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A STUDY FOR PALLADIUM-CATALYZED CHEMOSELECTIVE VINYLATION AT C-3 POSITION OF 4-BROMO-1-TOSYLINDOLE[a]

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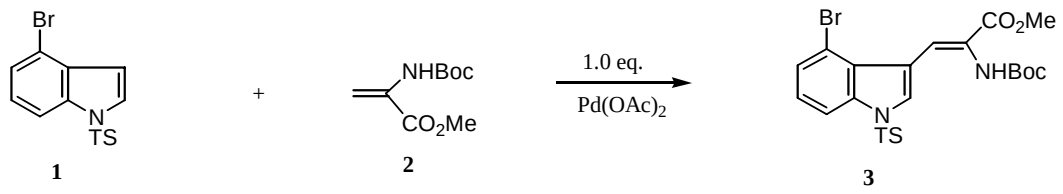
Abstract — Palladium-catalyzed direct activation of carbon-hydrogen bond at C-3 position of 4-bromo-1-tosylindole (**1**) was investigated. The reaction of **1** with ethyl acrylate (**4**) in the presence of 0.1 eq. of $Pd(OAc)_2$ and MnO_2-$Cu(OAc)_2$-O_2 system afforded C-3 vinylated product (**5**) in 52% yield, and by-products (**6** and **7**) that were formed by the Michael addition of AcOH or H_2O to **5,** were obtained in 17% and 7% yields respectively.

INTRODUCTION

Carbon-carbon bond forming reaction by the direct activation of carbon-hydrogen bond of aromatic compounds by Pd (II) is one of the most attractive reactions for synthesizing complex organic molecules.[1] We reported that chemoselective C-3 vinylation of 4-bromo-1-tosylindole (**1**) with methyl 2-*tert*-butoxycarbamoylacrylate (**2**) gave 4-bromodehydrotryptophan (**3**) (Scheme 1).[2] This reaction was especially synthetically useful, because selective introduction of different carbon side chain at C-3 and C-4 position of **1** was possible by carrying out successive C-3 vinylation and Heck reaction at C-4 position.[2] This methodology was applied to the syntheses of optically active ergot alkaloids such as costaclavine,[3] chanoclavine-I,[4] DMAT[5] and clavicipitic acids, [2] *via* optically active 4-bromotryptophan derivatives. The direct vinylation, however, has a disadvantage requiring a stoichiometric amount of expensive palladium salt (stoichiometric vinylation), while vinylation of aromatic bromides (Heck reaction) proceeded in catalytic manner. All attempts for catalytic reaction of **1** with **2** in the presence of chloranil as an oxidant were failed.[6] Fujiwara[7] and Itahara[8] reported that the direct vinylation of electron rich hetero-aromatic compounds such as indole, pyrrole and furan proceeded in catalytic manner

Scheme 1 : Direct C-3 Vinylation of 4-Bromo-1-tosylindole (**1**) for Synthesizing 4-Bromodehydrotryptophan Derivative (**3**)



1 **2** **3**

[a] This paper is dedicated to Professor James P. Kutney in celebration of the 70th birthday.

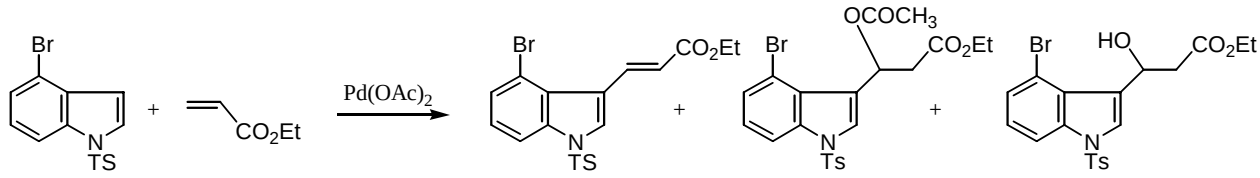
by_adding the oxidant. On this reaction, they used AcOH as a solvent that could not be used on the reaction of **1** with **2,** because **2** was not stable under acidic condition. Therefore, more simple olefin that was stable under acidic condition should be used on the above selective vinylation. We wish to report here the development of catalytic condition of our selective vinylation of 4-bromo-1-tosylindole (**1**) with ethyl acrylate (**4**) (Scheme 2).

RESULTS AND CONSIDERATION

At first, we examined the improvement of stoichiometric vinylation. In our previous results,[9] the yield of C-3 vinylated product (**5**) was 55% in the presence of stoichiometric amount of $Pd(OAc)_2$. While we have found[2] that the yield of 4-bromodehydrotrptophan (**3**) in the stoichiometric vinylation was much improved from 31% to 84% by adding chloranil as an oxidant for Pd(0) that was formed *in situ.* Therefore, we studied the effect of chloranil in the stoichiometric reaction of **1** with **4**. The effect of chloranil was obvious as shown in Table 1. When AcOH was used as a solvent, the yield of **5** was increased from 55% to 78% by the addition of 1.0 eq. of chloranil (Run 1 *vs.* Run 4). While the yield of **5** was not improved obviously by the use of aprotic solvent such as 1,2-dichloroethane (DCE) (Run 2 *vs.* Run 5) or 1,2,4-trichlorobenzene (TCB) (Run 3 *vs* Run 6). The trace amount of by-product (**6**), which might be formed by the addition of AcOH to **5**, was isolated in the case of using chloranil.

Next, we attempted the catalytic reaction. Table 2 summarizes the results of the reaction by the use of 0.1 eq. of $Pd(OAc)_2$. The yield was increased from 7% to 35% by the addition of chloranil accompanied with small amount of by-product (**6**, 4%) (Run 7 *vs*. Run 8). Although the yield of **5** in Run 8 revealed that the Pd (II) worked as catalyst [350% yield based on $Pd(OAc)_2$], the practical yield based on **1** was

Scheme 2 : Direct C-3 Vinylation of 4-Bromo-1-tosylindole (**1**) with Ethyl Acrylate (**4**)



1 **4** **5** **6** **7**

Table 1 : Reaction of **1** with **4** in the Presence of Stoichiometric Amount of $Pd(OAc)_2$

Run	Solvent	Chloranil (eq.)	Condition		Product (%)		SM. Recov. (**1**) (%)
			Temp.(^oC)	Time (h)	**5**	**6**	
1	AcOH	none	100	2	55		38
2	DCE[b)]	none	reflux	3	24		36
3	TCB[c)]	none	120	3	40		10
4	AcOH	1.0	100	3	78	3	
5	DCE[b)]	1.0	reflux	3	30	0.6	
6	TCB[c)]	1.0	120	3	55	4	

a) Reaction Condition : 1.0 eq. $Pd(OAc)_2$, under Ar atmosphere . b) 1,2-Dichloroethane, c) 1,2,4-Trichlorobenzene,

Table 2 : Reaction of **1** with **4** in the Presence of 0.1 eq. of $Pd(OAc)_2$[a)]

Run	Additive (eq.)	Solvent	Product (%)			SM (%).
			5	**6**	**7**	**1**
7	none	AcOH	7			90
8	Chloranil (1.0)	AcOH[b)]	35	4		
9	Benzoquinone	AcOH	8	2		79
10	$Cu(OAc)_2$ (3.0)	AcOH	24	5		60
11	MnO_2 (3.0)	AcOH	30	14	2	45
12	MnO_2 (3.0) + Benzoquinone (0.1)	AcOH	51	6	7	17
13	MnO_2 (3.0) + Benzoquinone (0.1)[e)]	AcOH	38	6	6	33
14	MnO_2 (3.0) + $Cu(OAc)_2$ (0.1)	AcOH	51	17	7	3
15	MnO_2 (3.0) + Chloranil (0.1)	AcOH	28	12	3	
16	MnO_2 (3.0) + Benzoquinone (0.1)	DMF	5			88
17	MnO_2 (3.0) + Benzoquinone (0.1)	TCB[c)]	2	1		93
18	MnO_2 (3.0) + $Cu(OAc)_2$ (0.1)	MeCN	12			85
19	MnO_2 (3.0) + $Cu(OAc)_2$ (0.1)	DCE[d)]	7	1		

a) Reaction Condition : 0.1 eq. $Pd(OAc)_2$, 110 ^oC, 5 h under O_2 atmosphere. b) Reaction Time : 3 h, Reaction Temperature : 100 ^oC. c) TCB : 1,2,4-Trichlorobenzene. d) DCE : Dichloroethane. e) under Ar atmosphere

still unsatisfactory. Other mild oxidizing reagents such as benzoquinone, $Cu(OAc)_2$, and MnO_2 were attempted. Benzoquinone was completely ineffective (Run 9) and $Cu(OAc)_2$ was less effective (Run 10) than chloranil (Run 8). Although the addition of MnO_2 gave almost the same yield (Run 11) as chloranil did, serious amount of by-product (**6**) was formed, accompanied with trace amount of new by-product (**7**), which might be also formed by the Michael addition of H_2O to **5**.

Bäckvall[10] reported that the MnO_2-benzoquinone-O_2 system was effective for recycling Pd(0) in the reaction of Pd(II)-catalyzed oxidation of 1,3-dienes to 1,4-diol derivatives. Tottie[11] also reported that the same combination of oxidant worked well in the Pd(II)-catalyzed oxidative cyclization of *cis*-1,2-divinylcyclohexane. Thus, we attempted the reaction using the same combination of oxidants. We carried out the reaction in the presence of MnO_2 : benzoquinone : $Pd(OAc)_2$ = 3 : 0.1 : 0.1 under oxygen atmosphere. The yield of C-3 vinylated product (**5**) was increased from 30% to 51% accompanied by 6 and 7% of by-products (**6**) and (**7**) respectively (Run 12). It was interesting that the combination of MnO_2 with benzoquinone was more effective than the single use of MnO_2 or benzoquinone respectively. In argon atmosphere, the reaction was slightly retarded as shown in Run 13. The combination of MnO_2 with $Cu(OAc)_2$ was also effective to give 3-vinylated product in 51% yield (Run 14), but the by-product (**6**) was increased to 17% accompanied with 7% of another by-product (**7**). The combination of other oxidizing reagents such as chloranil, *o*-chloranil, α-naphthoquinone, quinoline *N*-oxide, gave worse results. Since other aprotic solvent such as TCB, TCE, MeCN, and DMF gave less than 12% yield under the same conditions (Runs 16, 17, 18 and 19), AcOH was the only effective solvent for this catalytic reaction.[12]

CONCLUSION

The yield of the desired C-3 vinylated product (**5**) was still unsatisfactory, and the serious amount of by-products (**6** and **7**) was formed. The by-products (**6** and **7)**, however, are essentially the C-3 vinylated products, which were apparently formed from **5** by Michael addition of AcOH or H_2O. Since the combined yield of C-3 vinylated products (**5**, **6** and **7**) was 64% and 75% as in runs 12 and 14, the present investigation clearly shows usefulness of palladium catalyzed reaction on the selective activation of carbon-hydrogen bond on aromatic bromide. We are still going to develop a more practically useful condition of our selective vinylation.

EXPERIMENTAL

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Optical rotations were recorded on a JASCO DIP-1000 instrument. IR spectra were performed with a JASCO FT/IR-230 spectrophotometer. ^{1}H- NMR spectra were taken with a JEOL EX-400 spectrometer in $CDCl_3$. Chemical shifts of protons are referenced to tetramethylsilane as an internal standard, or the residual chloroform (7.26 ppm) was used as the internal reference when measured in $CDCl_3$. MS spectra were measured on a JEOL JMS-AM II 50. TLC was performed on Merck 25 DC-Platten 20×20 cm Kieselgel 60 F_{254} (Art 5715). In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise indicated.

Typical Procedure for Vinylation of 4-Bromo-1-tosylindole (1) with Ethyl Acrylate (4) in the Presence of Stoichiometric Amount of Palladium.

To the mixture of 4-bromo-1-(toluene-4-sulfonyl)indole (**1**, 176 mg, 0.5 mmol), chloranil (123 mg, 0.5 mmol) and $Pd(OAc)_2$ (113 mg, 0.5 mmol) in AcOH (4.2 mL) was added ethyl acrylate (**4**, 0.12 mL, 1.1 mmol) under Ar atmosphere, and the mixture was stirred at 100 ^{o}C for 3 h. Then the precipitated palladium was removed by filtration through Celite and washed thoroughly with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl successively and dried over $MgSO_4$. After evaporation of solvent, the resulted yellow oily residue (313 mg) was subjected to silica gel chromatography eluted with hexane : AcOEt (10 :1). The first fraction was the mixture of chloranil and starting **1**, which could not be separated. The second fraction was the desired ethyl 3-[4-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]acrylate (**5**, 175 mg) as pale yellow oil which was solidified spontaneously. This solid was recrystallized from EtOH to give pale yellow needles. mp 107 - 109°C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J = 7.3 Hz), 2.37 (3H, s), 4.28 (2H, q, *J* = 7.3 Hz), 6.31 (1H, d, *J* = 15.6 Hz), 7.17 (1H, dd, *J* = 8.3, 8.3 Hz), 7.26 (2H, d, *J* = 8.3 Hz), 7.44 (1H, d, *J* = 7.8 Hz), 7.77 (2H, d, *J* = 8.3 Hz), 7.91 (1H, s), 7.96 (1H, d, J = 8.3 Hz), 8.54 (1H, dd, J = 16.1, 1.0 Hz). EI-MS *m/z* : 449 (M^++2, 20.7), 447 (M^+, 19.8), 91 (100). IR (KBr) cm^{-1}: 1700. *Anal.* Calcd for $C_{20}H_{18}NO_4BrS$: C, 53.58; H, 4.05; N, 3.12. Found: C, 53.49; H, 3.94; N, 2.96. The third fraction was the ethyl 3-acetoxy-3-[4-bromo-1-(toluene-4-sulfonyl)-1*H*-indole-3-yl]propionate (**6**, 7.3 mg, 2.9%), which was pale yellow oil. This oil was solidified spontaneously and recrystallized from MeOH. mp 126-130 ^{o}C. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J = 7.3 Hz), 2.13(3H, s), 2.35 (3H, s), 2.90 (1H, dd, J = 8.3, 15.6 Hz), 3.10 (1H, dd, J = 4.9, 15.6 Hz), 4.05 – 4,25 (2H, m), 6.96 (1H, dd, *J* = 4.9, 8.3 Hz), 7.14

(1H, dd, *J* = 8.3, 8.3 Hz), 7.24 (2H, d, *J* = 8.3 Hz), 7.40 (1H, d, *J* = 7.8 Hz), 7.67 (1H, s), 7.72 (2H, d, *J* = 8.3 Hz), 7.93 (1H, d, J = 8.3). EI-MS *m/z* : 509 (M^++2, 1.59), 507 (M^+, 3.48), 43 (100). IR (KBr) cm^{-1}: 1738. *Anal*. Calcd for $C_{22}H_{22}NO_6BrS$: C, 51.98; H, 4.36; N, 2.76. Found: C, 51.69; H, 4.29; N, 2.96.

Typical Procedure for Vinylation of 4-Bromo-1-tosylindole (1) with Ethyl Acrylate (4) in the Presence of Catalytic Amount of $Pd(OAc)_2$.

To the mixture of 4-bromoindole (**1**, 176 mg, 0.5 mmol), MnO_2 (131 mg, 1.5 mmol), benzoquinone (5.4 mg, 0.05 mmol) and $Pd(OAc)_2$ (11.3 mg, 0.05 mmol) in AcOH (4.2 mL) was added ethyl acrylate (**4**, 0.12 mL, 1.1 mmol) under O_2 atmosphere, and the mixture was stirred at 110 ^oC for 5 h. Then the precipitates were removed by filtration through Celite and washed thoroughly with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl successively and dried over $MgSO_4$. After evaporation of the solvent, the resulted yellow oily residue (256 mg) was subjected to silica gel chromatography eluted with hexane : AcOEt (15 : 1 - 4 :1). The first fraction was the starting material (**1,** 29.1 mg, 16.5% recovery). The second fraction was **5** (114.1 mg, 50% yield) as pale yellow oil which was solidified spontaneously. The third fraction was the by-product (**6**, 15.9 mg, 6 %). The fourth fraction was ethyl 3-acetoxy-3-[4-bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]propionate (**7**, 15.3 mg, 7%), which was an orange oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J = 7.2 Hz), 2.35 (3H, s), 2.69 (1H, dd, J = 16.6, 9.3 Hz), 3.09 (1H, dd, J = 16.6, 2.9 Hz), 3.50 (1H, br s), 4.21 (2H, q, *J* = 7.2 Hz), 5.93 (1H, dd, J = 6.3, 2.9 Hz), 7.14 (1H, dd, *J* = 8.3, 8.3 Hz), 7.24 (2H, d, *J* = 8.3 Hz), 7.39 (1H, d, *J* = 7.8 Hz), 7.75 (2H, d, *J* = 8.3 Hz), 7.76 (1H, s), 7.97 (1H, d, J = 8.3 Hz). IR ($CHCl_3$) cm^{-1}: 3565, 1730. ^{13}C-NMR ($CDCl_3$) δ: 14.1, 21.5, 42.7, 60.9, 63.5, 112.3, 113.7, 124.7, 125.5, 126.9, 127.3, 130.0, 134.8, 136.5, 145.4, 172.2. EI-MS *m/z* : 465 (M^++2, 8.23), 467 (M^++2, 8.95), 43 (100).

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6. When 0.25 eq. of $Pd(OAc)_2$ was used in the presence of 1.0 eq. of chloranil in TCB, the yield of **3** was 38%. See *ref*. 2.
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12. In the case of using *tert*-butylcarbamoylacrylate (**2**) as olefin (Scheme 1), DCE and TCB were good solvent to give 4-bromodehydrotryptophan (**3**) in the presence of stoichiometric amount of $Pd(OAc)_2$ and chloranil. See *ref*. 2.