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Use of palladium-mediated allylic substitution reactions in the synthesis of 2,5-disubstituted-2,5-dihydrofurans

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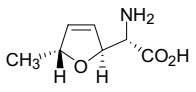
Abstract—2,5-Disubstituted-2,5-dihydrofurans were synthesised in both one- and two-pot reactions starting from 2,5-diacetoxy-2,5-dihydrofuran. These palladium-mediated allylic substitution reactions were useful in preparing symmetrical or unsymmetrical products by employing the same nucleophile twice or two different nucleophiles, respectively.

1. Introduction

Palladium-mediated allylic substitution reactions are important reactions in carbon–carbon,[1] carbon–nitrogen[2] and carbon–oxygen bond forming reactions,[3a,b] and have been employed in the synthesis of a number of physiologically active[4] and natural products.[5] 2,5-Disubstituted dihydrofurans and tetrahydrofurans are important moieties in Nature, examples being furanomycin **1**[6] and nonactic acid **2**.[7] Furanomycin displays antibiotic activity while nonactic acid is the precursor for the ionophoric antibiotic nonactin. We have previously made use of 2,5-diacetoxy-2,5-dihydrofuran as a precursor to several aflotoxin analogues in palladium-mediated allylic substitution reactions,[3a] while Trost et al. later used 2,5-dibenzoyloxy-2,5-dihydrofuran as a starting material for the preparation of nucleosides, which contain nitrogen and carbon functionality in the 2- and 5-positions, respectively.[8] We now disclose an effective method of synthesising 2,5-disubstituted dihydrofurans with two carbon substituents in the 2- and 5-positions in both two- and one-pot reactions, starting from 2,5-diacetoxy-2,5-dihydrofuran.[9]



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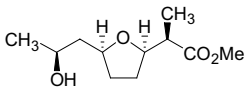

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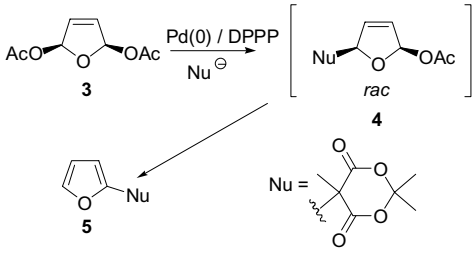
2. Results and discussion

Initially, when diacetate **3** was reacted with a stabilised carbon nucleophile,[3a] in the presence of a palladium catalyst at 65 °C, only the aromatised derivative **5** of our intended product **4** was obtained (Scheme 1). In an attempt to minimise the propensity for aromatisation, subsequent reactions were performed at room temperature. While intermediate **4** could be observed by TLC analysis of the reaction mixture, standard column chromatography on silica caused large-scale degradation of the product, and only trace amounts could be isolated.

To minimise the decomposition, milder techniques were needed during purification. Therefore, all extractions were performed at 0 °C and column chromatography was performed at −15 °C. This resulted in higher yields of **4** but some amount of the decomposed product was



3 **4** **5**

Scheme 1.

Keywords: Allylic acetates; Palladium; Homogeneous catalysis; Nucleophilic substitution.
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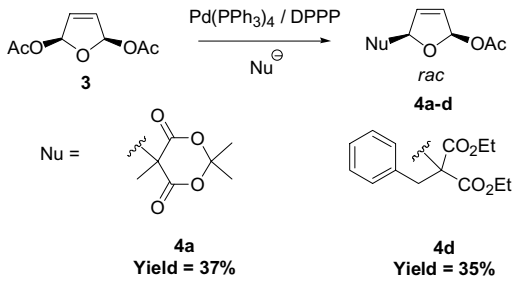


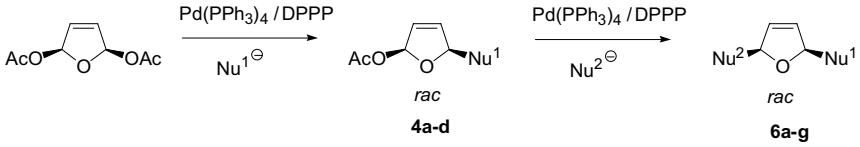
Scheme 2.

still observed. It was then decided to neutralise the silica in order to prevent the product from decomposing on the column. This was readily accomplished by the addition of 2% Et_3N to the eluent, and the adducts **4** could thereafter be readily isolated, albeit in moderate yields. The improved conditions allowed us to isolate products **4**, as indicated in Scheme 2.[10]

Compounds **4** were subsequently allowed to react with a second carbon nucleophile resulting in 2,5-disubstituted-2,5-dihydrofurans **6**. The purification of **6** was not complicated by aromatisation or decomposition, as was the case for intermediates **4**. Using this methodology, a range of disubstituted dihydrofurans was synthesised (Scheme 3), in acceptable yields.

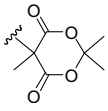
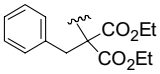
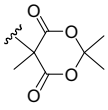
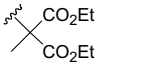
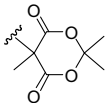
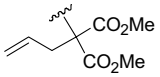
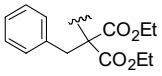
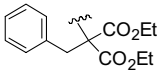
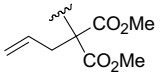
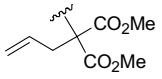
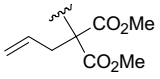
This successful outcome prompted us to investigate the consecutive reaction of diacetate **3** with two different nucleophiles in a one-pot process. This sequence produced the disubstituted products **6a–e** in higher yields than the two-pot route, and eliminated the problematic purification of **4** (Table 1, Scheme 3).

None of the two-pot or one-pot reactions have been optimised, and at present the one-pot procedure affords higher overall yields of products **6**. For symmetric products **6f** and **6g** an excess of the nucleophile could be added at the onset to ensure a fuller conversion to the



Scheme 3.

Table 1. Yields of 2,5-dihydrofurans synthesised by one- and two-pot reactions

Entry	Nu^1	Nu^2	Yield[a]		
			Product	One-pot (%)	Two-pot (%)
1			**6a**	34	21
2			**6b**	27	19
3			**6c**	33	20
4			**6d**	38	26
5			**6e**	40	28
6			**6f**	70	—
7			**6g**	68	—

[a] Yields are of isolated products and are calculated over two steps, in unoptimised reactions.

disubstituted dihydrofuran, affording these products in yields of approximately 70%. This work clearly demonstrates the usefulness of 2,5-diacetoxy-2,5-dihydrofuran as an effective substrate for the preparation of 2,5-di-'*C*'-substituted analogues thereof in palladium-mediated reactions. Ongoing work in our laboratories on the application of this methodology to physiologically active compounds will be published in due course.

3. General procedure for substitution reactions

3.1. Compounds 4a and 4d

$Pd(PPh_3)_4$ (0.1 equiv, 0.054 mmol, 62 mg) and DPPP (0.15 equiv, 0.081 mmol, 34 mg) were mixed together in THF (2 mL). After stirring for 10 min 2,5-diacteoxy-2,5-dihydrofuran (0.54 mmol, 100 mg) was added. In a separate flask, the nucleophile (1 equiv, 0.54 mmol) was dissolved in 2 mL THF at 0 °C and NaH (1.3 equiv, 60% dispersion in mineral oil, 28 mg) was then added and the solution was stirred until the bubbling had subsided. The two reaction mixtures were then combined and stirred at room temperature until the reaction was complete as indicated by TLC.

The solvent was removed in vacuo at 15 °C and the residue was extracted with ice-cold DCM and H_2O. The product was then purified using column chromatography with neutralised silica (2% Et_3N in the mobile phase) at −15 °C [hexane–EtOAc 4:1 (**4a**) and 7:1 (**4d**)].

4a ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.73 (app. q, 1H, $J = 1.2$ Hz), 6.42 (ddd, 1H, $J = 6.0$, 2.4 and 1.2 Hz), 5.99 (ddd, 1H, $J = 6.0$, 2.4 and 1.2 Hz), 5.25 (app. q, 1H, $J = 1.4$ Hz), 2.02 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.7, 168.8, 166.1, 131.5, 126.9, 105.6, 101.6, 90.7, 53.8, 29.8, 28.5, 21.3, 20.7; IR: ν_{max} ($CHCl_3$)/cm^{-1} 3025, 1775, 1749, 1705, 1219, 1215; CI-MS: 225 ([M−$COOCH_3$]$^+$), 12%), 43 ([C_2H_3O]$^+$, 100%); HRMS: Calcd for $C_{11}H_{13}O_5$ (M−$C_2H_3O_2$): 225.0763, Found: 225.0757.

4d ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.20–7.25 (m, 5H), 6.80 (app. q, 1H, $J = 1.2$ Hz), 6.46 (ddd, 1H, $J = 6.0$, 2.4 and 1.2 Hz), 5.78 (ddd, 1H, $J = 6.0$, 2.4 and 1.2 Hz), 5.00 (app. q, 1H, $J = 1.2$ Hz), 4.10–4.25 (m, 4H), 3.53 (d, 1H, $J = 13.5$ Hz,), 3.27 (d, 1H, $J = 13.5$ Hz), 2.06 (s, 3H), 1.23 (t, 3H, $J = 7.2$ Hz), 1.22 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.9, 168.8, 167.8, 135.4, 130.2, 128.0, 126.9, 124.1, 101.1, 85.2, 62.6, 61.1, 61.0, 37.5, 21.4, 13.9, 13.9; IR: ν_{max} ($CHCl_3$)/cm^{-1} 3018, 2989, 2945, 1735, 1715, 1703, 1649, 1458, 1448, 125, 1221, 1212; CI-MS: 316 ([M−$COOCH_3$–H]$^+$, 100%); HRMS: Calcd for $C_{18}H_{20}O_5$ (M−$C_2H_4O_2$): 316.1311, Found: 316.1312.

3.2. Synthesis of 6a–e in a one-pot reaction

The procedure was the same as for the synthesis of **4a** and **4d**. Once the desired product was observed by TLC analysis, the second nucleophile was introduced as follows:

In a separate flask, the second nucleophile (1 equiv, 0.54 mmol) was dissolved in THF (2 mL) at 0 °C and NaH (1.3 equiv, 60% dispersion in mineral oil, 28 mg) was then added and the reaction mixture was allowed to stir until the bubbling had ceased. The two solutions were then combined and stirred until the reaction was shown to be complete by TLC analysis.

The solvent was removed in vacuo and the reaction mixture was extracted with DCM and H_2O. The product was then purified using column chromatography on silica [hexane–EtOAc 5:1 (**6a**), 7:1 (**6b**), 6:1 (**6c**), 7:1 (**6d**) and 7:1 (**6e**)].

6a ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.14–7.08 (m, 5H), 6.17 (ddd, 1H, $J = 6.3$, 2.7 and 1.2 Hz), 6.06 (ddd, 1H, $J = 6.3$, 2.5 and 1.2 Hz), 5.19 (ddd, 1H, $J = 6.0$, 2.4 and 1.2 Hz), 4.87 (ddd, 1H, $J = 6.0$, 2.4 and 1.2 Hz), 4.27–4.06 (m, 4H), 3.28 (d, 1H, $J = 13.5$ Hz), 3.19 (d, 1H, $J = 13.5$ Hz), 1.93 (s, 3H), 1.73 (s, 3H), 1.63 (s, 3H) 1.24 (t, 3H, $J = 7.2$ Hz), 1.18 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.1, 169.2, 167.9, 166.9, 135.6, 131.1, 130.4, 128.3, 127.0, 125.8, 105.6, 90.0, 84.9, 61.5, 61.3, 61.2, 52.5, 37.0, 29.8, 28.7, 21.2, 13.9, 13.7; IR: ν_{max} ($CHCl_3$)/cm^{-1} 2252, 1728, 1379 and 1290; CI-MS: 475 ([M+H]$^+$, 1.5%), 317 ([M−$C_7H_9O_4$]$^+$, 100%), 243 ([M−$C_{10}H_{15}O_6$]$^+$, 98%), 91 ([C_7H_7]$^+$, 93%); HRMS: Calcd for $C_{25}H_{31}O_9$ (M+H): 475.1968, Found: 475.1955.

6b ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.15 (ddd, 1H, $J = 6.3$, 2.1 and 1.0 Hz), 6.11 (ddd, 1H, $J = 6.3$, 2.1 and 1.0 Hz), 5.24 (ddd, 1H, $J = 6.3$, 2.1 and 1.0 Hz), 5.11 (ddd, 1H, $J = 6.3$, 2.1 and 1.0 Hz), 4.17 (q, 1H, $J = 7.0$ Hz), 4.16 (q, 1H, $J = 7.0$ Hz), 4.15 (q, 1H, $J = 7.0$ Hz), 4.14 (q, 1H, $J = 7.0$ Hz), 1.79 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.25 (s, 3H), 1.21 (t, 6H, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.0, 169.5, 169.3, 169.0, 129.7, 127.9, 105.6, 90.5, 87.5, 61.5, 61.4, 56.4, 52.4, 30.0, 28.5, 21.0, 15.7, 14.0, 13.9; IR: ν_{max} ($CHCl_3$)/cm^{-1} 3026, 2983, 1735, 1292 and 1070; EI-MS: 340 ([M−C_3H_6O]$^+$, 100%), 241 ([M−$C_7H_9O_4$], 100%), 167 ([M−$C_{10}H_{15}O_6$]$^+$, 50%); HRMS: Calcd for $C_{19}H_{26}O_9$: 398.1577, Found: 398.1604.

6c ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.30–6.21 (m, 1H), 6.11–6.09 (m, 1H), 5.67 (ddt, 1H, $J = 17.0$, 10.0 and 8.0 Hz), 5.12–5.05 (m, 4H), 3.70 (s, 3H), 3.68 (s, 3H), 2.75 (dd, 1H, $J = 14.0$ and 7.1 Hz), 2.55 (dd, 1H, $J = 14.0$ and 7.1 Hz), 1.84 (s, 3H), 1.70, 1.61 (2 × s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.6, 169.4, 168.5, 166.7, 132.3, 130.6, 126.5, 119.5, 105.6, 90.1, 85.9, 61.0, 52.4, 52.3, 52.3, 35.3, 29.9, 28.6, 21.2; IR: ν_{max} ($CHCl_3$)/cm^{-1} 3028, 1753, 1292 and 1224; EI-MS: 239 ([M−$C_7H_9O_4$]$^+$, 75%), 179 ([M−$C_9H_{13}O_6$]$^+$, 82%), 139 ([M−$C_{12}H_{17}O_6$]$^+$, 66%); HRMS: Calcd for $C_{19}H_{24}O_9$: 396.1420, Found: 396.1409.

6d ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.15–7.26 (m, 5H), 6.07 (ddd, 1H, $J = 5.7$, 2.7 and 1.2 Hz), 5.84 (ddd, 1H,

$J = 5.7$, 2.7 and 1.2 Hz), 5.25 (ddd, 1H, $J = 5.4$, 2.7 and 1.2 Hz), 4.77 (ddd, 1H, $J = 5.4$, 2.7 and 1.2 Hz), 4.23–3.97 (m, 8H), 3.43 (d, 1H, $J = 13.5$ Hz), 3.14 (d, 1H, $J = 13.5$ Hz) 1.28–1.18 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.8, 169.3, 169.2, 168.6, 135.9, 133.2, 130.4, 130.3, 128.6, 128.1, 126.8, 118.8, 84.8, 83.6, 61.7, 61.4, 61.1, 61.1, 52.3, 52.1, 36.8, 36.1, 13.8, 13.7; IR: ν_{max} ($CHCl_3$)/cm^{-1} 3025, 2986, 2961, 1736, 1251, 1070, 908, 766, 732; CI-MS: 491 ($[M+H]^+$, 36%), 317 ($[M-C_8H_{13}O_4]^+$, 51%), 241 ($[M-C_{14}H_{17}O_4]^+$, 100%).

6e ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.25–7.15 (m, 5H), 6.11–6.05 (m, 2H), 5.81–5.72 (m, 2H), 5.15–4.79 (m, 3H), 4.21–4.01 (m, 4H), 3.74 (s, 3H), 3.67 (s, 3H), 3.64 (d, 1H, $J = 13.8$ Hz), 3.15 (d, 1H, $J = 13.8$ Hz), 2.86 (dd, 1H, $J = 14.1$ and 7.8 Hz), 2.55 (dd, 1H, $J = 14.1$ and 7.8 Hz), 1.25–1.21 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.8, 169.3, 169.2, 168.6, 135.9, 133.2, 130.4, 130.3, 128.6, 128.1, 126.8, 118.8, 84.8, 83.6, 61.4, 61.8, 61.1, 61.0, 52.3, 52.1, 36.8, 35.1, 13.8, 13.7; IR: ν_{max} ($CHCl_3$)/cm^{-1} 3025, 2986, 1731, 1261, 1207, 903, 761; CI-MS: 489 ($[M+H]^+$, 100%), 317 ($[M-C_8H_{11}O_4]^+$, 52%), 239 ($[M-C_{14}H_{17}O_4]^+$, 22%).

3.3. Compounds 6f–g

$Pd(PPh_3)_4$ (0.1 equiv, 0.054 mmol, 62 mg) and DPPP (0.15 equiv, 0.081 mmol, 34 mg) were dissolved in THF (2 mL). After stirring for 10 min 2,5-diacteoxy-2,5-dihydrofuran (0.54 mmol, 100 mg) was added. In a separate flask, the nucleophile (2.5 equiv, 0.54 mmol) was added to 4 mL THF at 0 °C. NaH (3.3 equiv, 60% dispersion in mineral oil, 70 mg) was then added and the solution was stirred until the bubbling had subsided. The two reaction mixtures were then combined and allowed to stir at room temperature until complete typically requiring around 6 h.

The solvent was removed in vacuo and the residue was extracted with DCM and H_2O. The product was then purified using column chromatography on silica [hexane–EtOAc 10:1 (**6f**) and 9:1 (**6g**)].

6f ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.02 (s, 2H), 5.17 (s, 2H), 4.15 (q, 4H, $J = 7.0$ Hz), 4.12 (q, 4H, $J = 7.0$ Hz), 1.31 (s, 6H), 1.21 (t, 6H, $J = 7.0$ Hz), 1.20 (t, 6H, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.2, 169.9, 129.8, 86.5, 61.3, 61.3, 57.0, 16.3, 14.1, 14.0; IR: ν_{max} ($CHCl_3$)/cm^{-1} 3021, 3020, 3013, 2990, 1733, 1704, 1224, 1220, 1218, 1213; CI-MS: 415 ($[M+H]^+$, 100%), 241 ($[M-C_8H_{13}O_4]^+$, 7%); HRMS: Calcd for $C_{20}H_{30}O_9$: 414.1890, Found: 414.1894.

6g ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.11 (s, 2H), 5.75–5.66 (m, 2H), 5.05 (m, 6H), 3.71 (s, 6H), 3.66 (s, 6H), 2.79 (dd, 2H, $J = 14.0$ and 7.5 Hz), 2.54 (dd, 2H, $J = 14.0$ and 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.5, 168.9, 132.7, 129.3, 118.9, 84.7, 61.2, 52.2, 52.1, 35.2; IR: ν_{max} ($CHCl_3$)/cm^{-1} 3024, 3017, 2958, 1743, 1738, 1703, 1640, 1228, 1223, 1220, 1214, 1212, 1208; CI-MS: 411 ($[M+H]^+$, 100%), 239 ($[M-C_8H_{11}O_4]^+$, 94%); HRMS: Calcd for $C_{20}H_{26}O_9$: 410.1577, Found: 410.1578.

Acknowledgements

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10. The stereochemistry of products **4** and **6** was determined on the basis of NOE experiments, which clearly indicated the *cis* relative stereochemistry due to interactions shown between ring hydrogen atoms on positions 2 and 5, together with interactions between various functionalities of the pendant moieties on positions 2 and 5. This indicated that the acetate leaving groups were replaced with net retention of stereochemistry in moving from products **4** to **6**, as is typically expected of such reactions. The stereochemistry of the starting material **3** has not yet been determined, but is the subject of a current crystallographic study. (The C_2 symmetry of this material prevents useful NOE studies.) It is reasonably anticipated that this crystalline material will also prove to possess the *cis* relative stereochemistry on the basis of literature precedent (see Ref. 8) and the fact that the one- and two-pot reactions afforded identical products **6** in the relevant instances, the *cis* relative stereochemistry of which has herein been established.