SYNTHESIS OF 5-ARYL-3-HYDROXY-4*H*-PYRAN-4-ONES

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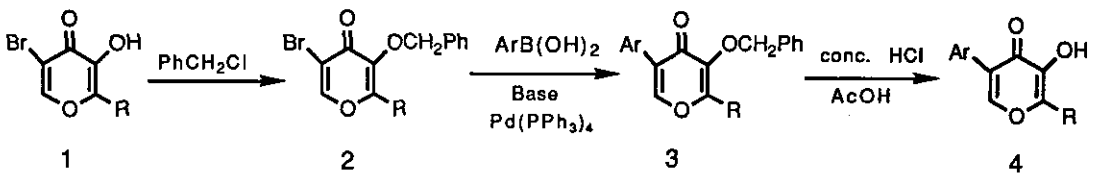
Abstract --- The palladium-catalyzed coupling reaction of 3-benzyloxy-5-bromo-2-methyl-4*H*-pyran-4-one (**2b**) with phenylboronic acid afforded efficiently 3-benzyloxy-2-methyl-5-phenyl-4*H*-pyran-4-one (**3b-1**), and the benzyloxy group of the resultant product was cleaved by hydrolysis with conc. hydrochloric acid in acetic acid to give 5-phenyl-3-hydroxy-2-methyl-4*H*-pyran-4-one (**4b-1**) in high yield. This method was applicable as a general method for synthesizing 5-aryl-3-hydroxy-4*H*-pyran-4-ones (**4**) from the 5-bromo-4*H*-pyran-4-ones(**1**).

In our previous work,[1] it has been found that some phosphoro derivatives of 3-hydroxy-4*H*-pyran-4-ones have potent insecticidal activity. We have been studying the synthesis of 3-hydroxy-4*H*-pyran-4-ones in order to survey more active compounds and reported a convenient synthesis of 3,5-dihydroxy-4*H*-pyran-4-ones and 5-halo-3-hydroxy-4*H*-pyran-4-ones.[2] In this paper, we describe a convenient synthesis of 5-aryl-3-hydroxy-4*H*-pyran-4-ones (**4**) from 5-bromo-3-hydroxy-4*H*-pyran-4-ones (**1**) by the palladium-catalyzed coupling reaction.

The palladium-catalyzed cross-coupling reaction of haloarenes with arylboronic acids by Suzuki *et al.*[3] is usable for the introduction of aryl groups in organic synthesis and widely applied to the synthesis of aryl

substituted compounds such as 3-arylpyrroles[4], 3-phenyl-4*H*-1-benzopyran-4-ones[3c] (isoflavones), and 2-aryl-7-methoxytropones.[5] The result shows that 5-aryl-3-hydroxy-4*H*-pyran-4-ones (**4**) are easily synthesized from 5-bromo-3-hydroxy-4*H*-pyran-4-ones (**1**) *via* their benzyl ethers (**2**) as shown in Scheme 1.

Scheme 1



1 2 3 4

a: R=H, b: Me, c: R=i-Pr

The hydroxy group in **1** was easily benzylated with benzyl chloride using sodium hydride to give benzyl ethers (**2**) in high yield. The cross-coupling reaction between 3-benzyloxy-5-bromo-2-methyl-4*H*-pyran-4-one (**2b**) and phenylboronic acid in benzene in the presence of 3 mole percent of tetrakis-(triphenylphosphine)palladium(0) and 2M sodium carbonate afforded the desired product (**3b-1**) in high yield, although long reaction time (18 h) was required for completion. In this case, use of 1,2-dimethoxyethane (DME) as a solvent accelerated the reaction and the reaction time was reduced to about 1/3. That is, DME as a solvent in the reaction was more suitable than benzene for the synthesis of **3**. The shortening of the reaction time was also possible by using strong base such as sodium hydroxide and barium hydroxide, but many colored materials were formed because of low stability of the starting material in the conditions used, and the yield of **3b-1** fell down to 40-50%.

In the optimum conditions, thirteen 5-aryl-4*H*-pyran-4-ones (**3**) were synthesized from the bromo compounds (**2**) and arylboronic acids, and the results are shown in Table 1. All reactions except 2,4,6-trimethoxy-phenylboronic acid proceeded smoothly without any electronic and steric effect of the substituents in the phenylboronic acid to give desired

products in high yields. The results are similar to those of the reaction of 3-bromochromones in benzene by Suzuki *et al.*[3c] and show that the reaction is useful as a general method for the introduction of aryl groups to 4*H*-pyran-4-ones.

Table 1 5-Aryl-4*H*-pyran-4-ones (**3**) Prepared and their Analytical Data

Compd	R	Xn	Yield (%)	Mp (°C)	^{1}H Nmr C_6-H	Formula	Found(%) C	Found(%) H	Calcd(%) C	Calcd(%) H
3a-1	H	H	89	101-102	7.74	$C_{18}H_{14}O_3$	77.44	5.17	77.68	5.07
3b-1	Me	H	71	90-91	7.72	$C_{19}H_{16}O_3$	78.27	5.50	78.06	5.52
3c-1	Et	H	81	oil	7.76	$C_{20}H_{18}O_3$	78.69	5.78	78.41	5.92
3d-1	i-Pr	H	88	oil	7.78	$C_{21}H_{20}O_5$	78.97	6.19	78.73	6.29
3b-2	Me	2-MeO	87	78-79	7.70	$C_{20}H_{18}O_4$	74.79	5.68	74.52	5.63
3b-3	Me	2-Me	82	oil	7.72	$C_{20}H_{18}O_3$	78.59	6.01	78.41	5.92
3b-4	Me	3-Me	77	oil	7.70	$C_{20}H_{18}O_4$	74.71	5.60	74.52	5.63
3b-5	Me	3-NO_2	81	83-84	7.84	$C_{19}H_{15}NO_5$	67.38	4.59	67.65	4.48
3b-6	Me	4-MeO	80	72-74	7.72	$C_{20}H_{18}O_4$	74.13	5.59	74.52	5.63
3b-7	Me	4-Me	83	91-92	7.72	$C_{20}H_{18}O_3$	78.41	5.92	78.60	6.08
3b-8	Me	4-Cl	77	81-82	7.74	$C_{19}H_{16}O_3Cl$	69.85	4.69	69.62	4.92
3b-9	Me	4-F	79	oil	7.74	$C_{19}H_{16}O_3F$	73.54	5.09	73.30	5.18
3b-10	Me$_{2,4,6}$-(MeO)$_3$		21	oil	7.74	$C_{22}H_{22}O_6$	69.37	5.71	69.10	5.80

The benzyloxy group in 5-aryl-3-benzyloxy-4*H*-pyran-4-ones (**3**) obtained was cleaved with conc. hydrochloric acid in acetic acid to give 5-aryl-3-hydroxy-4*H*-pyran-4-ones (**4**) in high yield as shown in Table 2. 2-Phenyl-3-hydroxy-4*H*-pyran-4-one (**8**)[6] was also easily synthesized from 2-bromo-3-hydroxy-4*H*-pyran-4-one (**5**)[7] by a similar method *via* the benzyl ethers **6** and **7**. The results show that the process is applicable as a general method for synthesizing aryl substituted 4*H*-pyran-4-ones.

Insecticidal study of phosphoro derivatives of 3-hydroxy-4*H*-pyran-4-ones (**4**) synthesized here is now in progress.

Table 2 5-Aryl-3-hydroxy-4*H*-pyran-4-ones (**4**) Prepared and their Analytical Data

Compd	R	Xn	Yield (%)	Mp (°C)	^{1}H Nmr C$_6$-H	Formula	Found(%) C	Found(%) H	Calcd(%) C	Calcd(%) H
4a-1	H	H	88	140-142	7.80	$C_{11}H_8O_3$	70.37	4.43	70.21	4.28
4b-1	Me	H	90	204-206	7.80	$C_{12}H_{10}O_3$	70.99	5.01	71.28	4.98
4c-1	Et	H	87	164-165	7.80	$C_{13}H_{12}O_3$	72.21	5.59	71.94	5.65
4d-1	i-Pr	H	89	133-134	7.80	$C_{14}H_{14}O_3$	73.11	6.05	73.03	6.13
4b-2	Me	2-MeO	81	144-145	7.82	$C_{13}H_{12}O_4$	67.37	5.25	67.24	5.21
4b-3	Me	2-Me	83	172-173	7.80	$C_{13}H_{12}O_3$	72.24	5.59	71.94	5.65
4b-4	Me	3-MeO	78	114-115	7.82	$C_{14}H_{12}O_5$	67.24	5.20	67.24	5.21
4b-5	Me	3-NO$_2$	80	192-194	7.86	$C_{12}H_9NO_5$	58.49	3.71	58.30	3.67
4b-6	Me	4-MeO	84	184-186	7.82	$C_{13}H_{12}O_4$	67.45	5.00	67.24	5.21
4b-7	Me	4-Me	86	185-187	7.80	$C_{13}H_{12}O_3$	71.95	5.51	71.94	5.65
4b-8	Me	4-Cl	82	169-171	7.82	$C_{12}H_9O_3Cl$	60.91	3.85	61.22	4.17
4b-9	Me	4-F	79	170-171	7.82	$C_{12}H_9O_3F$	65.74	4.03	65.46	4.12
4b-10	Me,2,4,6-(MeO)$_3$		70	243-245	7.80	$C_{15}H_{16}O_6$	61.95	5.61	61.64	5.52

EXPERIMENTALS

All melting points were uncorrected. ^{1}H Nmr spectra were recorded on a Hitachi R-24B spectrometer (60 MHz) in $CDCl_3$ using tetramethylsilane as an internal standard and chemical shifts were given in δ value. Elemental analyses were performed with a Yanaco CHN corder Model MT-2. Phenylboronic and *m*-nitrophenylboronic acids were purchased from Aldrich Chemical Co. Other phenylboronic acids were prepared by the known procedures.[8] Tetrakis-(triphenylphosphine)palladium(0) was purchased from Aldrich Chemical Co, and stored at 5°C until use.

3-Benzyloxy-5-bromo-4*H*-pyran-4-ones (2): To a mixture of 60% NaH (48 mg, 120 mmol) and 5-bromo-3-hydroxy-4*H*-pyran-4-ones (**1**) (100 mmol) in *DMF* (20 ml), was added dropwise benzyl chloride (15.2 g, 120 mmol) at room temperature. The reaction mixture was heated with stirring at 80-90°C for 4-5 h, and then diluted with water. The oily products were extracted with EtOAc. The extract was washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was purified by recrystallization from MeOH or silica gel column chromatography using benzene/EtAc (10:1) as an eluent.

3-Benzyloxy-5-bromo-4*H*-pyran-4-one (1a): 84%, colorless needles, mp 130-131°C, ^{1}H nmr δ: 5.04 (2H, s, $PhCH_2O$), 7.58 (1H, s, C_2-H), 7.98 (1H, s, C_6-H). Anal. Calcd for $C_{12}H_9O_3Br$: C, 51.27; H, 3.23. Found: C, 51.64; H, 3.33

3-Benzyloxy-5-bromo-2-methyl-4*H*-pyran-4-one (1b): 86%, pale yellow oil, ^{1}H nmr δ: 5.12 (2H, S, $PhCH_2O$), 7.94 (1H, s, C_6-H). Anal. Calcd for $C_{13}H_{11}O_3Br$: C, 52.91; H, 3.76. Found: C, 53.13; H, 3.69.

3-Benzyloxy-5-bromo-2-ethyl-4*H*-pyran-4-one (1c): 81%, pale yellow oil, ^{1}H Nmr δ: 5.12 (2H, s, $PhCH_2O$), 7.94 (1H, s, C_6-H). Anal. Calcd for $C_{14}H_{13}O_3Br$: C, 54.39; H, 4.24. Found: C, 54.62; H, 4.12.

3-Benzyloxy-5-bromo-2-isopropyl-4*H*-pyran-4-one (1d): 79%, pale yellow oil, ^{1}H nmr δ: 5.16 (2H, s, $PhCH_2O$), 7.96 (1H, s, C_6-H). Anal. Calcd for $C_{15}H_{15}O_3Br$: C, 68.46; H, 5.74. Found: C, 68.71; H, 5.63.

5-Aryl-3-benzyloxy-4*H*-pyran-4-ones (3): To a solution of 5-bromo-3-benzyloxy-4*H*-pyran-4-one (**1**) (10 mmol) and tetrakis(triphenylphosphine)-palladium(0) (530 mg, 0.5 mmol) in DME (50 ml), were added arylboronic acid (12 mmol) and aq. 2M Na_2CO_3 (10 ml), and the mixture was refluxed with stirring until the starting material disappeared by tlc (about 6 h) and cooled to room temperature. After 30% H_2O_2 (5 ml) was added, the mixture was stirred for 30 min, diluted with water, and extracted with benzene. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was cromatographed on a silica gel column using hexane/EtOAc (2:1) as an eluent to give **3** (*Table 2*).

5-Aryl-3-hydroxy-4*H*-pyran-4-ones (4): A mixture of **3** (5 mmol) and conc. *HCl* (3 ml) in AcOH (10 ml) was heated at 90-100°C for 1 h, diluted with water, and extracted with $CHCl_3$. The extract was washed with brine, then dried over $MgSO_4$, and concentrated. The residue was recrystallized from

benzene to give 5-aryl-3-hydroxy-4*H*-pyran-4-ones (**4**) as colorless needles (Table 3).

Compound (**8**) was synthesized from 2-bromo-3-hydroxy-4*H*-pyran-4-one[5] (**5**) via its benzyl ethers (**6**) and (**7**) according to the procedures described in the synthesis of **1**, **2**, and **3**.

3-Benzyloxy-2-bromo-4*H*-pyran-4-one (6): 74%, yellow brown oil; ^{1}H nmr δ: 5.18 (2H, s, $PhCH_2O$), 6.32 (1H, d, *J*=6 Hz, C_6-H), 7.52 (1H, d, *J*=6 Hz, C_5-H). Anal. Calcd for $C_{12}H_9O_3BrCl$: C, 45.53; H, 2.89. Found: C, 45.81; H, 2.83.

3-Benzyloxy-2-phenyl-4*H*-pyran-4-one (7): 87%, pale yellow oil; ^{1}H nmr δ: 5.10 (2H, s, $PhCH_2O$), 6.38 (1H, d, *J*=6 Hz, C_6-H), 7.70 (1H, d, *J*=6 Hz, C_5-H). Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.96; H, 5.01.

3-Hydroxy-2-phenyl-4*H*-pyran-4-one (8): 90%, colorless needles; mp 159-161°C from i-PrOH (lit.,[6] 161-163°C). ^{1}H Nmr δ: 6.48 (1H, d, *J*=6 Hz, C_6-H), 7.84 (1H, d, *J*=6 Hz, C_5-H).

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