a palladium coupling reaction of the stannane (**1b**) with Z-iodoacrylic acid (**20**) was investigated. Although the desired spirocycle (**19**) could be isolated upon acidification of the reaction mixture, the yield for the overall process was only 15%. The analogous lactone (**22**) was best prepared in a two-step sequence: coupling of 2-bromo benzyl alcohol with the stannane (**1b**) in the usual manner, followed by dissolution in CDCl$_3$ led to the direct isolation of the spirocycle (**21**) (55% yield), and, oxidation of the activated benzylic methylene group[8] (^{t}BuOOH, 3 eq.; Cr(CO)$_6$, cat.; CH$_3$CN, reflux, 26 hrs.) of (**21**) afforded the crystalline lactone (**22**) in 55% yield.



Reagents:- (i) (2-BrC_6H_4)CH_2CH_2OH, (**14**); Pd$(OAc)_2$; Et_3N; CH_3CN; (iii) $CDCl_3$; (iv) Davis Oxaziridine; Pyridine; CH_2Cl_2; 40°C.

In conclusion, we have demonstrated that a variety of spiroketal containing systems are accessible utilising a palladium-catalysed coupling reaction in the pivotal carbon-carbon bond forming step[9]. Work is now in hand to further delineate this basic reaction scheme.





Reagents:- (i) (2-BrC_6H_4)CH_2OH; Pd$(OAc)_2$; (2-Tol)$_3$P; Et_3N; CH_3CN; 80°C;
(ii) $CDCl_3$; 20°; (iii) ^{t}BuOOH; Cr$(CO)_6$; CH_3CN; 80°C.

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References and notes

(1) D. MacLeod, D. Moorcroft, P. Quayle, M. J. R. Dorrity, J. F. Malone, and G. M. Davies, Tetrahedron Letters, 1990, 31, 6077; C. Booth, H. Immanieh, P. Quayle, and Y.-S. Lu, Tetrahedron Letters, 1991, submitted. For related processes see R. W. Friesen and D. F. Sturino, J. Org. Chem., 1990, 55, 2572; S. L. Schreiber and J. A. Porco, J. Org. Chem., 1989, 54, 4721; M. Kosugi, T, Sumiga, Y. Obara, M. Suzuki, H. Sano, and T. Migita, Bull. Chem. Soc. Jpn., 1986, 60, 767; L. Del Valle, J. K. Stille, and L. S. Hegedus, J. Org. Chem., 1990, 55, 3019; H. Boong Kwon, B. H. McKee and J. K. Stille, J. Org. Chem., 1990, 55, 3114; D. G. Ciattini, E. Morera, and G. Ortar, Tetrahedron Letters, 1990, 31, 1889; L. A. Paquette, C. S. Rae, and S. D. Edmonson, J. Org. Chem., 1990, 55, 2443; R. F. Friesen and A.K. Daljeet, Tetrahedron Letters, 1990, 31, 6133; E. Dubois and J.-M. Beau, J. Chem. Soc., Chem. Commun., 1990, 1191; M. A. Tius, X.-Q. Gu, and J. Gomez-Galeno, J. Am. Chem. Soc., 1990, 112, 8188.

(2) For an in-depth treatment of recent approaches to these systems see T. L. Boivin, Tetrahedron, 1987, 43, 3309; F. Perron and K. F. Albizati, Chem. Rev. 1989, 89, 1617.

(3) R. Whitby and P. Kocienski, Tetrahedron Letters, 1987, 28, 3619.

(4) Curiosly however, reaction with lithium diphenylcuprate (1 equ., -78°C to -10°C) resulted in exclusive double bond isomerisation to afford the E-acrylate rather than 1,2- or 1,4- addition in 70% isolated yield.

(5) c.f. J. Leonard, G. Ryan, and P. A. Swain, Synlett, 1990, 613.

(6) c.f. D. Diez-Martin, P. Grice, H. C. Kolb, S. V. Ley, and A. Madin, Tetrahedron Letters, 1990, 31, 3445; M. Kitamura, M. Isobe, Y. Ichikawa, and T. Goto, J. Org. Chem.,1984, 49, 3517.

(7) For a review see F. A. Davis and A. C. Sheppard, Tetrahedron, 1989, 45, 5703.

(8) A. J. Pearson and G. R. Han, J. Org. Chem., 1985, 50, 2791.

(9) Whilst our studies were in progress two independent reports of similar approaches to spirocyclic systems were reported:- E. Dubois and J.-M. Beau, Tetrahedron Letters, 1990, 31, 5165; R. W. Friesen and C. F. Sturino, J. Org. Chem., 1990, 55, 5808.

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