Decarboxylative Diarylation Reaction of 2-Methoxypropanoic Acid in a Phosphorus Pentoxide−Methanesulfonic Acid Mixture Yielding 1,1-Diarylethanes

Noriyuki Yonezawa,* Yoshimi Tokita, Tetsuo Hino, Hiroyuki Nakamura, and Ryoichi Katakai

Department of Chemistry, Gunma University, Tenjin-cho, Kiryu 376, Japan

The anomalous arylation reaction of 2-alkoxyalkanoic acid involving oxidative decarboxylation mediated by P_2O_5−$MeSO_3H$ (phosphorus pentoxide−methanesulfonic acid mixture)[1] is reported.

The reaction of 2-methoxypropanoic acid (*O*-methyllactic acid, **1**)[2] with aromatic compounds **2** in P_2O_5−$MeSO_3H$ unexpectedly gave 1,1-diarylethanes (**3**)[3] instead of the anticipated phenones (**4**) (Scheme 1). Surprisingly, carboxyl and methoxy groups were replaced by two aryl groups, i.e., *acid **1** was oxidatively arylated*.

This novel reaction shows some characteristic specificities and selectivities.

In this reaction, phosphorus pentoxide/phosphoric acid moieties play critically important roles. The reaction of acid **1** with anisole (**2a**) in polyphosphoric acid (PPA) also afforded 1,1-dianisylethane (**3a**), but that in methanesulfonic acid gave no diarylethanes **3** (Table 1).

To perform this reaction, an alkoxy or a hydroxy group on the 2-C position is essential. When 2-chloropropanoic acid (**5**), 2-methylbutanoic acid (**6**), propanoic acid (**7**), or 2-phenylpropanoic acid (**8**) was used in place of acid **1**, diarylethanes **3** did not form, and instead the corresponding phenones **9**−**12**, the direct condensation products, were obtained in moderate to good yields (Scheme 2). 2-Ethoxypropanoic acid (**13**) afforded dianisylethane **3a** in a good yield similarly, but for 2-hydroxypropanoic acid (lactic acid, **14**) the conversion to diarylethanes **3** was rather low.

The carboxylic group, strictly speaking, the hydrogen of the free carboxylic group, is also essential. When the corresponding ester, ethyl 2-methoxypropanoate (**15**), was used, no diarylethanes were obtained.

This new type of tandem diarylation reaction is greatly affected by the substituent on the nucleophilic aromatic compounds **2**. The reaction of acid **1** with anisole (**2a**) in P_2O_5−$MeSO_3H$ proceeded smoothly to give dianisylethane **3a** in high yields. An excess amount of anisole (**2a**) and elevated temperature or longer reaction time were needed to achieve high yields. In the reaction with benzene (**2d**), the formation of 1,1-diphenylethane (**3d**) could not be confirmed. Toluene (**2b**) and *p*-xylene (**2c**) gave the corresponding 1,1-diarylethanes **3b** and **3c** in yields up to 47% and 32%.

* To whom correspondence should be addressed. Phone: +81-277-30-1342. Fax: +81-277-30-1340. E-mail: yonezawa@tech.gunma-u.ac.jp.

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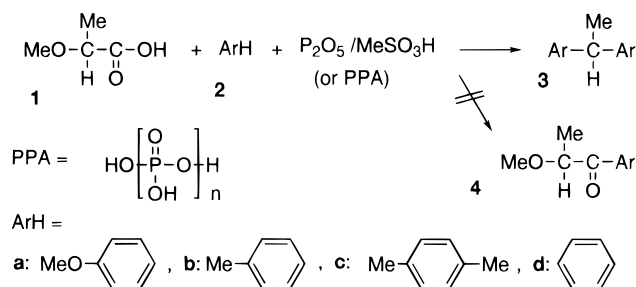
Scheme 1

Table 1. Reaction of 2-Methoxypropanoic Acid (1) and Aromatic Compounds 2 in Phosphorus Pentoxide−Methanesulfonic Acid Mixture (P_2O_5−$MeSO_3H$) and Related Reactions
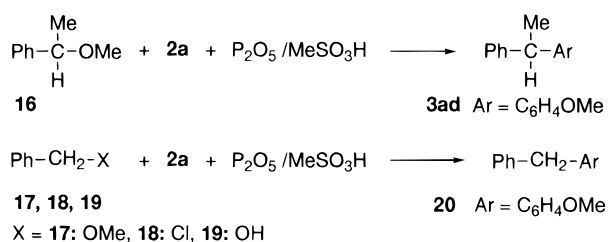
Acid	ArH	ArH/acid (mol/mol)	time (h)	T (°C)	product	yield[a] (%)
1	**2a**	2	2	rt	**3a**	48
	2a	2	1	60	**3a**	46
	2a	40	24	rt	**3a**	85
	2a	40	2	60	**3a**	90 (86[b])
	2b	40	48	rt	**3b**	47
	2b	40	2	60	**3b**	25
	2c	40	48	rt	**3c**	32
	2c	40	2	60	**3c**	31
	2d	40	3	60	**(3d)**	∼0
	2a	2[c]	0.5	rt	**3a**	21
	2a	2[d]	2	rt		0
13	**2a**	40	48	rt	**3a**	80
14	**2a**	40	24	rt	**3a**	11
15	**2a**	40	24	rt		0
8	**2a**	40	5	rt	**12**	100

[a] Yields were determined on the basis of ^{1}H NMR spectra. [b] Isolated yield. [c] PPA was used instead of P_2O_5−$MeSO_3H$. [d] $MeSO_3H$ was used instead of P_2O_5−$MeSO_3H$.

Scheme 2
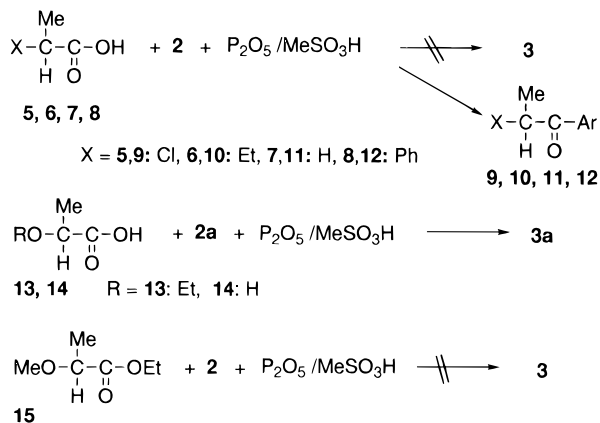
Finally, in all cases, only the ordinary Friedel−Crafts-type ketone products **9**−**12** or decarboxylation−arylation product **3** formed. A mixture of the two types of products was never obtained.

P_2O_5−$MeSO_3H$ is considered to be one of the most effective reagents for direct condensation between carboxylic acids and aromatic compounds yielding phenones as well as PPA. Plausible formation of a highly activated mixed anhydride intermediate between the carboxylic acids and methanesulfonic acid and the good solvent properties of P_2O_5−$MeSO_3H$ may enable direct condensation to proceed under rather mild reaction conditions. In addition, its acidic environment often facilitates the further rearrangement reactions of the preliminary products.[4]

Scheme 3

$$\text{Ph}-\overset{\overset{\displaystyle Me}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\text{OMe} \ + \ \textbf{2a} \ + \ \text{P}_2\text{O}_5\,/\text{MeSO}_3\text{H} \ \longrightarrow \ \text{Ph}-\overset{\overset{\displaystyle Me}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\text{Ar}$$

16   **3ad**   Ar = C_6H_4OMe

$$\text{Ph}-\text{CH}_2-\text{X} \ + \ \textbf{2a} \ + \ \text{P}_2\text{O}_5\,/\text{MeSO}_3\text{H} \ \longrightarrow \ \text{Ph}-\text{CH}_2-\text{Ar}$$

17, 18, 19   **20**   Ar = C_6H_4OMe

X = **17**: OMe, **18**: Cl, **19**: OH

Contrarily, this tandem arylation is suspected to proceed by a different mechanism than that for direct condensation described above. If the reaction proceeded through the corresponding α-methoxyphenone (**4**), the aryl group in this phenone intermediate must shift to α-carbon. Though the propagation of this demethoxylative rearrangement step still has possibility via formation of a hemiacetal-like intermediate formed from α-methoxyphenones **4** and P_2O_5/PPA, we think such an aryl 1,2-shift is less plausible. There are a few reports about the acid-catalyzed or photochemical aryl 1,2-shift of acetals having a leaving group on the α-position,[5] but the absence of the phenone products in this system strongly opposes the intermediacy of such phenone derivatives.

In addition, 2-phenylpropanoic acid (**8**) gave the corresponding condensation product (**12**) quantitatively. This fact clearly demonstrates that the replacement of the methoxy group of acid **1** by aryls **2** can not be the preliminary reaction of this novel tandem arylation.

Accordingly, the decarboxylation and the first arylation are considered to precede demethoxylation. Further, the distinct dependency of the conversion on the nucleophilic character of the aromatic compounds, as well as other characteristic features of this reaction, indicates that the critical step of this tandem reaction is the first arylation step. In the second step, acid-catalyzed demethoxylation is supposed to occur followed by second arylation according to ordinary electrophilic aromatic substitutions. In fact, benzyl methyl ethers **16** and **17**, which are possible intermediates for this reaction, gave diarylethane **3ad** and diarylmethane **20** quantitatively, as did benzyl chloride (**18**) and benzyl alcohol (**19**) (Scheme 3).

The electrophilic attack of the α-carbon of acid **1** to the aromatic ring implies that, in the course of the reaction, the acid was oxidatively arylated. Acid **1** and aromatic compound **2** lost, between them, one carboxyl group with one electron and one proton. At this stage we speculate the reaction mechanism as follows: The phosphorus of P_2O_5/PPA is considered to be reduced, which could provide the driving force of the reaction. This mechanism coincides with the substrate specificity that this reaction did not undergo when acid **1** was replaced with the corresponding ester (**15**).

We supposed that the first step of this reaction occurs concertedly. The bonds of P−H (from COO*H*), Ar−C (C_α), and P−O−H (from Ar*H*) are presumed to be formed and the bonds of Ar−H, C(C_α)−C(*C*OOH), and O−H (of COOH) to be cleaved simultaneously. At the same time, the C−O single bond of COOH is suspected to be transformed to a double bond of CO_2 and the P=O double bond to a P−O(−H) single bond. Indispensability of the hydrogen of COOH of acid **1** is considered to be due to completion of the electron transfer in this concerted reaction. The preference of an alkoxy group rather than a free hydroxy group on the 2-C carbon is interpreted to arise from the difference in the stabilization of the intermediate.

The reaction mechanism of this novel concurrent oxidative decarboxylation and arylation reaction via intermediacy of P_2O_5−MeSO$_3$H or PPA will be discussed with other possible reaction mechanisms such as evolution of carbon monoxide elsewhere.

Experimental Section

General. Purification of reagents was performed according to the literature[6] as occasion calls. NMR spectra were recorded at 200 or 500 MHz for ^{1}H and at 50 or 125 MHz for ^{13}C in CDCl$_3$ using TMS as an internal reference. The melting point is uncorrected. P_2O_5−MeSO$_3$H was prepared by stirring the 1:10 mixture of P_2O_5 and MeSO$_3$H at rt according to the literature method.[1]

Typical Procedure for Reaction of Acid 1 and Anisole (2a). P_2O_5−MeSO$_3$H (6 mL, 6 mmol) was added to an ice-cooled mixture of acid **1** (156 mg, 1.5 mmol) and anisole (**2a**, 6.48 g, 60 mmol) under vigorous stirring. The mixture was stirred at the prescribed temperature for the prescribed time interval. Then the mixture was poured into ice−water. The aqueous solution was extracted with ether (40 mL × 2). The combined organic layer was washed with saturated aqueous NaCl solution, dried over MgSO$_4$ overnight, and concentrated under reduced pressure. Dianisylethane (**3a**) was obtained as an isomeric mixture. The major product is the isomer that has two methoxy groups at 4- and 4′-positions. The product ratio of 4,4′-dianisylethane, 2,4′-dianisylethane, and 2,2′-dianisylethane is 78:20:2. By silica gel column chromatography (eluent benzene:hexane = 1:1 v/v) each isomer was obtained ^{1}H NMR spectrometrically pure. The data for the major isomer of dianisylethane **3a** are as follows: mp 71.5−72 °C; ^{1}H NMR (200 MHz) δ (CDCl$_3$) 7.15 (pseudo d of AA′MM′ pattern, 4H), 6.85 (pseudo d of AA′MM′ pattern, 4H), 4.10 (q, *J* = 7.5 Hz, 1H), 3.80 (s, 6H), 1.60 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz) δ (CDCl$_3$) 157.7, 138.9, 128.4, 113.7, 55.1, 43.0, 22.2. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.59. Found: C, 79.20; H, 7.53.

The reactions using other condensation reagents (PPA, MeSO$_3$H) were undertaken in a similar manner. The reactions of the acids (**5**, **6**, **7**, **8**, **13**, and **14**), ester **15**, benzyl ethers **16** and **17**, benzyl chloride (**18**), and benzyl alcohol (**19**) were undertaken in the essentially same manner. The structures of 1,1-diarylethanes **3** and other products were identified by ^{1}H NMR spectroscopy.

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