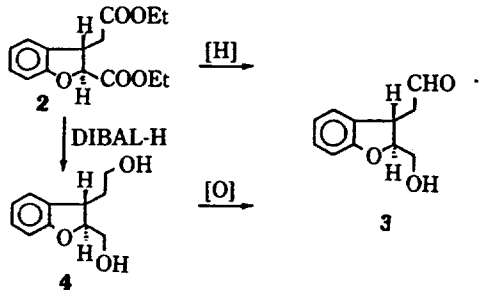
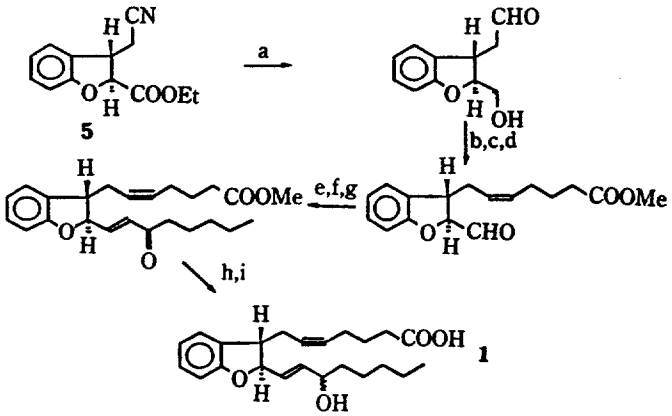


Scheme 2



a. DIBAL-H, THF, 0°-rt, 2 hrs, and then 5% H_2SO_4, 82%. b. t-Bu $(Me)_2SiCl$, imidazole, DMF, rt, 16 hrs, 95%. c. $P(Ph)_3{}^+(CH_2)_4$ $COOH\ Br^-$, t-BuO^-K^+, THF, rt, 4 hrs, 73%[4]. d. CH_2N_2, Et_2O, 0 °C, 0.5 hrs, 100%. e. $(n\text{-}Bu)_4NF$, THF, rt, 1 hr, 87%. f. DMSO, $(COCl)_2$, -50 °C, 1 hr, Et_3N, rt, 1 hr, 72%. g. $(EtO)P(=O)CH_2CO$ $(CH_2)_4CH_3$, LiCl, $(i\text{-}Pr)_2NEt$, CH_3CN, rt, 1 hr, 90%[5]. h. $Zn(BH_4)_2$, Et_2O, 0 °C, 3 hrs, 85% i. NaOH, MeOH, rt, 8 hrs, 95%.

Scheme 3

Therefore, we turned our attention to the cyanoester derivative, **5**, which was also obtained efficiently by the intramolecular Michael reaction described earlier. The DIBAL-H reduction followed by the acidic workup of the cyanoester **5** provided the desired aldehyde-alcohol **3** in high yield. The conversion of **3** to the target molecule **1** proceeded uneventfully as described in scheme 3 and the desired compound **1** was obtained as a thick oil.[3]

Acknowledgement. Financial support for this work by the Ministry of Science and Technology is gratefully appreciated.

References and Footnotes

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   NMR ($CDCl_3$, 270MHz).
   0.88(t, 3H, J = 6.4), 1.29(m, 6H), 1.54(m, 2H), 1.68(m, 2H), 2.09(t, 2H, J = 6.3), 2.33(t, 2H, J = 6.0), 2.45(m, 2H), 3.24(distorted quartet, 1H, J = 6.9), 4.17(m, 1H), 4.74(m, 1H), 5.50(m, 2H).
   IR (neat) 1,713 cm^{-1}.
   Mass (CI-CH4) 373.2 $(M + H)^+$, 257.1, 245.1, 127.0
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Palladium(O) Complex Catalyzed Mono-Carbonylation of Xylylene Dihalides under Phase Transfer Agent(II)

Sang Chul Shim*, Woo Hyun Park, Chil Hoon Doh, and Jin Ook Baeg

Department of Industrial Chemistry, Engineering College, Kyungpook National University. Taegu 702-701

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Phase transfer catalysis is a widely used method in synthetic organic chemistry.[1-3] Recent publications indicate the considerable potential of phase transfer catalysis in effecting metal induced reaction under exceedingly mild condition.[4] Of particular notes are the carbonylation catalyzed by palladium (0) compounds which occurs with high selectivity.[5-6]

In spite of extensive investigations of palladium(0) complex-catalyzed carbonylation of organic halides for the syntheses of esters, amides, aldehydes, and ketones,[7] little attention, however, has been paid to the normal carbonylation of xylylene dihalides.[8]

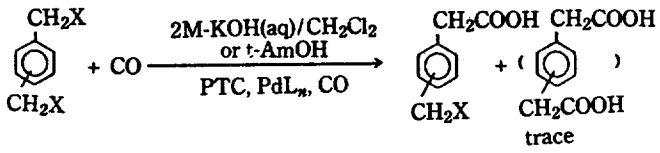
We reported recently the carbonylation of xylylene dihalides(X = Cl, Br) by using the method of organometallic phase transfer catalysis under an atmospheric pressure of carbon monoxide at room temperature or below.[9] In the course of the study, we found that the carbonylation of xylylene dihalides gave the selectively mono-carbonylated products, (halomethyl)phenylacetic acids.

Various xylylene dihalides could react with carbon monoxide in the presence of dibenzo-18-crown-6-ether or 18-crown-6-ether as a phase transfer agent and palladium(0) complex to afford the corresponding (halomethyl)phenylacetic acid in good yields and phenylenediacetic acid in trace amount under this two-phase system, KOH(aq)/CH_2Cl_2 or

Table 1. Products Obtained from the Carbonylation of Xylylene Dibromides by Organometallic Phase Transfer Catalysis

Entry No.	Substrate	Metal[a] Cat.	PTC[b]	Organic Phase	Reaction Time(hr)	Yield(%)[c]
1	*para-*	A	DBCE	CH_2Cl_2	20	51
2	*meta-*	A	DBCE	CH_2Cl_2	20	38
3	*ortho-*	A	DBCE	CH_2Cl_2	24	tr
4	*para-*	B	BTEC	t-AmOH	24	6
5	*para-*	B	CE	CH_2Cl_2	24	48
6	*meta-*	B	CE	t-AmOH	24	30
7	*ortho-*	B	CE	t-AmOH	24	tr
8[d]	*para-*	A	DBCE	CH_2Cl_2	20	32

[a] A; Tetrakis(triphenylphosphine)palladium(0), B; bis(1,2-diphenylphosphinoethane)palladium(0). [b] DBCE; Dibenzo-18-crown-6-ether, CE: 18-crown-6-ether, BTEC; benzyltriethylammonium chloride. [c] Yields were based on the amount of the starting materials. [d] *para-*Xylylene dichloride was used as a substrate.



PTC = Crown ether, BTEC
L = PPh_3, n = 4, L = $Ph_2PCH_2CH_2PPh_2$, n = 2

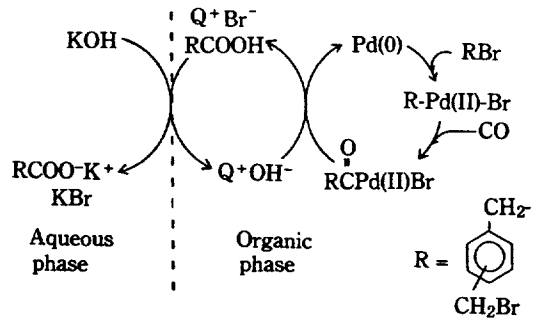
Scheme 1

t-amyl alcohol(org) at room temperature for 24 hours.

The reaction is described in scheme 1 and the results are shown in table 1.

Table 1 shows that palladium(0) complexes in the presence of crown ether as a phase transfer agent are active catalysts for selective mono-carbonylation of xylylene dihalides. Accordingly, in the case using tetrakis(triphenylphosphine) palladium(0) and dibenzo-18-crown-6-ether, 4-(bromomethyl)phenylacetic acid was obtained as a major product in good yield(entry No. 1) and 4-(chloromethyl)phenylacetic acid was as well(entry No. 8). In the above condition of bis(1,2-diphenylphosphinoethane)palladium(0) and 18-crown-6-ether, the same product was obtained in almost the same yield(entry No. 5). However, phenylenediacetic acid was always produced in trace amount in all cases. Table 1 also shows that the different combinations of palladium(0) complexes and crown ethers has little influence on the formations and distributions of the products and the chemical yields. It is further to be noted from table 1 that meta-xylylene dibromide is also selectively mono-carbonylated in moderate yield as though yield is slightly lower than those from the para-xylylene dibromide analogues. However, the carbonylation of ortho-xylylene dibromide gave intractable unknown materials with a trace amount of the corresponding carbonylated products(entry Nos. 3 and 7). Among the phase transfer catalysts examined, dibenzo-18-crown-6-ether and 18-crown-6-ether in methylene chloride or t-amyl alcohol solution were mildly active, affording the corresponding acids while benzyltriethylammonium chloride in t-amyl alcohol was inactive (entry No. 4).

The possible mechanism of this mono-carbonylation reaction catalyzed by palladium(0) complex is described in



Scheme 2

scheme 2.[10-11] Alkylpalladium(II) complex is produced by oxidative addition of first carbon-bromine bond of xylylene dibromides, and carbon monoxide is successively inserted into Pd-C bond. The produced acylpalladium(II) complex thought to be a key intermediate in this reaction reacts with a hydroxide ion to give the corresponding acids, which is immediately changed into carboxylate ions.

Finally, in connection to the mono-carbonylation reported here, it should be pointed out that di-carbonylation was predominant when iron(0) complex was used as previously reported by us.[9] This difference is caused by catalysts, yet being further investigated.

A typical procedure for the reaction is as follows; carbon monoxide was slowly bubbled through the reaction mixture containing 30 m*l* of 2M-KOH(aq), 20 m*l* of methylene chloride, and phase transfer catalyst such as dibenzo-18-crown-6-ether(0.30mmoles) or 18-crown-6-ether(0.30 mmoles) and benzyltriethylammonium chloride(0.60 mmoles) for 30 minutes. A solution of palladium(0) complex (0.25 mmoles) in 3-4 m*l* of methylene chloride was added and then the reaction mixture was vigorously stirred at room temperature for 1 hour. Xylylene dihalide(3.00 mmoles) dissolved in 10 m*l* of methylene chloride was injected. Stirring and carbon monoxide bubbling was continued for reaction time. After the phases were carefully separated, the aqueous phase was washed with two portions of ether, acidified with concentrated HCl, and extracted with four portions of ether. The combined ether extracts washed with water, dried with magnesium sulfate and then evaporated to give the acid products. The crude products were isolated and purified by vacuum sublimation apparatus or thin layer chromatography. The products were identified by ir, ^{1}H-nmr, and mass and the results are as follows; 4-(bromomethyl)phenylacetic acid: mp: 128-131 °C. ^{1}H-nmr($CDCl_3$) δ (ppm) 3.52(s, 2H, -CH_2COOH), 4.51(s, 2H, -CH_2Br), 7.27(s, 4H, Ar). ir ν_{CO}: 1700 cm^{-1}. m/e: 228(M^+) and 230($M+2^+$). 3-(Bromomethyl)phenylacetic acid: mp: 117-120 °C. ^{1}H-nmr($CDCl_3$) δ (ppm) 3.56(s, 2H, -CH_2COOH), 4.52(s, 2H, -CH_2Br), 7.25(s, 4H, Ar). ir ν_{CO}: 1700 cm^{-1}. m/e: 228(M^+) and 230($M+2^+$).

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Utilization of 1-Methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS) as a Coupling Agent for the Esterification of Dihydropyridine-3-Carboxylic Acid

Young Key Shim*, Kyeong Sook Kim, Cheol Hae Lee, Wan Joo Kim

Korea Research Institute of Chemical Technology, Dae Jeon 302-343. *Received February 20, 1988*

It has been reported that 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole(FMS)(**1**) is the effective coupler for acylation[1]. Now we found that FMS is also effective for esterification of dihydropyridine derivatives(**2**) which are widely used as calcium channel blocker. For the preparation of the dihydropyridine di-ester derivatives the well-known Hantsch reaction is generally applied[2]. On the other hand reactions on the mono-acid intermediate(**3**), which is resolvable, are intensively investigated in order to prepare stereochemically pure compound. In this case the acid chloride[3] and the other acid activating agents were used somewhere[4], but using the FMS instead is not reported yet. We found that this reaction is a neat and economic procedure specially for the industrial purpose. The typical procedure is followed: to the solution of the acid(**3**) and 1 eq. of triethylamine in DMF was added FMS at 0 °C and stirred for 40 min to give the 6-trifluoromethylbenzotriazole(FOBT) intermediate(**4**) in 90% yield. This FOBT intermediate is easily separable if needed by column chromatography (eluted with toluene: ethyl acetate = 7:3) and is very stable in the air at room temperature, no decomposed product was detected over 3 months. The addition of 1.5 eq. of the alcohol to the DMF solution of this intermediate and the subsequent stirring at 60 °C for 2 hr gave the desired product in 80-100% yield (Table 1)[5]. The organic base was not necessary with the simple alkyl alcohols but with the aryl or long chain alcohols 1 eq. of triethylamine or 4-dimethylaminopyridine(DMAP) should be added. DMAP gave the better results compared to triethylamine. The FOBT intermediate can be used with or without isolation and no differences were found in the point of yield. Satisfactory analytical data and NMR spectra were obtained for the compounds.

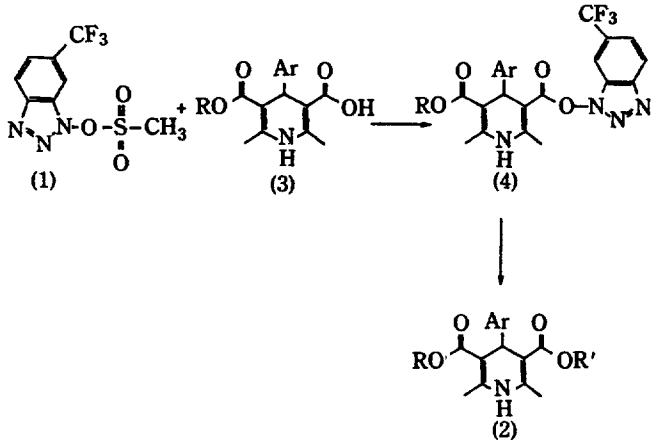
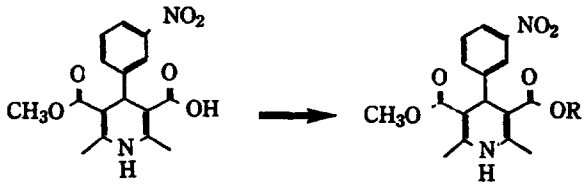


Table 1. Reactons with FMS



	R	Yields
1	$-CH_2CH_3$	90%
2	$-CH_2CH_2OCH_3$	95%
3	$-CH(CH_3)_2$	95%
4	$-(CH_2)_9CH_3$[a]	80%
5	$-CH_2CH_2N(CH_3)CH_2Ph$[b]	85%
6	-cyclohexyl[a]	80%
7	$-CH_2Ph$[b]	100%
8	-Ph[b]	95%

[a] 1 eq. of triethylamine added. [b] 1 eq. of DMAP added.

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