SYNTHESIS OF METHYL 2-(HETEROARYL)PROPANOATES *VIA* PALLADIUM-CATALYZED REACTION

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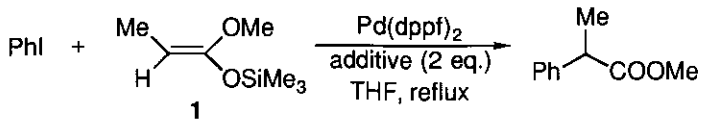
Abstract–Methyl 2-(nitrogen-heteroaryl)propanoates were synthesized by the palladium-catalyzed reaction of heteroaryl halides with (*E*)-1-methoxy-1-trimethylsiloxypropene.

Palladium-catalyzed reaction of aryl halides and triflates with various carbon nuclephiles has been a powerful method to introduce carbon functional groups into aromatic nuclei.[1] There have been so many papers dealing with alkynylation[1c] and alkenylation,[1c] but relatively few papers which describe synthesis of carbonylmethylarenes has been reported. Among such compounds, arylacetates were synthesized by the palladium-catalyzed reaction with alkoxycarbonylmethylzinc bromide[2-5] and the reaction with ethyl tributylstannylacetate in the presence of zinc bromide.[6] Recently, Carfagna *et al.*[7] reported a new route to synthesize arylacetates by the palladium-catalyzed reaction of aryl halides and triflates with ketene trimethylsilyl acetals. Since arylacetic acid derivatives such as ibuprofen or indomethacin are supplied as good nonsteroidal antiinflamatories, we aim to ascertain the generality of this method and to develop the synthesis of nitrogen-heteroarylacetates, particularly α-(heteroaryl)propanoates, that is the subject of this paper.

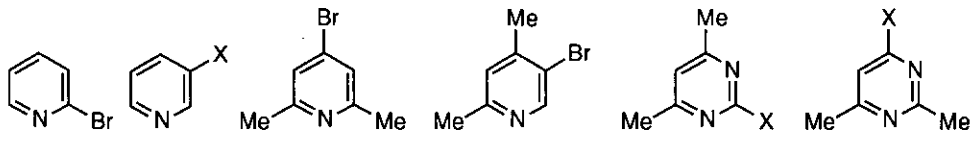
At first, the palladium-catalyzed reaction of iodobenzene with (*E*)-1-methoxy-1-trimethylsiloxypropane (**1**) in the presence of some additives was examined. Although Carfagna *et al.*[7] used $(\eta^3\text{-}C_4H_7PdOAc)_2$ and 1,1'-bis(diphenylphosphino)ferrocene (dppf) as a palladium catalyst, we chose another palladium(0) catalyst prepared from the reaction of $Pd(dppf)Cl_2$ and dppf with butyllithium in THF.[8] Namely, the reaction of iodobenzene and **1** in the presence of the palladium(0) catalyst and two equivalents of TlOAc in THF under reflux gave methyl 2-phenylpropanoate in 81 % yield. As a result, the palladium(0) catalyst was found to be effective similarly to Carfagna's catalyst system. As shown in Table I, the other additives such as LiOAc, AgOAc, and CsOAc were less effective than TlOAc.

Table I. Palladium-Catalyzed Reaction of Iodobenzene with **1**

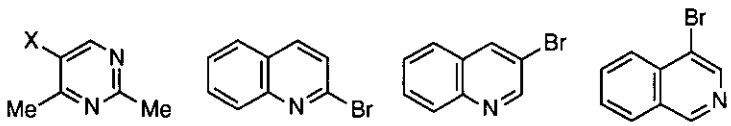


1

Additive	Reaction time (h)	Yield (%)
TlOAc	5	81
LiOAc	20	6
AgOAc	24	12
CsOAc	22	16



2 **3a**: X=Br, **3b**: X=I **4** **5** **6a**: X=Cl, **6b**: X=I **7a**: X=Cl, **7b**: X=I



8a: X=Br, **8b**: X=I **9** **10** **11**

Table II. Palladium-Catalyzed Reaction of π-Deficient Heteroaryl Halides (**2**-**11**) with **1**

Entry	Substrate	Reaction time (h)	Yield (%)
1	**2**	8	69
2	**3a**	17	82
3	**3b**[a)]	5	61
4	**3b**	4	89
5	**4**	5	81
6	**5**	17	9
7	**6a**	18	22
8	**6b**	5	74
9	**7a**	18	29
10	**7b**	4	65
11	**8a**	23	0[b)]
12	**8b**	18	0[c)]
13	**9**	6	63
14	**10**	6	82
15	**11**	23	25

a) $Pd(PPh_3)_4$ was used as a catalyst. *b*) Recovery of **8a**: 41%. *c*) Recovery of **8b**: 20%.

Next, the reaction conditions were applied to the reaction of nitrogen-heteroaryl halides (**2**-**11**). From the results shown in Table II, the palladium-catalyzed reaction of bromopyridines (**2**, **3a**, and **4**), iodopyrimidines (**6b** and **7b**) and bromoquinolines (**9** and **10**) with **1** gave the expected products in 63-89% yields, but the reaction of 2,4-dimethyl-5-bromopyridine (**5**) and 4-bromoisoquinoline (**11**) afforded the products in low yields. Furthermore, the reaction of 5-bromo- and 5-iodo-2,4-dimethylpyrimidine (**8a,b**) afforded no product, and the starting materials were recovered in 41 and 20% yields, respectively. From the results, it is regarded as the reaction was controlled by certain steric effect.

EXPERIMENTAL

Melting points were determined in capillary tubes and uncorrected. Ir spectra were recorded on a JASCO IRA-1 spectrophotometer. ^{1}H Nmr spectra were recorded on a JEOL PMX-60 (60 MHz) using tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in Hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, and br=broad. Ms and high resolution ms (HRms) were recorded on a JEOL JMS-DX303 spectrometer. Elemental analyses were performed by the staff of the Central Analysis Room of Pharmaceutical Institute, Tohoku University.

Preparation of Palladium(0) Catalyst

To a dry THF solution (10 ml) of Pd(dppf)Cl_2 (110 mg, 0.15 mmol) and dppf (83 mg, 0.15 mmol), butyllithium in hexane (0.3 mmol) was added. The mixture was stirred at room temperature for 1 min and used in the next reaction as the palladium catalyst.

General Procedure for the Palladium-Catalyzed Reaction of Aryl Halides with (*E*)-1-Methoxy-1-trimethylsiloxypropane (1)

The palladium catalyst in dry THF (10 ml) as described as above was added to 90% TlOAc (1.78 g, 6 mmol) in dry THF (20 ml) under argon atmosphere. The mixture was stirred at room temperature for 5 min, followed by addition of an aryl halide (3 mmol) in dry THF (10 ml) and **1** (0.96 g, 6 mmol). The whole mixture was refluxed for the time shown in Table II. After evaporation of the THF, the residue was mixed with Et_2O and H_2O. The mixture was filtered through Celite® pad, and the filtrate was extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$, and the Et_2O was evaporated. The residue was purified by SiO_2 column chromatography using hexane-AcOEt (2:1) for the reaction of nitrogen-heteroaryl halides and hexane-AcOEt (19:1) for the reaction of iodobenzene. The product was distilled under reduced pressure using bulb-to-bulb apparatus.

Methyl 2-(Pyridin-2-yl)propanoate

bp 110°C/4 mmHg. Ir ($CHCl_3$, cm^{-1}): 1745. ^{1}H-Nmr ($CDCl_3$, ppm): 1.57 (3H, d, *J*=7.0), 3.70 (3H, s), 3.96 (1H, q, *J*=7.0), 7.0-7.8 (3H, m), 8.56 (1H, dd, *J*=2.0, 5.0). HRms Calcd for $C_9H_{11}NO_2$: 165.0789. Found: 165.0793.

Methyl 2-(Pyridin-3-yl)propanoate

bp 115°C/4 mmHg. Ir ($CHCl_3$, cm^{-1}): 1740. ^{1}H-Nmr ($CDCl_3$, ppm): 1.52 (3H, d, *J*=7.0), 3.69 (3H, s), 3.77 (1H, q, *J*=7.0), 7.1-7.8 (2H, m), 8.4-8.6 (2H, m). *Anal.* Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.11; H, 6.73; N, 8.44.

Methyl 2-(2,6-Dimethylpyridin-4-yl)propanoate
bp 125°C/6 mmHg. Ir ($CHCl_3$, cm^{-1}): 1739. ^{1}H-Nmr ($CDCl_3$, ppm): 1.46 (3H, d, *J*=7.0), 2.50 (6H, s), 3.62 (1H, q, *J*=7.0), 3.67 (3H, s), 6.87 (2H, s). HRms Calcd for $C_{11}H_{15}NO_2$: 193.1102. Found: 193.1103.

Methyl 2-(2,4-Dimethylpyridin-5-yl)propanoate
bp 110°C/3 mmHg. Ir ($CHCl_3$, cm^{-1}): 1740. ^{1}H-Nmr ($CDCl_3$, ppm): 1.51 (3H, d, *J*=7.0), 2.29 (3H, s), 2.47 (3H, s), 3.65 (3H, s), 3.88 (1H, q, *J*=7.0), 6.91 (1H, s), 8.27 (1H, s). HRms calcd for $C_{11}H_{15}NO_2$: 193.1102. Found: 193.1103.

Methyl 2-(4,6-Dimethylpyrimidin-2-yl)propanoate
bp 130°C/4 mmHg. Ir ($CHCl_3$, cm^{-1}): 1740. ^{1}H-Nmr ($CDCl_3$, ppm): 1.57 (3H, d, *J*=7.0), 2.44 (6H, s), 3.69 (3H, s), 4.02 (1H, q, *J*=7.0), 6.88 (1H, s). *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 726; N, 14.42. Found: C, 62.00; H, 7.28; N, 14.62.

Methyl 2-(2,6-Dimethylpyrimidin-4-yl)propanoate
bp 130°C/3 mmHg. Ir ($CHCl_3$, cm^{-1}): 1745. ^{1}H-Nmr ($CDCl_3$, ppm): 1.51 (3H, d, *J*=7.0), 2.46 (3H, s), 2.65 (3H, s), 3.68 (3H, s), 3.78 (1H, q, *J*=7.0), 6.91 (1H, s). *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.74; H, 7.36; N, 14.63.

Methyl 2-(Quinolin-2-yl)propanoate
bp 145°C/3 mmHg. Ir ($CHCl_3$, cm^{-1}): 1739. ^{1}H-Nmr ($CDCl_3$, ppm): 1.80 (3H, d, *J*=7.0), 3.83 (3H, s), 4.32 (1H, q, *J*=7.0), 7.4-8.4 (6H, m). *Anal.* Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.28; H, 6.11; N, 6.49.

Methyl 2-(Quinolin-3-yl)propanoate
bp 145°C/1 mmHg. Ir ($CHCl_3$, cm^{-1}): 1739. ^{1}H-Nmr ($CDCl_3$, ppm): 1.43 (3H, d, *J*=7.0), 3.50 (3H, s), 3.76 (1H, q, *J*=7.0), 7.1-8.2 (5H, m), 8.72 (1H, d, *J*=2.0). *Anal.* Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.26; H, 6.10; N, 6.49.

Methyl 2-(Isoquinolin-4-yl)propanoate
bp 135°C/1 mmHg. Ir ($CHCl_3$, cm^{-1}): 1736. ^{1}H-Nmr ($CDCl_3$, ppm): 1.71 (3H, d, *J*=7.0), 3.66 (3H, s), 4.38 (1H, q, *J*=7.0), 7.4-8.2 (4H, m), 8.51 (1H, s), 9.19 (1H, s). HRms Calcd for $C_{13}H_{13}NO_2$: 215.0946. Found: 215.0947

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