AN EXPEDIENT PALLADIUM-MEDIATED ROUTE TO METHYL 3-BENZOFURANYLACETATE

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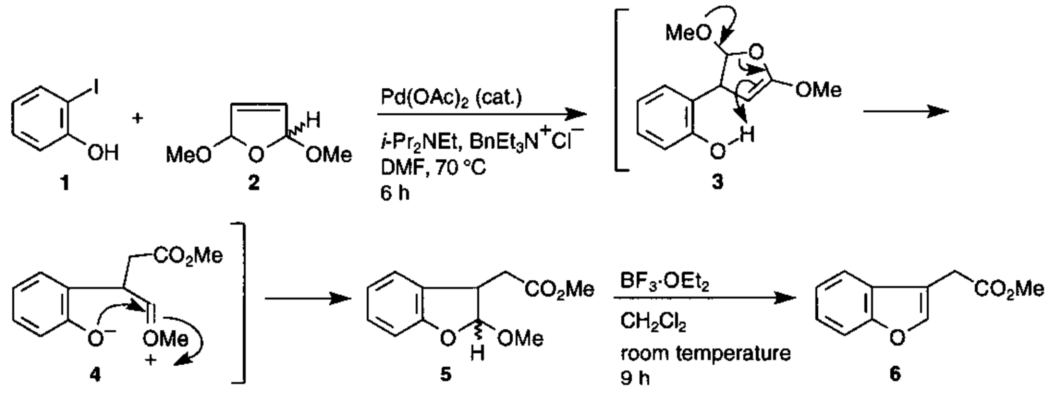
Abstract —— An expedient synthesis of methyl 3-benzofuranylacetate has been developed by employing the Heck reaction between 2-iodophenol and 2,5-dihydro-2,5-dimethoxyfuran as a key step.

Although a number of methods have been developed for the synthesis of 3-indolylacetates, little attention has been paid to the synthesis of their oxygen analogues. We now report a new expedient route to methyl 3-benzofuranylacetate[1] (**6**) employing the Heck reaction[2] between 2-iodophenol[3] (**1**) and 2,5-dihydro-2,5-dimethoxyfuran[4] (**2**) as a key step.

Thus, a mixture of 2-iodophenol (**1**) (1.03 g, 4.66 mmol), 2,5-dihydro-2,5-dimethoxyfuran (**2**) (0.85 ml, 7.01 mmol), ethyldiisopropylamine (1.62 ml, 9.30 mmol), and benzyltriethylammonium chloride (1.06 g, 4.66 mmol) was stirred in *N,N*-dimethylformamide (DMF) (12 ml) at 70 °C for 6 h in the presence of a catalytic amount of palladium diacetate (20.9 mg, 93.1 μmol). The reaction mixture, after being diluted with ether, was washed successively with water and saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, and evaporated to leave the crude dihydrobenzofuran[5] (**5**) (1.14 g).

The crude product (**5**), without purification, was then treated with boron trifluoride etherate (1.72 ml, 14.0 mmol) in dichloromethane (15 ml) at room temperature for 9 h. The mixture was washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, evaporated under reduced pressure, and chromatographed on silica gel column (50g: elution with 1:8 v/v AcOEt-hexane) to give methyl 3-benzofuranylacetate[6] (**6**) (567 mg, 64.0% from **1**) as a pale yellow oil. The overall reaction was presumed to proceed from the initially generated transient Heck product (**3**) to leave the dihydrobenzofuran (**5**), *via* **4**, which gave the benzofuran (**6**) on exposure to the acid catalyst (**Scheme 1**). Application and the extension of the present synthesis are now under investigation.[7]



Scheme 1

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2. For example, R. F. Heck, "Palladium Reagents in Organic Syntheses," Academic Press, London, 1985.
3. Commercially available from Tokyo Chemical Industry Co.
4. Commercially available from Merck AG as a mixture of diastereomers.
5. **5** could be isolated as a diastereomeric 3:2 mixture: Ir (neat): v=1738 cm^{-1}. ^{1}H Nmr (CDCl$_3$, 90 MHz): δ=7.28-7.10 (m, 2H), 6.89 (br t, 2H, J=7.4 Hz), 5.65 (d, 0.4 H, J=5.9 Hz), 5.36 (d, 0.6 H, J=1.7 Hz), 3.89-3.39 (m, 1H), 3.75 (s, 1.2 H), 3.72 (s, 1.8 H), 3.52 (s, 1.8H), 3.48 (s, 1.2 H), 2.91 (d, 0.8 H, J=5.8 Hz), 2.59 (d, 1.2 H, J=7.8 Hz).
6. Ir (neat): v=2952, 1741, 1453, 1436, 1278, 1165, 1097, 1009, 744 cm^{-1}. ^{1}H Nmr (CDCl$_3$, 300 MHz): δ=7.63 (s, 1H), 7.56 (dd, 1H, J=7.0, 1.8 Hz), 7.48 (dd, 1H, J=7.3, 1.5 Hz), 7.31 (td, 1H, J=7.3, 1.5 Hz), 7.25 (td, 1H, J=7.3, 1.5 Hz), 3.73 (s, 3H), 3.71 (br s, 2H). Ms: m/z=190 (M$^+$), 162, 131 (100%), 103, 77.
7. Using 2-iodoaniline derivatives in place of 2-iodophenol we also have developed an expedient route to 3-indolylacetates which will be published elsewhere: K. Samizu and K. Ogasawara, *Synlett*, in press.

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