Specific and Chemoselective Multi-α-arylation Reaction of Benzoylformic Acid with or without Decarbonylation in P_2O_5−MsOH and Related Acidic Media

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In P_2O_5−MsOH, or related acidic media, benzoylformic acid (**1**) undergoes three types of di- or mono-α-arylation reactions with or without decarbonylation ((1) decarbonylative α,α-diarylation, yielding triarylmethanols **6**, (2) decarbonylative α-monoarylation, giving benzophenone derivatives **7**, and (3) α,α-diarylation without decarbonylation, affording diarylated carboxylic acids **5**) and one simple decarbonylation, without arylation, to form benzoic acid (**8**), instead of the conventional Friedel−Crafts acylation type reaction. The product ratios are governed by the capability of the acidic medium to form mixed anhydrides with carboxylic acids and the ability of the arenes to accept electrophiles.

The Friedel−Crafts reaction is widely used for the synthesis of aromatic compounds.[1] Various mediators, other than conventional Lewis acids, such as metal trifluoromethanesulfonates for catalytic Friedel−Crafts acylation reaction[2,3] and heterogeneous mediators (inorganic-solid-supported reagents or solid acids) for Friedel−Crafts reaction[2,4] have recently been reported. Electrophilic aromatic substitution reactions in acidic solvents such as TfOH (trifluoromethanesulfonic acid),[5,6] PPA (polyphosphoric acid), and P_2O_5−MsOH (phosphorus pentoxide−methanesulfonic acid mixture)[7] have also been widely investigated.

P_2O_5−MsOH is an excellent direct condensing reagent for solubilizing various organic compounds.[8,9] It has generally been explained that in P_2O_5−MsOH or PPA, mixed carboxylic−phosphoric anhydrides should act as acyl cation equivalents in an electrophilic aromatic substitution reaction. We have recently communicated that P_2O_5−MsOH mediated specific α,α-diarylation and α-monoarylation reactions of pyruvic acid, with or without decarbonylation, compete with Lewis acid mediated simple ketone formation with pyruvoyl chloride.[10] We subsequently studied the reactions of other α-keto acids. In contrast, when benzoylformic acid (**1**) was allowed to react with arenes **2a**−**i** in several acidic media, various decarbonylated/nondecarbonylated products **5**−**10** were obtained, with all of the arylations occurring at the α-keto carbon. Neither of the conventional Friedel−Crafts acylation type products, α-diketones **3** or triarylmethyl aryl ketones **4**, were obtained (Scheme 1).

In this paper, we describe three types of specific α-arylation and simple decarbonylation reactions of benzoylformic acid (**1**) that show distinguishable chemoselectivity as compared to the expected Friedel−Crafts and related reactions. Table 1 shows the results of the various

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[7] P_2O_5−MsOH is a convenient alternative to PPA because of its reduced viscosity and circumstantially better solvent power. See: Eaton, P. E.; Carson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38,* 4071.

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10.1021/jo990524l CCC: $19.00

Scheme 1

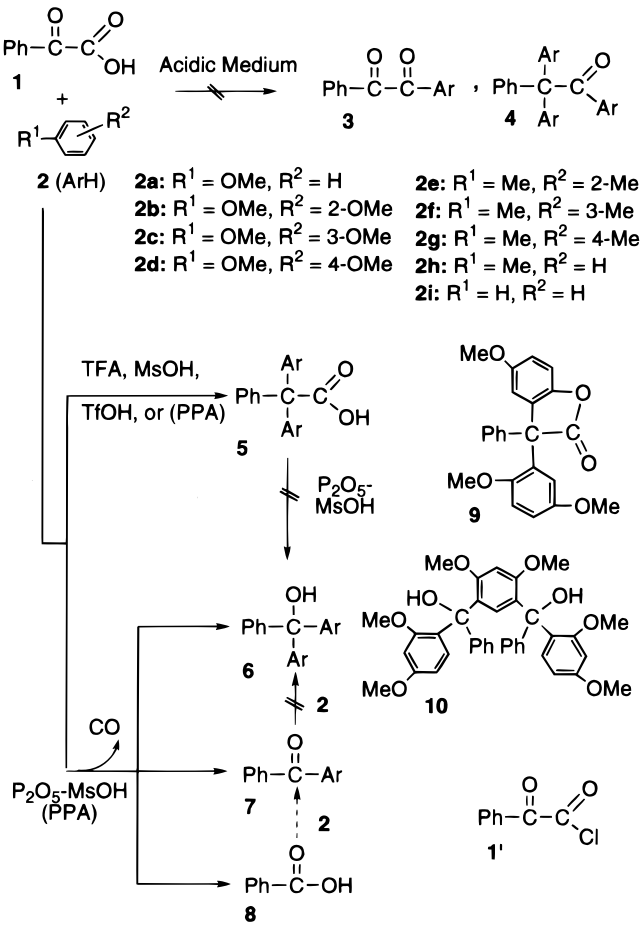

Table 1. Reactions of Benzoylformic Acid (1) with Arene (2) in Several Acidic Media[a]

run	ArH (2)	acidic medium	rt, 24 h: 5	rt, 24 h: 6	rt, 24 h: 7	rt, 24 h: 8	60 °C, 2 h: 5	60 °C, 2 h: 6	60 °C, 2 h: 7	60 °C, 2 h: 8
1, 2	**2a**	TFA	4	0	0	0	7	0	0	0
3, 4	**2a**	MsOH	100	0	0	0	100	0	0	0
5, 6	**2a**	TfOH	98	0	0	0	87	0	0	0
7, 8	**2a**	PPA	92	0	0	0	39	34	10	0
9, 10	**2a**	P_2O_5–MsOH	0	95	0	0	0	92	0	0
11, 12	**2b**	P_2O_5–MsOH	0	88	0	0	0	78	0	0
13, 14	**2c**	P_2O_5–MsOH	0	38[b]	0	0	0	28[c]	0	0
15, 16	**2d**	P_2O_5–MsOH	0[d]	21	20	0	0[e]	0	48	0
17, 18	**2e**	P_2O_5–MsOH	0	13	73	11	0	0	100	0
19, 20	**2f**	P_2O_5–MsOH	0	0	100	0	0	0	88	0
21, 22	**2g**	P_2O_5–MsOH	0	0	52	37	0	0	86	0
23, 24	**2h**	P_2O_5–MsOH	0	6	36	57	0	0	86	0
25	**2i**	P_2O_5–MsOH	0	0	0	90				
26	none	P_2O_5–MsOH	0	0	0	99				
27,[f] 28[f]	**2a**	TFA	0	7	13	53	0	5	14	55
29,[f] 30[f]	**2a**	MsOH	0	45	0	20	0	36	4	60
31,[f] 32[f]	**2a**	PPA	0	18	33	26	0	40	45	0
33,[f] 34[f]	**2a**	P_2O_5–MsOH	0	50	44	0	0	45	54	0

isolated yield/%

[a] Reaction conditions: for every 1 mmol portion of benzoylformic acid (**1**), 2 mL of P_2O_5–MsOH and 2 mmol of arene were used. [b] Phenylenebis(diarylmethanol) **10** was also obtained in a 17% yield. [c] Phenylenebis(diarylmethanol) **10** was also obtained in a 22% yield. [d] Lactone **9** was also obtained in a 37% yield. [e] Lactone **9** was also obtained in a 16% yield. [f] Phenylglyoxyl chloride (**1′**) was used instead of benzoylformic acid (**1**).

reactions of acid **1** or phenylglyoxyl chloride (**1′**) with arenes **2a**–**i** in TFA (trifluoroacetic acid), MsOH, TfOH, PPA, and P_2O_5–MsOH at room temperature for 24 h and at 60 °C for 2 h.

The reactions with anisole (**2a**) were highly dependent on the acidity of the media. The reactions in TFA, MsOH, or TfOH at both room temperature and 60 °C produced α,α-dianisylcarboxylic acid **5a** (Table 1, runs 1–6) exclusively. The reaction in PPA (room temperature, Table 1, run 7) afforded acid **5a** exclusively, but at 60 °C (Tabel 1, run 8) new components were formed (triarylmethanol **6a** and phenone **7a**) with acid **5a**. In P_2O_5–MsOH, (room temperature, Table 1, runs 9 and 10) triarylmethanol **6a** was obtained exclusively.

In contrast, the product distribution with arenes **2b**–**i** in P_2O_5–MsOH, at various temperatures, was distinctly different (Table 1, runs 11–25). The reactions with *o*- and *m*-dimethoxybenzenes (**2b**,**c**) yielded triarylmethanols **6b**,**c** (Table 1, runs 11–14). Phenylenebis(diarylmethanol) **10** was also obtained in the reaction with arene **2c** (Table 1, runs 13–14). The treatment of *p*-dimethoxybenzene (**2d**) with acid **1** (room temperature, Table 1, run 15) afforded triarylmethanol **6d**, together with phenone **7d** and lactone **9**, but at 60 °C (Table 1, run 16) triarylmethanol **6d** was not formed. Although the reactions with *o*-xylene (**2e**), *p*-xylene (**2g**), and toluene (**2h**) (room temperature, Table 1, runs 17, 21, and 23) gave phenones **7** together with triarylmethanols **6** and/or benzoic acid (**8**), those at 60 °C (Table 1, runs 18, 22, 24) yielded phenones **7** only. The reaction with *m*-xylene (**2f**) exclusively afforded phenone **7f** (Table 1, runs 19 and 20). The reaction with benzene (**2i**) or without arenes gave solely acid **8** (Table 1, runs 25–26). The similar reactions of acid chloride **1′** with anisole (**2a**) yielded the mixture of decarbonylated products (triarylmethanol **6a**, benzophenone **7a**, and/or benzoic acid (**8**)), even in TFA or MsOH, and diarylated acid **5a** was never obtained (Table 1, runs 27–34).

The reactions of acid **1** with arenes in various acidic media occur in four mechanistic categories (Scheme 1): (1) α,α-diarylation without decarbonylation (acids **5** and lactone **9**), (2) decarbonylative α,α-diarylation (triarylmethanols **6** and phenylenebis(diarylmethanol) **10**), (3) decarbonylative α-monoarylation (substituted benzophenones **7**), and (4) decarbonylation without arylation (benzoic acid (**8**)). The selectivity, whether or not decarbonylation proceeds, is anticipated to be governed by the capacity of the acidic medium to form mixed anhydrides (or equivalents) at the initial step.[11,12]

TFA, MsOH, and TfOH were too inert to attain a significant concentration of the mixed anhydride with acid **1**, even at 60 °C. In those acidic media, only the α,α-diarylations proceeded to give acids **5** (Table 1, runs 1–6).[13] In PPA at room temperature, the simple α,α-

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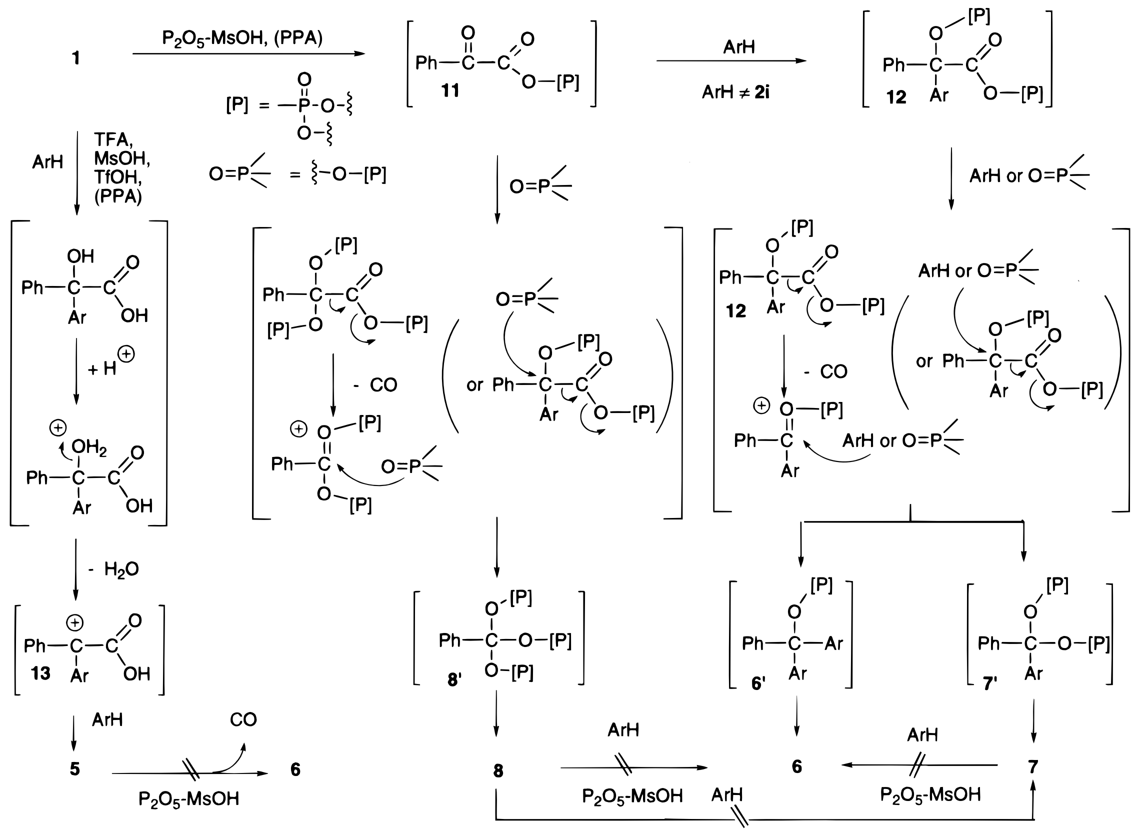
(11) In comparison of runs 9/33 or 10/34 (Table 1), our interpretation of the highly chemoselective reaction of acid **1** is that it should be readily converted to a more labile intermediate (mixed anhydrides or the equivalent) than should acid chloride **1′**. In addition, the low selectivity of the reaction of acid chloride **1′** is interpreted to indicate the formation of the acyl cation and mixed anhydrides, which gives the various decarbonylated products **6a**–**8a** (Table 1, runs 27–34). On the other hand, with regard to these results, one of the reviewers proposed that the chloride ion is quite a strong nucleophile and would be able to compete with the arene to trap the oxonium ion PhArC=O^+–[P] (which had very stable arenium-type resonance structures) to afford phenone **7a** after hydrolysis.

(12) In ref 9d, the P_2O_5–MsOH mediated specific decarbonylative α,α-diarylation of 2-methoxypropanoic acid, giving 1,1-diarylethane and 1,1-diarylethene, was concluded to proceed only after the formation of carboxylic–phosphoric anhydride at the initial step.

(13) Because the resultant cation **13** from an α-monoarylated intermediate is highly electrophilic, the second α-arylation is considered to proceed more readily. In contrast, the first α,α-arylation in TFA is hardly even considered to proceed at 60 °C (Table 1, run 2).

Scheme 2



diarylation progressed to exclusively yield acid **5,** presumably because formation of mixed carboxylic–phosphoric anhydrides **11** would be very slow compared to that at 60 °C (Table 1, run 7). P_2O_5–MsOH is assumed to form mixed carboxylic–phosphoric (methanesulfonic) anhydrides **11** spontaneously, even at room temperature.

It is thought that three kinds of decarbonylative reactions of mixed anhydride **11** may proceed according to the reactivity of each arene (Table 1, runs 9–25): (1) One or more methoxy groups on the benzene ring may give enough potential to promote decarbonylative α,α-diarylation (Table 1, runs 9–16).[14] (2) Considerably less-activated arenes, such as xylenes (**2e–g**) and toluene (**2h**), may primarily undergo decarbonylative α-monoarylation (Table 1, runs 17–24). (3) The reactivity of benzene (**2i**) may be too low to propagate α-arylation (Table 1, run 25). The formation of acid **8** in the reactions with arenes **2e**,**g–i** shows the relatively weak electrophile accepting ability of these arenes (Table 1, runs 17, 21, 23, and 25).

The decarbonylative α,α-diarylation triarylmethanols **6** are expected to be generated from acid **1** via decarbonylation of acids **5**[15,16] (Scheme 1, **1** → **5** → **6**) or addition of arenes to phenones **7**[17] (**1** → **7** → **6**). However, neither of them converted to triarylmethanols **6** in P_2O_5–MsOH under the present conditions; the starting material was recovered in each case. On the other hand, the decarbonylative α-arylation phenones **7** are also anticipated to be produced from acid **1** via direct condensation of carboxylic acids and arenes **(1** → **8** → **7)**.[2] In P_2O_5–MsOH, however, the yield of phenone **7h** from the reaction of acid **8** with toluene (**2h**), under the same conditions (room temperature, 24 h), was lower than that of acid **1** by 23%. Accordingly, phenones **7** are considered to be mainly formed via a distinctly different intermediate other than acid **8** under such conditions.

On the basis of the above considerations, the plausible reaction pathways for the decarbonylative reactions of acid **1** are as follows (Scheme 2): (1) Mixed anhydride **11** forms from acid **1** and the phosphoric anhydride moiety (O = [P]) of P_2O_5–MsOH, or PPA, at the initial step. (2) When the reactivity of the arenes (**2**) is higher than that of the phosphoric anhydride moiety, the first arylation to the α-carbon of the α-keto acids proceeds,

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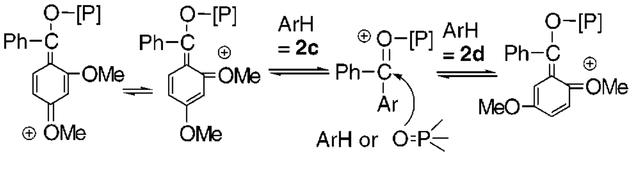
[14] One of the reviewers pointed out that the results showing that arene **2c** afforded only decarbonylative diarylation compounds **6c** and **10**, whereas arene **2d** gave a mixture of two types of compounds, **6d** and **7d** (Table 1, runs 13–16), indicated the lack of stabilization of the arenium ion $PhArC{=}O^{+}{-}[P]$ derived from arene **2d.** This is due to the 1,4-substitution pattern and, consequently, its lack of selectivity when reacting with the nucleophile in the last step (see Scheme 2). On the other hand, we supposed that the lower reactivity of the arene (**2d**), than that of other dimethoxybenzene isomers, should give rise to the lack of selectivity.



[15] Decarbonylation of α,α-trisubstituted carboxylic acids: (a) Gillespie, R. J. *J. Chem. Soc.* **1950**, 2997. (b) Burton, H.; Praill, P. F. G. *J. Chem. Soc.* **1951**, 726.

[16] Diarylation to the α carbon of free α-keto acids in cold concentrated sulfuric acid or in the presence of $AlCl_3$: (a) March, J. *Advanced Organic Chemistry, Reaction, Mechanisms, and Structure,* 3rd ed.; Wiley-Interscience: New York, 1985. (b) Wegmann, J.; Dahn, H. *Helv. Chim. Acta* **1946,** *29,* 415.

[17] Addition of arenes to ketones or diketones in strong/superacid media such as H_2SO_4 and TfOH: (a) Olah, G. A. *Friedel–Crafts and Related Reaction;* Wiley-Interscience: New York, 1964, Vol. 2, pp 597–640. (b)Yamazaki, T.; Saito, S.; Ohwada, T.; Shudo, K. *Tetrahedron Lett.* **1995**, *36,* 5749.

giving α-monoarylated intermediate **12**. (3) In accordance with the electrophile accepting abilities of the arenes, the replacement of the carboxy moiety on intermediate **12** by the arenes **2** (**12** → **6′** → **6**) and the phosphoryloxy moiety (O = [P]) (**12** → **7′** → **7**) takes place, resulting in the evolution of carbon monoxide, thereby yielding the decarbonylative di- and monoarylated products (**6**, **7**), respectively.[18] Whether the arylation and the nucleophilic attack of the phosphoryloxy moiety with decarbonylation proceed in a concerted or a stepwise manner has not yet been specified.[19] (4) In the reaction of acid **1** with benzene (**2i**), or without arenes, mixed anhydride **11** undertakes nucleophilic attack of the phosphoryloxy moiety to yield acid **8**, instead of the α-arylation (**1** → **11** → **8′** → **8**). (5) In the reactions with TFA, MsOH, and TfOH (or PPA at room temperature), both the first and the second arylations proceed prior to the formation of mixed anhydrides **11** to yield acid **5** (**1** → **13** → **5**).

Experimental Section

General. The purification of reagents, when needed, was performed according to the literature.[20] NMR spectra were recorded at 200 and 500 MHz (^{1}H) and at 50 and 125 MHz (^{13}C) in $CDCl_3$, using TMS as an internal reference. P_2O_5−MsOH was prepared by stirring the 1:10 wt/wt mixture of P_2O_5 and MsOH at room temperature, according to the literature.[7]

Typical Reaction Procedure for Reaction of Benzoylformic Acid (1) in P_2O_5−MsOH: Reaction of Acid 1 and Anisole (2a). To an ice-cooled mixture of acid **1** (75 mg, 0.5 mmol) and anisole (**2a**, 108 mg, 1.0 mmol) was added P_2O_5−MsOH (1 mL), under vigorous stirring. The mixture was stirred at the prescribed temperature and duration and poured into ice−water. The aqueous solution was extracted with benzene (40 mL × 2).[21] The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$ overnight, and concentrated under reduced pressure. The mixture was chromatographed over silica gel column chromatography (benzene/hexane 1/1).

4,4′-Bis(methoxy)trityl alcohol (6a): IR (KBr) 3484, 2836, 1609, 1510, 830, 756, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.74 (1H, s), 3.80 (6H, s), 6.85 (4H, pseudo d of AA′BB′ pattern), 7.18 (4H, pseudo d of AA′BB′ pattern), 7.24−7.32 (5H, m); ^{13}C NMR δ ($CDCl_3$) 55.21, 81.49, 113.11, 127.15, 127.88, 127.90, 129.34, 139.52, 147.48, 158.65. Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.19; H, 6.36. Found: C, 77.87; H, 6.33.

The structures of compounds **6h**,[22] **7a**,[23] **7e**−**h**,[23] and **8**[23] were identical to that described in the literature. Compound **1′** was prepared according to the literature.[24]

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Supporting Information Available: The other synthesis of methanol **6a**, identification of the evolved carbon monoxide gas, and spectral data for compounds **5a**,**d**, **6b**−**e**, **9**, and **10**. This material is available free of charge via the Internet at htpp://pubs.acs.org.

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[18] The predominant formation of phenones **7d**−**h** in the reactions with arenes **2d**−**h** at 60 °C indicates that the relative nucleophilicity of phosphoryloxy moiety (O−[P]) in the reaction system, after the first arylation, is enhanced to a level able to overcome the second arylation (Table 1, runs 16, 18, 20, 22, 24).

[19] Our consideration about the main reaction pathway is that a stepwise manner, via cation intermediates formed by the elimination of carbon monoxide, should somewhat implausible, because such cations will be too inert to propagate electrophilic aromatic substitution reactions. On the other hand, one of the reviewers insisted that the stepwise manner was best one when arenium ions were involved.

[20] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.

[21] For this extraction procedure, ether is not an effective solvent. Aromatic solvents are more suitable. We have ascertained that toluene, the solvent preferred over benzene, is also employable without causing a large drop in efficiency.

[22] Hellwinkel, D.; Heidelberg, U. *Chem. Ber.* **1989**, 2351.

[23] Pouchert, C. J.; Behnke, J. *Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*; Aldrich Chemical: Milwaukee, 1992.

[24] Ottenheijm, H. C. J.; de Man, J. H. M. *Synthesis* **1975,** 163.