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PALLADIUM CATALYZED STEREOSPECIFIC MICHAEL ARYLATION OF 6-ALKYL-5,6-DIHYDRO-2H-PYRAN-2-ONES

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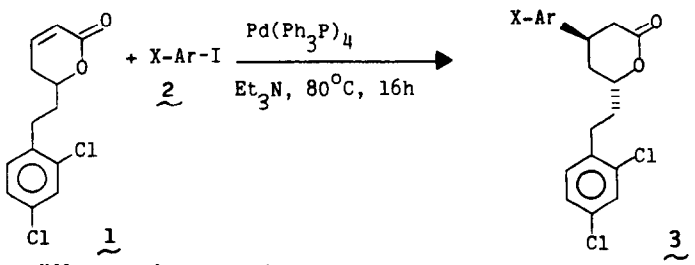
SUMMARY: The Michael arylation of 6-[2-(2,4-dichlorophenyl)ethyl]-5,6-dihydro-2H-pyran-2-one with aryl iodides in the presence of Pd [0] resulted in a stereospecific addition followed by a hydrogen abstraction from triethylamine.

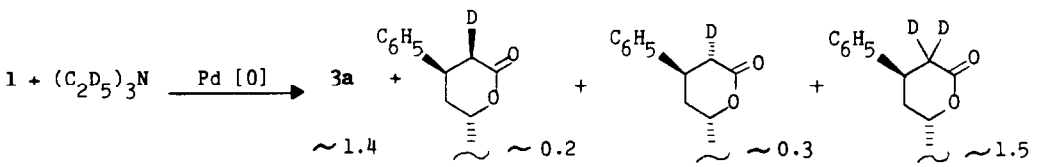
In the course of our studies on lactone modifications of synthetic HMG-CoA reductase inhibitors,[1] we found that aryl iodides added stereospecifically in a Michael fashion to α,β-unsaturated lactone **1** in the presence of a catalytic amount of palladium [0] and triethylamine to afford adducts **3**. In a typical procedure, a mixture of 6-[2-(2,4-dichlorophenyl)ethyl-5,6-dihydro-2H-pyran-2-one[2] (270 mg, 1 mmol), phenyliodide (125 μL, 1.1 mmol), triethylamine (160 μL, 1.1 mmol) and tetrakis(triphenylphosphine)palladium [0] (10 mg) was stirred at 80°C under argon for 16h and distributed dark mixture between ethyl acetate and dilute hydrochloric acid. The organic layer was washed twice with water, dried ($MgSO_4$), and evaporated. Flash chromatography of the resulting residue on silica gel with chloroform-acetone (10:1) provided **3a** (280 mg, 77%).[3]

During this period Cacchi and coworkers published their results on Michael type additions of aryl iodides to acyclic α,β-unsaturated aldehydes[4] and ketones[5] in the presence of a catalytic amount of palladium [II] and an excess of trialkylammonium formate. In our hands, the use of Cacchi's conditions [phenyl iodide (5 mmol), triethylamine (7 mmol), formic acid (6 mmol), and acetonitrile (300 μL)] provided **3a** in comparable yield.



The major difference between these two procedures is the source of the hydrogen in the reduction of the alkylpalladium iodide adduct. In the trialkylammonium formate media, the hydrogen

is delivered as a hydride ion from the in situ generated alkyl palladium formate following expulsion of carbon dioxide and collapse of the alkyl palladium hydride by reductive elimination. In the present case, the iodide is displaced from the alkylpalladium iodide by the nitrogen atom of the triethylamine, instead of formate ion, followed by metal insertion into the adjacent C-H bond, and then β-hydride elimination[6] to provide the same alkylpalladium hydride as above (the ridgidity of the ring precludes the aryl pallidated adduct from achieving a syn relationship between the β-hydrogen and the palladium (α) which is normally required for a β-elimination as in the Heck reaction). When perdeuterated triethylamine was used with phenyliodide, the reductively arylated product obtained was a mixture of tetrahydropyran **3a** plus the two diastereomeric α-monodeuterated and the α,α-dideuterated lactones (determined by 300 MHz NMR and high resolution MS).



The addition of a methyl group at the β-carbon of lactone **1** prevented arylation. Replacement of iodide in **2a** by bromide provided none of the arylated adduct **3a**. Instead, only Z,E-7-(2,4-dichlorophenyl)-2,4-heptadienoic acid was isolated.

As shown in the table, compounds **3**, when formed, were prepared in poor to good yields. Neither tlc analyses of the reaction mixtures nor 300 MHz ^1H NMR spectra of crude or purified compounds **3** indicated the presence of any cis isomers.[7] The complete lack of reactivity of the ortho methyl compound (**k**) is interesting when compared to the reactivity (albeit poor) of the corresponding hydroxymethyl (**l**) and methoxy (**m**) compounds.

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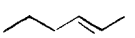
Table: Stereospecific Michael additions to α-β-unsaturated lactone 1.

Aryl iodide 2		Yield 3 %[a]	C-4 H(dddd)[b]
a	C_6H_5-	77	3.39 (3.19)[c]
b	4-C_6H_5-C_6H_4-	47	3.42
c	4-CH_3O_2C-C_6H_4-	37	3.46
d	4-Br-C_6H_4-	0	
e	4-CH_3O-C_6H_4-	63	3.33
f	4-HO-C_6H_4-	49	3.30
g	4-F_3CCO_2NH-C_6H_4-	35	3.36
h	4-H_2N-C_6H_4-	0	
i	3-CH_3O-C_6H_4-	40	3.36
j	3-H_2N-C_6H_4-	0	
k	2-CH_3-C_6H_4-	0	
l	2-$HOCH_2$-C_6H_4-	23	3.75
m	2-CH_3O-C_6H_4-	29 (46)[d]	3.58
n	3-iodopyridine	0	
o	3-iodopyrazole	(83)[e]	4.80
p	3-iodothiophene	30	3.47
q	C_6H_5  I	0	

[a]Isolated pure compounds as oils, each of which gave satisfactory NMR data and elementary combustion analysis. [b]Diagnostic signal for the C-4 methine of the trans arylated product. Spectra obtained on a Varian XL-300 spectrometer in $CDCl_3$. Chemical shifts given in δ values relative to $SiMe_4$. [c]For cis isomer, J = 4, 6, 11, 12 Hz. [d]Heated for 40h. [e]Only normal Michael adduct with N-H, mp 127-128°C.

REFERENCES AND NOTES

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2. Lactone 1 was prepared by dehydration of the corresponding 4-hydroxytetrahydropyran-2-one using acetylchloride (2 equiv.) and triethylamine (4 equiv.) in chloroform at room temperature for 16 h. After usual workup, the yield of 1 was 89%, mp 69-70°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.90-2.12 (m, 2H, $ArCH_2\underline{CH_2}$-), 2.35-2.4 (m, 2H, -$\underline{CH_2}CH$=C-), 2.85 (ddd, $ArC\underline{H}CH_2$-, H, J=6,8,17 Hz), 3.0 (ddd, $ArC\underline{H}CH_2$-, H, J=5,8,17 Hz), 4.37-4.46 (m, H, -CHOCO), 6.04 (dt, H, -C=CHCO, J=9.6, 1.8 Hz), 6.88 (ddd, H, -$CH_2C\underline{H}$=C-, J=4.1, 4.6, 9.6 Hz), 7.16-7.22 (m, 2H, ArH), 7.36 (d, H, ArH, J=1Hz).

3. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.84 ~ 2.0 (m, 2H, $ArCH_2\underline{CH_2}$-), ~2.0-2.18 (m, 2H, -$\underline{CH_2}CHOCO$), 2.72-2.89 (m, 3H, $ArC\underline{H}CH_2$- and -CH_2CO), 2.98 (ddd, H, $ArC\underline{H}CH_2$-, J=5,8,17 Hz), 3.39 (dddd, H, ArCH-, H, J=6,6,6,8 Hz), 4.42 (dddd, H, -CHOCO, J=5,5,8,8 Hz), 7.18-7.4 (m, 8H, ArH).

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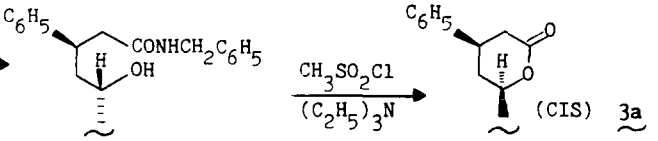
7. The cis isomer of **3a** was prepared by epimerization of **3a** using a 2 step procedure described by us recently to prepare the corresponding cis epimer of mevinolin (lovastatin).[8]



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