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Palladium-catalysed synthesis of 3- and 4-substituted 2*H*-pyran-2-ones

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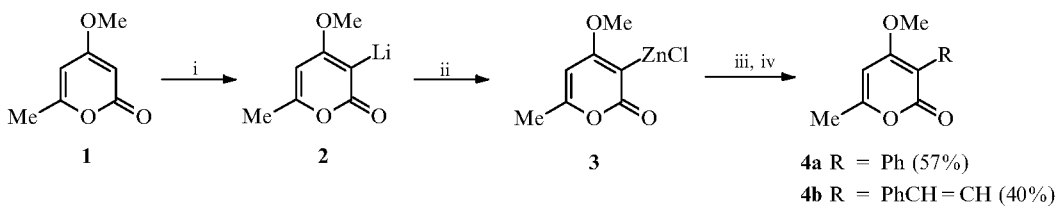
Palladium(0)-catalysed cross-coupling reactions of 4-methoxy-6-methyl-3-chlorozinco-2-pyrone with aryl- and vinyl-halides and 4-bromo-2-pyrone with organozinc compounds such as aryl-, heteroaryl- and ethynyl-zinc chlorides produce 3- and 4-substituted 2*H*-pyran-2-ones in moderate to good yields.

The synthesis of substituted 2*H*-pyran-2-ones has recently attracted considerable attention due to the possibility of using them as masked dienes in the stereoselective synthesis of biologically active compounds in Diels–Alder reactions.[1,2] The preparation of aryl-, heteroaryl- and unsaturated-derivatives of 2*H*-pyran-2-ones is of great importance since it greatly enhances the potential of diene synthesis because of the inaccessibility of the usual dienes bearing these substituents.

Transition metal complexes are effective catalysts in the coupling of organometallics with organohalides or triflates thus providing an efficient method for carbon–carbon bond formation.[3] This method has been widely used to prepare



1 **2** **3**

4a R = Ph (57%)
4b R = PhCH=CH (40%)

Scheme 1 *Reagents and conditions*: i, 1 equiv. Bu^{n}Li, THF, 30 min, −60 °C; ii, 1 equiv. $ZnCl_2$, THF, 30 min, −60 to 20°C; iii, **a** 1 equiv. PhI, 5 mol% $Pd(PPh_3)_4$, THF, 9 h, reflux, **b** 1 equiv. PhCH=CHBr, 5 mol% $Pd(PPh_3)_4$, THF, 4 h, reflux; iv, H_2O.

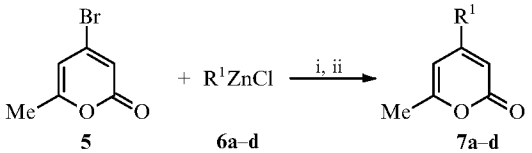
various substituted heterocycles.[4]

It is already known that 6-methyl-4-methoxy-2*H*-pyran-2-one **1** is metallated by *n*-butyllithium or lithium diisopropylamide at the 3-position at low temperatures.[5] We have found that 6-methyl-4-methoxy-3-lithio-2*H*-pyran-2-one **2** reacted with anhydrous $ZnCl_2$, yielding the organozinc derivative **3** which coupled with iodobenzene and ω-bromostyrene in the presence of $Pd(PPh_3)_4$ to give the corresponding 3-substituted 2-pyrones **4a**,**b** (Scheme 1).†

The reactions described are the first examples in which an organozinc pyrone derivative is obtained, and of its use in synthesis.

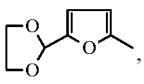
Halide derivatives of 2-pyrone also engage in palladium-catalysed cross-coupling reactions. Sex pheromone Supellapyrone was obtained by the reaction of 2,4-dimethylheptylzinc(II) chloride with 5-bromo-3-methyl-2*H*-pyran-2-one.[6]

We have found that 4-bromo-6-methyl-2*H*-pyran-2-one[7] reacted with organozinc compounds **6a–d** under mild conditions in the presence of $Pd(PPh_3)_4$ to form 4-substituted 2*H*-pyran-2-ones **7a–d** (Scheme 2).‡



a R^1 = Ph, 3.5 h, 44%

b R^1 =  , 0.5 h, 40%

c R^1 =  , 2 h, 60%

d R^1 = PhC≡C, 1 h, 76%

Scheme 2 *Reagents and conditions*: i, 1 equiv. **6**, 5 mol% $Pd(PPh_3)_4$, THF, 50–66 °C; ii, H_2O.

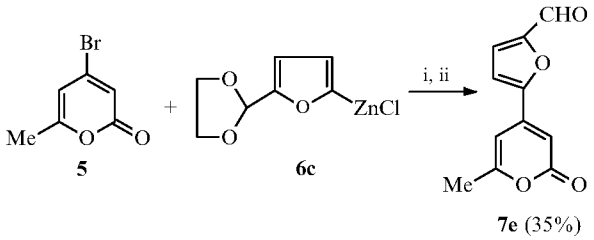
Interaction of **5** and **6c** followed by treatment with dilute HCl resulted in acetal hydrolysis and formation of 6-methyl-4-(5-formylfur-2-yl)-2*H*-pyran-2-one **7e** (Scheme 3).

The reactions investigated are the first examples of $C_{sp^2} - C_{sp}$ and $C_{sp^2} - C_{sp^2}$ bond formation *via* organozinc compounds in 2*H*-pyran-2-ones, and promise a wide range of synthetic applications.

† *General procedure and spectral characteristics*. All operations were performed in an inert atmosphere using absolute solvents. $Pd(PPh_3)_4$ was synthesized by the method described in ref. 8. ^{1}H NMR spectra were measured on a Brucker-WP-200 NMR spectrometer (200 MHz) in $CDCl_3$ with 1,1,1,3,3,3-hexamethyldisilazane.

To a solution of **1** (0.7 g, 5 mmol) in 30 ml THF at −60 °C was added 3.2 ml of 1.6 M Bu^nLi hexane solution. After 30 min stirring at −60 °C anhydrous $ZnCl_2$ (0.68 g, 5 mmol) in 15 ml THF was added. The mixture was allowed to warm to 20 °C, then cooled to 0 °C and a solution of iodobenzene (1.02 g, 5 mmol) and $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol) in 20 ml THF was added. After refluxing for 9 h and cooling to 20 °C, 100 ml of dilute HCl was added and the mixture was extracted with ether (3×30 ml). The extracts were dried with $CaCl_2$ and solvent was removed. Recrystallization of the residue with heptane–ethyl acetate gave 0.61 g **4a**, mp 156–158 °C. Found: C 72.23; H 5.78. Calc. for $C_{13}H_{12}O_3$: C 72.21; H 5.59%. ^{1}H NMR (δ, ppm) 2.27 (s, 3H, Me), 3.79 (s, 3H, OMe), 6.11 (s, 1H, =CH-), 7.19–7.45 (m, 5H, Ph).

Analytical and spectral data for **4b**: mp 187 °C. Found: C 73.65; H 5.80. Calc. for $C_{15}H_{14}O_3$: C 74.36; H 5.82%. ^{1}H NMR (δ, ppm) 2.24 (s, 3H, Me), 3.90 (s, 3H, MeO), 5.98 (s, 1H, =CH-), 7.05–7.73 (m, 7H, Ph and CH=CH).



Scheme 3 *Reagents and conditions*: i, 5 mol% $Pd(PPh_3)_4$,, THF, 2 h, reflux; ii, H_2O, HCl.

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‡ *General procedure and spectral characteristics for* **7a–e**. Organozinc compounds **6a**,**b**,**d** were obtained by methods described in ref. 4. The derivative **6c** was obtained by treatment of 2-(1,3-dioxolane-2-yl)furan with Bu^nLi in THF (30 min, −60 to −70 °C) followed by treatment with anhydrous $ZnCl_2$ (15 min, −60 to −70 °C THF).

To a solution of 2-thienylzinc chloride [obtained from thiophene (0.42 g, 5 mmol) in 30 ml absolute THF] was added solution of **5** (0.95 g, 5 mmol) and $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol) in 20 ml absolute THF at 20 °C. The mixture was heated to 55 °C for 1 h then cooled to 20 °C. 150 ml H_2O was added, the organic layer was separated and the aqueous layer was extracted with ether (3×30 ml). The combined extracts were dried with Na_2SO_4 and solvent was removed. Recrystallization of the residue from heptane–ethyl acetate resulted in 0.4 g **7b**: mp 141 °C. Found: C 62.40; H 4.18; S 16.56. Calc. for $C_{10}H_8O_2S$: C 62.50; H 4.20; S 16.65%. ^{1}H NMR, (δ, ppm) 2.21 (s, 3H, Me), 6.17 (s, 1H), 6.25 (s, 1H) (H_3 and H_5 of pyrone ring), 7.05–7.39 (m, 3H, 2-thienyl).

Spectral data for **7a**: mp 85–87 °C (lit.,[9] mp 88–90 °C). ^{1}H NMR (δ, ppm) 2.27 (s, 3H, Me), 6.25 (s, 1H), 6.34 (s, 1H) (H_3 and H_5 of pyrone ring), 7.29–7.61 (m, 5H, Ph).

Analytical and spectral data for **7c**: mp 128–129 °C. Found: C 62.98; H 4.82. Calc. for $C_{13}H_{12}O_5$: C 62.90; H 4.87%. ^{1}H NMR (δ, ppm) 2.30 (s, 3H, Me), 4.03–4.25 (m, 4H, –CH_2–CH_2–), 6.00 [s, 1H, O–CH(O)–], 6.25 (s, 1H), 6.41 (s, 1H) (H_3 and H_5 of pyrone ring), 6.58 (d, J<1 Hz, 1H, =CH-), 6.89 (d, J<1 Hz, 1H, =CH-).

Analytical and spectral data for **7d**: mp 88–89 °C. Found: C 79.40; H 4.76. Calc. for $C_{14}H_{10}O_2$: C 79.98; H 4.79%. ^{1}H NMR (δ, ppm) 2.24 (s, 3H, Me), 6.06 (s, 1H), 6.25 (s, 1H) (H_3 and H_5 of pyrone ring), 7.38–7.56 (m, 5H, Ph).

Analytical and spectral data for **7e**: mp 176–177 °C. Found: C 64.01; H 3.86. Calc. for $C_{11}H_8O_4$: C 64.71; H 3.95%. ^{1}H NMR (δ, ppm) 2.28 (s, 3H, Me), 6.35 (s, 1H,), 6.51 (s, 1H) (H_3 and H_5 of pyrone ring), 6.96 (d, J<1 Hz, 1H, =CH-), 7.26 (d, J<1 Hz, 1H, =CH-), 9.68 (s, 1H, –CHO).