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ACID-MEDIATED SPECIFIC α,α-DIARYLATION AND α-MONOARYLATION REACTIONS OF PYRUVIC ACID WITH/WITHOUT DECARBONYLATION

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Abstract: Pyruvic acid (**3**) was found to be arylated chemoselectively at the α-ketocarbonyl carbon in P_2O_5-MsOH affording decarbonylative α,α-diarylated products **5**, decarbonylative α-monoarylated compounds **6**, or non-decarbonylative α,α-diarylated adducts **7** depending on the reactivity of arenes (**4a-g**), in contrast to Lewis acid-catalyzed reaction of its acid chloride (**2**).

α-Ketocarboxylic acids (**1**) have two carbonyl carbons: carboxyl carbon and ketone carbonyl one. There have been reported addition reactions of amines at α-ketocarbonyl carbon of α-keto acids (**1**) and condensation reactions of the

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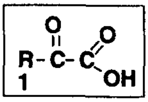
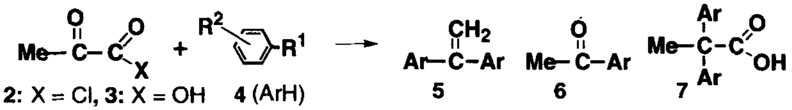
acids (**1**) and their acid chlorides with amines and alcohols at carboxyl carbon.[1] However, as far as we aware, specific or preferential electrophilic aromatic substitution reaction at α-ketocarbonyl and carboxyl carbons of free α-keto acids (**1**) has not been described. The lability of α-keto acids (**1**) is assumed to cause various side-reactions such as decarboxylation or spontaneous polymerization.[2]

Discrimination of these two partially positive-charged carbons of acids **1** or their derivatives and chemoselective transformation of each of them under mild conditions imply highly performed utilization of the multifunctional properties of naturally produced α-keto acids (**1**) such as pyruvic acid (**3**).



In this communication, we present specific acid-mediated α-arylation reaction of pyruvic acid (**3**) with distinct dependence on the arene substrate (**4**) in comparison to that of pyvaroyl chloride (**2**)[3] (Scheme 1).

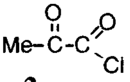
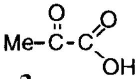
Scheme 1



The reaction of pyvaroyl chloride (**2**) with anisole [**4a** (**4**; R^1 = OMe, R^2 = H)] in the presence of Lewis acids (Runs 1-6 in Table 1) was found to progress with evolution of carbon monoxide giving complex mixtures of α-arylated compounds (diarylethene **5**, phenone **6**, or diarycarboxylic acid **7**) and many unidentified products. The reaction with $FeCl_3$ in CCl_4 gave dianisylethene **5a** and phenone **6a** in moderate yields (Run 1, 47% and 41%, respectively), and the yields in CH_2Cl_2 were rather low (Run 2, 34% and 39%, respectively). The reaction with $AlCl_3$ gave diarylethene **5a** and phenone **6a** (Run 3, 37% and 9%, respectively). On the other hand, the reactions with $TiCl_4$ and $SnCl_4$ mainly provided acetophenone derivative **6a** in 59% and 60% yields together with dianisylcarboxylic acid **7a**, and dianisylethene **5a** (Runs 4 and 5). The reaction in the presence of $ZnCl_2$ proceeded with rather poor efficiency (Run 6).

Compared to the reactions of pyvaroyl chloride (**2**) and anisole (**4a**) with Lewis acids, those of pyruvic acid (**3**) in PPA (polyphosphoric acid) and in P_2O_5-MsOH (phosphorus pentoxide-methanesulfonic acid mixture)[4] showed distinct

Table 1 Acid-Mediated Reactions of Pyvaroyl Chloride (**2**) and Pyruvic Acid (**3**) with Anisole (**4a**)[a]

Run	Substrate	Lewis Acid[b] or Acidic Medium	Yield (%) **5**	**6**	**7**
1 (2[c])		$FeCl_3$	47 (34)	41 (39)	0
3	 **2**	$AlCl_3$	37	9	0
4		$TiCl_4$	4	59	13
5		$SnCl_4$	5	60	3
6		$ZnCl_2$	2	7	6
7	 **3**	PPA	83	0	0
8		P_2O_5-MsOH	99	0	0

a) Reaction conditions: (Runs 1-6) to 1 mmol of substrate **2**, 2 mL of solvent (CCl_4[c]), 2 mmol of Lewis acid, and 2 mmol of anisole (**4a**) were used at rt for 24 h; (Runs 7 and 8) to 1 mmol of substrate **3**, 2 mL of acidic medium, and 2 mmol of anisole (**4a**) were used at rt for 24 h. b) Many unidentified products were also obtained. c) Dichloromethane was used as solvent.

specificities. Dianisylethene **5a** was solely obtained in good to quantitative yields (Runs 7 and 8).

The reactions of acid **3** with arenes **4b-i** in P_2O_5-MsOH were found to show highly specific behavior (Table 2). The reaction with *m*-dimethoxybenzene (**4b**) yielded diarylethene **5b** (43%) and bis(diarylethene) **8** (10%) (Run 9). The reaction with *o*-dimethoxybenzene (**4c**) gave the corresponding diarylcarboxylic acid (**7c**) together with diarylethene **5c** (Run 10), and that with *p*-isomer **4d** predominantly afforded lactone **9** (52%) along with acetophenone **4d** (Run 11). The reaction with toluene (**4e**), *m*-xylene (**4f**), or *o*-xylene (**4g**) provided the

Table 2 Reaction of Pyruvic Acid (**3**) with Arenes **4a-i** in P_2O_5-MsOH[a]

Run		ArH (4)		Isolated Yield (%)		
		R[1]	R[2]	**5** (**8**)	**6**	**7** (**9**)
8	**4a**	OMe	H	99	0	0
9	**4b**	OMe	*m*-OMe	43 (10[b])	0	0
10	**4c**	OMe	*o*-OMe	9	0	13
11	**4d**	OMe	*p*-OMe	0	4	0 (52[c])
12	**4e**	Me	H	0	68	0
13	**4f**	Me	*m*-Me	0	57	0
14	**4g**	Me	*o*-Me	0	68	0
15	**4h**	Me	*p*-Me	0	0	0
16	**4i**	H	H	0	0	0

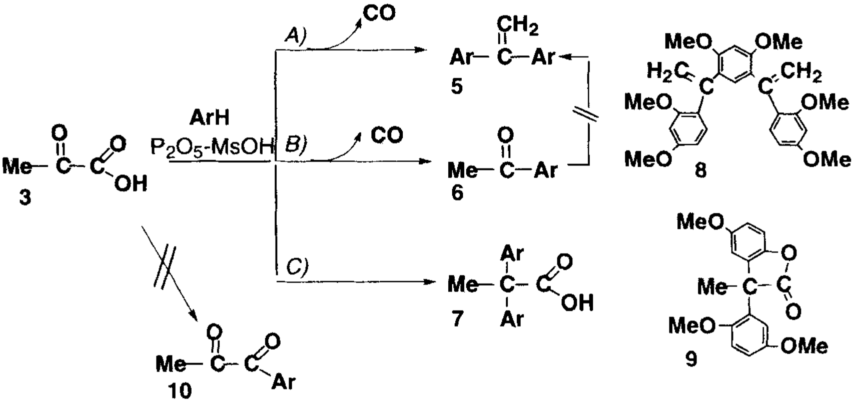
a) Reaction conditions: to 1 mmol of substrate **3**, 2 mL of acidic medium, and 2 mmol of arene **4** were used at rt for 8 h. b) Bis(diarylethene) **8** was also obtained in a 10% yield. c) Lactone **9** was obtained in a 52% yield.

corresponding acetophenones (**6**) in moderate yields (Runs 12-14), while that with *p*-xylene (**4h**) or benzene (**4i**) did not produce the corresponding α-arylated compounds (**5-9**) (Runs 15 and 16). No conventional Friedel-Crafts acylation type compounds **10** were detected even in the reaction with excess amount of arene **4a**. Arylation to ketone compounds under acidic conditions is well-known. However, acetophenones **6** were not converted to diarylethenes **5** under similar reaction conditions. This result means that arylated products **5** should be formed *via* an intermediate or a transition state other than phenones **6**.

There have been reported several decarbonylation reactions of keto acids **1**, their acid chlorides, and their esters.[5)] However, as far as we know, a combination of decarbonylation and selective α-arylation of α-keto acids (**1**) has not been ever presented.[6)]

The reactions of pyruvic acid (**3**) with arenes **4a-i** giving the α-arylated products (**5-9**) are considered to be divided into the following three types from the aptitude of decarbonylation and the multiplicity of α-arylation: A) decarbonylative α,α-diarylation with double bond formation [diarylethenes **5** and bis(diarylethene) **8**], B) decarbonylative α-monoarylation [phenones **6**], and C) non-decarbonylative

Scheme 2



α,α-diarylation [α,α-diarylated carboxylic acids **7** and lactone **9**] (Scheme 2). The lower selectivities and absence of conventional Friedel-Crafts acylation products (**10**) in the reactions of pyvaroyl chloride (**2**) are considered to be attributed to the high lability of acid chloride **2**. The formation of many unidentified by-products is considered to support this interpretation.

The selectivity in the reaction of pyruvic acid (**3**) whether decarbonylation proceeds or not is anticipated to depend on the interconverting ability in the reaction system from free carboxylic acid to mixed acid anhydride. P_2O_5-MsOH is supposed to readily form a mixed acid anhydride between acid **3** and phosphoric acid moiety (or methanesulfonic acid one). After that, the reaction routes are considered to separate according to the steric and electronic factors of the substituents in the aromatic compounds (**4a-i**). Methoxy group(s) on the benzene ring is supposed to give enough reactivity to progress the decarbonylative α,α- diarylation yielding diarylethenes **5**. However, the lower conversion to diarylethene **5b** in the reaction with *m*-dimethoxybenzene (**4b**), which is estimated to have more negative charge than anisole (**4a**), is supposed to indicate that the steric factor should considerably take part in. The fact that the reactions with *o*- and *p*-dimethoxybenzenes (**4c** and **4d**) scarcely gave the decarbonylative α-arylated products (**5** and **6**) is also considered to support above consideration. Arenes **4** having reactivity lower than that of anisole (**4a**), such as toluene (**4e**), *m*-xylene (**4f**), and *o*-xylene (**4g**), were proved to undergo decarbonylative monoarylation to give the corresponding phenones (**6**). The reactivity of *p*-xylene (**4h**) or benzene (**4i**) is estimated to be too low to afford arylated products.

In this series of reaction phenone compounds **6** were obtained in some cases (Runs 11-14). However they are not the conventional Friedel-Crafts acylation product (**10**) because the carboxyl carbonyl moiety was extruded as carbon monoxide and bond formation occurred between α-ketocarbonyl carbon and aromatic ring. Though the absence of Friedel-Crafts acylation type products, diketones **10** in the reaction of acid **3** has not been well understood yet, the conventional Friedel-Crafts acylation reaction between acid **3** and arenes **4a-i** is presumed to be overcome by other reactions.

The distinct specificities and the clear dependence on the medium for the electrophilic aromatic substitution reaction of pyruvic acid (**3**) together with recent establishment of the microbial technique of mass production of acid **3** by Yonehara and Miyata7) remind us its application to fine synthesis as a multifunctional electrophile acceptor under mild conditions without special activation.

Experimental

Typical reaction procedure: reaction of acid 3 and anisole (2a). P_2O_5-MsOH (3 mL) was added to an ice-cooled mixture of acid **3** (132 mg, 1.5 mmol) and anisole (**2a**, 324 mg, 3.0 mmol) under vigorous stirring. The mixture was stirred at rt for 24 h, and poured into ice-water. The aqueous solution was extracted with benzene (40 mL x 2). The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$ overnight, and concentrated under reduced pressure to give 1,1-dianisylethene (**5a**): ^{1}H NMR δ (200 MHz, $CDCl_3$) 3.83 (6H, s), 5.30 (2H, s), 6.83 (4H, pseudo d of AA'BB' pattern), 7.24 (4H, pseudo d of AA'BB' pattern) ppm; IR ν (KBr) 2838, 1466, 843 cm^{-1}; (Found: C, 79.65; H, 6.71. Calc. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%).

Bis(diarylethene) 8. ^{1}H NMR δ (200 MHz, $CDCl_3$) 3.67 (6H, s), 3.71 (6H, s), 3.81 (6H, s), 5.55 (4H, s), 6.39 (2H, dd, J = 2 and 8 Hz), 6.43 (3H, d, J = 2 Hz), 6.96 (1H, s), 7.04 (2H, d, J = 8 Hz); ^{13}C NMR δ (50 MHz, $CDCl_3$) 55.11, 55.37, 55.74, 96.20, 98.76, 103.88, 117.37, 123.86, 124.86, 130.87, 132.52, 143.17, 157.15, 158.10, 159.96 ppm. (Found: C, 72.39; H, 6.51. Calc. for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54%).

Lactone 9. ^{1}H NMR δ (200 MHz, $CDCl_3$) 1.76 (3H, s), 3.53 (3H, s), 3.80 (3H, s), 3.81 (3H, s), 6.38 (1H, d, J = 2Hz), 6.52-6.60 (2H, m), 6.73 (1H, d, J = 2Hz), 6.77 (1H, d, J = 8Hz), 7.44 (1H, d, J = 8Hz); ^{13}C NMR δ (50 MHz, $CDCl_3$) 23.78, 48.56, 55.55, 55.67, 56.06, 108.87, 110.51, 112.67, 112.97, 113.08, 114.37, 129.97, 134.69, 147.19, 150.94, 154.02, 156.57, 190.20 ppm; IR ν (KBr) 2837, 1794, 1607, 1507, 868, 802, 774, 752, 731, 694 cm^{-1}; (Found: C, 68.54; H, 5.99. Calc. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77%).

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