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THE Pd(0)-CATALYSED COUPLING REACTIONS OF 2-(TRI-N-BUTYLSTANNYL)-3,4-DIHYDROFURAN and -5,6-DIHYDROPYRAN.

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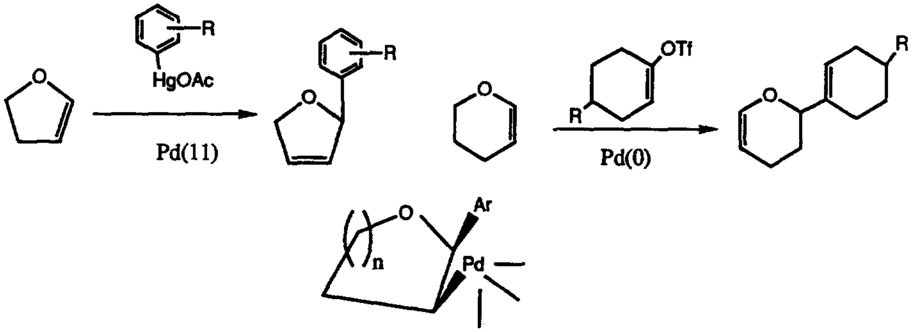
The palladium(0) catalysed reaction of dihydropyranyl and dihydrofuranylstannanes offers an attractive route to the synthesis of 2-vinyldihydropyrans and -furans.

The functionalisation at C-1 of dihydropyrans and dihydrofurans continues to be an area of intense interest[1]. This is primarily due to a host of natural products and related compounds exhibiting interesting biological activity which incorporate C-functionalisation at the anomeric position[2]. The palladium mediated(catalysed) alkylation of dihydropyrans and dihydrofurans has been extensively investigated by a number of workers, most notably by the groups of Daves[3] and Larock[4]. In many cases however, the direct functionalisation of dihydrofurans and dihydropyrans, initially leading to the palladated heterocycles (1), results in the isolation of a variety of unsaturated products, in which the locus of the unsaturation has migrated around the ring (Scheme 1). Whilst the outcome of this isomerization process has a number of useful synthetic possibilities[5], we wished to functionalise dihydrofurans and pyrans with retention of the locus of unsaturation. The results of our initial efforts in this area are detailed in this Letter.



(1)

Scheme 1

The transition metal catalysed cross coupling reactions of two sp^2-hybridised centres giving rise to functionalised 1, 3 - dienes has proven to be a versatile synthetic operation[6]. However, the coupling of α-heterofunctionalised organometallics with vinyl halides has been much less studied[7]. Hence, an investigation into the palladium (0) catalysed[8] coupling of the readily available[9] stannanes (2) and (3) with vinyl and aryl halides was undertaken (Scheme 2). Gratifyingly, reaction of the stannane (2) with 2-iodotoluene (4) in the presence of Pd(OAc)$_2$ (5 mol %), (o-Tol)$_3$P (10 mol %), triethylamine (excess) in refluxing acetonitrile[6a] (2 hours) cleanly led to the formation of the coupled product (5) in 84% yield[10]. Spectroscopic examination (300 MHz ^{1}H nmr) of both the crude and chromatographed product clearly indicated that the coupling reaction had proceeded without double bond migration. Similarly, the enol ether (6) could be isolated in 80% yield from reaction of the stannane (3) with the iodide (4). In an unoptimized reaction, the protected alcohol (7) was coupled with the stannane (3) to afford the pyran (8) in moderate yield (33%).

The coupling reactions of the stannanes (2) and (3) with the vinyl bromides (9) and (10) has also been briefly investigated. Monitoring of the reactions by ^{1}H nmr indicated that the coupling processess were complete after 1-3 hours reflux in acetonitrile, removal of the solvent at this stage, and partitioning between aqueous KF and ether removed most of the tin residues, affording the crude dienes (11), (12) and (13) which were used without further purification. Whilst oxygenated 1, 3 -dienes have been used extensively in Diels-Alder chemistry[11] the preparation and Diels-Alder chemistry of dienes such as (12) has remained virtually unexplored[12]. Hence, addition of a solution of Cookson's reagent (14) (ca.1 equivalent) in redistilled THF to the crude dienes (11), (12) and (13) in THF at -78°C and merely allowing the reaction mixtures to warm to room temperature afforded, after chromatography, the adducts (15), (16) and (17) in moderate overall yields (38%, 27%, 46% respectively) *from the stannanes (2) and (3).* In addition, the diene (11) underwent a Diels - Alder rection (THF, 16 hours, ambient temp.) with N-phenyl maleimide (18) to afford a single crystalline adduct (19) in 21% overall yield from the stannane (2). The structures of the adducts (16) and (17) were unambiguously assigned by single crystal X - ray diffraction studies[#], and in particular established the *cis* - relative stereochemistry between H_2 and H_5 in the adduct (16). Curiously, whilst reaction of the readily available *Z*- iodoacrylate (*Z:E* > 95:1)[13] (20) with the stannane (2) afforded the stable, crystalline diene (21) in good yield (64%) with inversion[14] of olefin geometry (E:Z > 95:1), coupling of the stannane (3) in a similar manner afforded the diene (22) largely as the *Z*-isomer (*Z:E* = 4:1) in 60% yield. The appropriate blank experiments indicated that the isomerisation reaction most probably occurs subsequent to the formation of the diene, presumably *via* the reversible addition of palladium hydride to the activated exocyclic double bond[15]; isomerization of the diene (21) being considerably faster than the diene (22)[16]. The ethers (21) and (22) proved to be reactive dienes and afforded the crystalline adducts (23) and (24) in acceptable yield (88% and 56%) upon reaction with Cookson's reagent at -78°C (5 minutes). The structure of the adduct (24) was confirmed by a single crystal X-ray diffraction study (Figure)[¶].

Enol ethers are versatile synthetic intermediates, thereby facilitating the functionalisation of the initial products of the arylation reactions described above. For example, *in situ* hydroboration-oxidation (BH_3.DMS, 12 hours; H_2O_2 / OH^-) of the enol ether (6) proceeded with a high degree of stereospecificity (only one diastereoisomer observed in the ^{1}H nmr of the crude reaction mixture) to afford the *trans* - alcohol[17] (26) in 29% overall yield from the stannane (3).

We are currently attempting to exploit the coupling and Diels - Alder reactions of more heavily functionalised substrates with a view to the synthesis of a number of carbohydrate derived systems (e.g. C-glycosides).

General experimental procedure

(a) Preparation and Diels - Alder reactions of Dienes

To a stirred mixture of palladium (II) acetate (17 mg; 5 mol. %), tri-(o-tolyl)phosphine (325 mg; 10 mol. %) and triethylamine (0.1 ml) in acetonitrile (5 ml) was added the stannane (3), (500 mg, 1.34 mmol) followed by α -bromostyrene (256 mg, 1.34 mmol). The reaction mixture was refluxed for 1.5 hours then poured into aq. ammonium chloride and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude diene was dissolved in anhydrous THF and cooled to -78°C and Cookson's reagent (234 mg, 1.34 mmol) in THF (6 ml) was added in one portion. The reaction mixture was allowed to warm up to room temperature and the solvent removed *in vacuo*. Flash chromatography of the residue afforded the adduct (17) as a crystalline solid. Yield 220mg (46%), mpt 173- 174°C.

(b) Arylation reactions

To a mixture of palladium (11) acetate (45 mg, 5 mol%), tri-(o-tolyl)phosphine (115 mg, 10 mol%, triethylamine (0.5 ml) and acetonitrile was added the stannane (3) followed by 2-iodotoluene (806 mg, 3.7 mmol). After a one hour at reflux and work up as above, the crude enol ether (6) was redissolved in anhydrous THF (10 ml) to which was added borane.DMS complex (1.88 ml, 2.0 M soln. in THF) at 0°C. After 12 hours at ambient temperature, hydrogen peroxide (5 ml of 20% soln.) and aqueous sodium hydroxide (8 ml of 3M soln.) was added and the reaction mixture stirred for 30 minutes. The reaction mixture was diluted with water (15 ml) and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* . Flash chromatography afforded the alcohol (20) as a mobile oil; yield 217 mg (29%).

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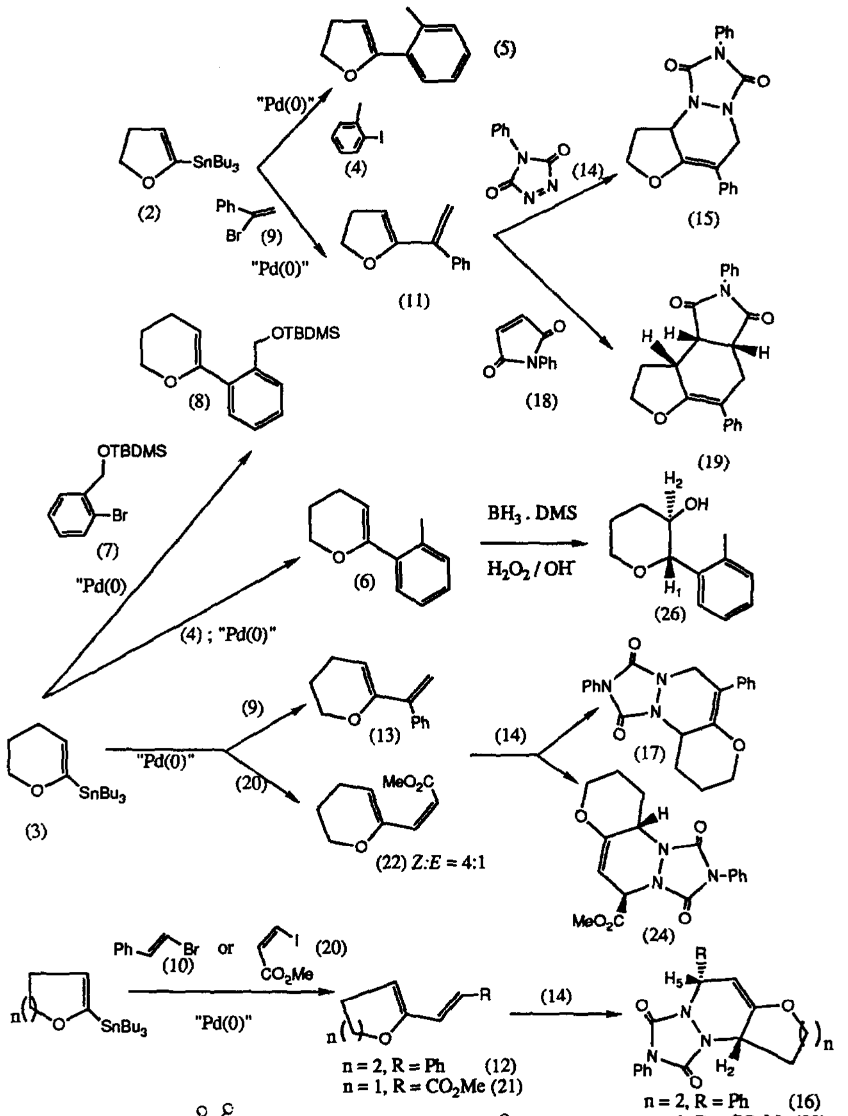
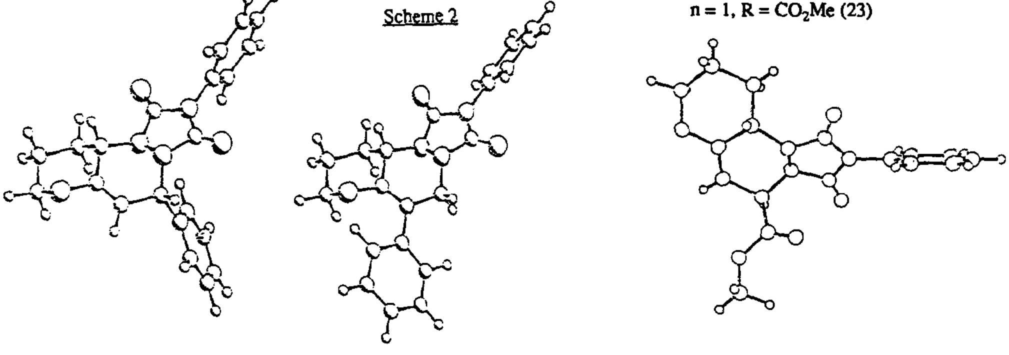


Scheme 2


(16) (17) (24)

FIGURE

reactions in related heterocyclic systems see K. Nilsson and A. Hallberg, J. Org. Chem., 1990, 55, 2464.
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(16) We thank Mr. J. A. Miller for these results.
(17) 'H nmr (300MHz) $CDCl_3$, ∂ 4.20 (1H, $J_{1,2}$ = 9Hz; H_1).

#Crystal Data for (16): $C_{21}H_{19}N_3O_3$. $0.5H_2O$, M = 370.4, monoclinic, a = 26.352(9), b = 5.587(2), c= 24.922(10)Å, β = 103.00(3)°, U = 3574.4(2.3)$Å^3$, Z = 8, D_x = 1.38 cm^{-3}, F(000) = 1560, space group C2/c (No. 15), Mo-Kα radiation, λ = 0.71073A, μ(Mo-Kα) = 0.56 cm^{-1}. Colourless, *elongated prisms; dimensions 0.2 x 0.35 x 0.8mm; Siemens P3/V2000 diffractometer, θ-2θ scans, θ* scan range 1.2°, $3 \leq 2\theta \leq 50°$; 3157 unique reflections measured, direct methods solution (SHELXS86) and least squares refinement (SHELX76); non-hydrogen atoms anisotropic oxygen atom of water molecule of crystallisation revealed in difference Fourier synthesis lying on a two-fold axis between two symmetry-related molecules of (16), [O_{water}-----$O_{carbonyl}$ = 2.91Å]; hydrogen atoms (except H_2O) located in difference Fourier but included at calculated positions. In the final cycles the 2180 data with $F > 4\sigma(F)$ gave R = 0.049, R_w = 0.053 with weighting scheme $w = 1.957/[\sigma^2(F) + 0.000790F^2]$.

Crystal Data for (17): $C_{21}H_{19}N_3O_3$, M = 361.4 monoclinic, a = 20.618(13), b = 13.280(11), c = 15.483(17)Å, β = 122.79(7)°, U = 3563.9(5.7)$Å^3$, Z = 8, D_x = 1.35 g cm^{-3}, F(000) = 1520, space group C2/c (No. 15), Mo-Kα radiation, λ = 0.71073Å, μ(Mo-Kα) = 0.54 cm^{-1}. Colourless flat plates; Siemens P3/V2000 diffractometer, θ-2θ scans, θ scan range 0.8°, $3 \leq 20 \leq 40°$; 1630 unique reflections measured, direct methods solution (SHELXS86) and least squares refinement (SHELX76); non-hydrogen atoms anisotropic, hydrogens located in a difference Fourier synthesis but included at calculated positions. In the final cycles the 629 data with $F > 4\sigma(F)$ gave R = 0.069, R_w = 0.057 with $w = 1.581/[\sigma^2(F) + 0.000250F^2]$.

Projections of both molecules are shown in the Figure. Full crystallographic results have been deposited with the Director, Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge, CB2 1EW, U.K.

¶ The details of this and related X-ray structure determinations will be reported elsewhere.

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