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THE REACTION OF ARYL METHYL KETONES WITH AROMATIC ALDEHYDES IN TRIMETHYLSILYL POLYPHOSPHATE (PPSE). FORMATION OF MESO-2,4,6-TRISUBSTITUTED-5-ACYL-1,3-DIOXANES

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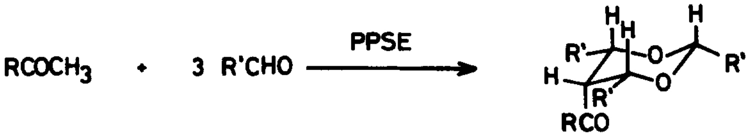
Summary: The reaction of aryl methyl ketones with three equivalents of aromatic aldehydes in the presence of trimethylsilyl polyphosphate (PPSE) afforded meso-2,4,6-trisubstituted-5-acyl-1,3-dioxanes in fair to good yields.

Recently, much attention has been focused on directed aldol reactions,1) and several creative methods have been developed for the regio- and stereoselective construction of acyclic systems, particularly for the syntheses of natural products.2,3) Almost all the investigations reported, hitherto, are concerned with the cross coupling of an enol equivalent with one molar equivalent of carbonyl component giving an aldol or a related compound. On the other hand, the reaction of a ketone with three equivalents of an aldehyde to give a meso-2,4,6-trisubstituted-5-acyl-1,3-dioxane has not been reported.4) We wish to describe herein a first example of the title reaction.

Previously, we exploited a new reagent, trimethylsilyl polyphosphate (PPSE), and employed it in the Beckmann rearrangement.5) The reagent, PPSE, is easily prepared from phosphorus pentoxide and hexamethyldisiloxane in benzene or dichloromethane. It differs from the commonly used polyphosphoric acid (PPA) in that it is essentially aprotic and neutral, and is soluble in organic solvent such as benzene at room temperature.

Employing this reagent, we examined the aldol reaction of aryl methyl ketones with aromatic aldehydes. Preliminary experiments showed that the isolated product was not the expected aldol but a 5-acyl-1,3-dioxane derivative.



1a-j

The reaction is best carried out using a mixture of a ketone and an aldehyde in a molar ratio of 1:3.5. A typical experimental procedure is described as follows. To a mixture of acetophenone (120 mg, 1 mmol) and benzaldehyde (371 mg, 3.5 mmol) was added PPSE[6] (3 g) under an argon atmosphere. The mixture was stirred at room temperature for 2 h, and was then quenched with aqueous saturated sodium bicarbonate solution (30 ml). The product was extracted with dichloromethane, and the combined extracts were dried over Na_2SO_4 and concentrated. After removal of unreacted benzaldehyde in vacuo (0.3 torr) at 60°C, the residue was purified by preparative thin-layer chromatography on silica gel. The product (307 mg) was assigned as 5-benzoyl-2,4,6-triphenyl-1,3-dioxane (<u>1a</u>) on the basis of spectral data (^{1}H-NMR,[7] ^{13}C-NMR,[8] MASS, and IR) together with elemental analysis. In a similar manner, various aryl methyl ketones and aromatic aldehydes were allowed to react in PPSE. The results are summarized in Table 1.

One of the characteristics of this new condensation is that the major product was <u>meso</u>-5-acyl-1,3-dioxane, with equatorially oriented triaryl groups at 2,4,6-positions and an acyl group in an axial position.[9] It is also noteworthy that the condensation reagent PPSE is essential for this reaction. The use of ethyl polyphosphate (PPE)[10,11] instead of PPSE resulted in the formation of α,β-unsaturated carbonyl compound as the major product.

Although the detailed reaction mechanism has not yet been investigated, the stereoselection might be explained in terms of thermodynamic control in which steric repulsions between substituents are minimized. The three substituents at 2,4,6-positions occupy equatorial positions to avoid 1,3-diaxial interaction. The acyl group at 5-position tends to lie axial where there is minimum steric interaction between adjacent substituents.

On the basis of the above results, we tried cross coupling of three different carbonyl compounds. This was achieved by the reaction of a preformed aldol with an aldehyde in PPSE. Thus, treatment of 3-(p-chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (<u>2a</u>) with benzaldehyde in PPSE at 0°C for 1.5 h gave 5-benzoyl-4-(p-chlorophenyl)-2,6-diphenyl-1,3-dioxane (<u>3a</u>; mp 177-178°C)[12] in 63% yield.

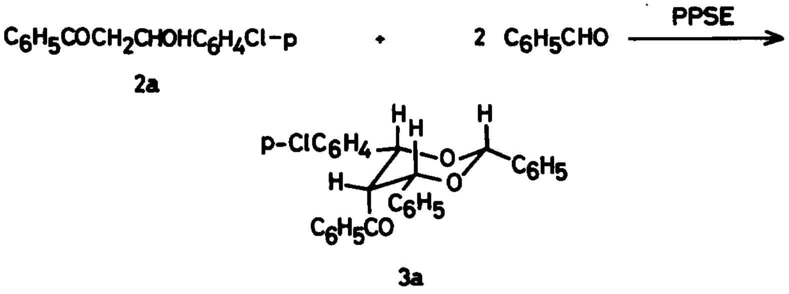


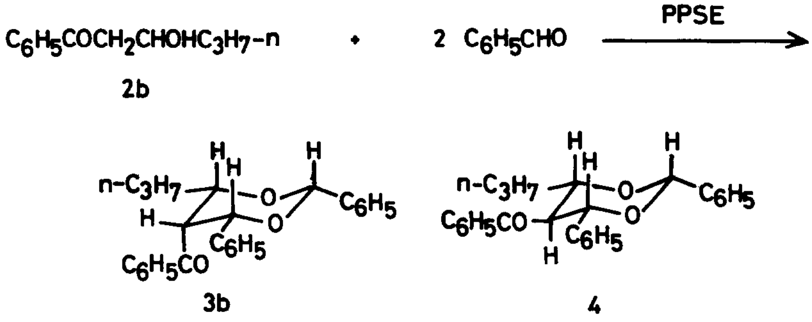
Table 1. The Reaction of Aryl Methyl Ketones with Aromatic Aldehydes in the Presence of PPSEa)

Entry	Ketone	Aldehyde	Time (h)	Productb)	(% Yield)	mp, °C
1	$C_6H_5COCH_3$	C_6H_5CHO	2	1a	(73)	199-200
2	"	p-ClC_6H_4CHO	2	1b	(50)	228-229
3	"	o-ClC_6H_4CHO	12	1c	(81)	191-192
4	p-$ClC_6H_4COCH_3$	C_6H_5CHO	1.5	1d	(63)	220-221
5	"	p-ClC_6H_4CHO	12	1e	(31)	208-210
6	"	o-ClC_6H_4CHO	12	1f	(70)	161-163
7	$C_{10}H_7COCH_3$ (β)	C_6H_5CHO	14	1g	(39)	243-244
8	p-$CH_3OC_6H_4COCH_3$	"	48	1h	(74)	212-213
9	"	o-ClC_6H_4CHO	40	1i	(63)	190-192
10	$C_6H_5CH{=}CHCOCH_3$	C_6H_5CHO	5	1j	(43)	179-181

a) The reactions were carried out at room temperature.

b) All products displayed satisfactory spectral data (^{1}H-NMR, IR, MASS) and gave satisfactory elemental analyses.

On the other hand, the reaction of 3-hydroxy-1-phenylhexan-1-one (2b) with benzaldehyde in PPSE gave two stereoisomers 3b (mp 143-145°C)13) and 4 (mp 127-128°C)14) in 36% and 44% yields, respectively.15) Formation of the isomer 4, which possesses benzoyl group in the equatorial position, is possibly due to the only small steric interaction between propyl and benzoyl groups.



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4) It was reported by Lumma and Ma that methyl ethyl ketone was condensed in trifluoroacetic acid with three equivalents of formaldehyde to afford 5-acetyl-1,3-dioxane ; W. C. Lumma and O. H. Ma, J. Org. Chem., 35, 2391 (1970).

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6) The reagent PPSE was prepared according to the procedure described in reference 5. The solution of PPSE in benzene or dichloromethane was concentrated on a rotary evaporator and the resulting syrup was used for the reaction.

7) ^{1}H-NMR ($CDCl_3$) δ 4.25 (t, 1H, J=3.5 Hz), 5.45 (d, 2H, J=3.5 Hz), 6.05 (s, 1H), 7.0-7.7 (m, 18H), 7.9-8.1 (m, 2H).

8) ^{13}C-NMR ($CDCl_3$) δ 51.2, 80.0, 102.3, 125.8, 126.9, 127.1, 127.6, 128.1, 128.2, 129.0, 131.3, 138.4, 138.6, 140.0, 197.7.

9) The structure of 5-(p-chlorobenzoyl)-cis-2,cis-4,cis-6-tris(o-chlorophenyl)-1,3-dioxane (1f) was unequivocally determined by single-crystal X-ray analysis.

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12) ^{1}H-NMR ($CDCl_3$) δ 4.2 (t, 1H, J=3.0Hz), 5.35-5.53 (m, 2H), 5.98(s, 1H), 7.0-7.6 (m, 17H), 7.75-8.00 (m, 2H).

13) ^{1}H-NMR ($CDCl_3$) δ 0.6-1.9 (m, 7H), 3.90(t, 1H, J=3.2Hz), 4.1-4.5 (m, 1H), 5.25 (d, 1H, J=3.2 Hz), 5.80(s, 1H), 7.00-7.95 (m, 15H); ^{13}C-NMR ($CDCl_3$) δ 13.7, 18.9, 35.6, 49.0, 78.8, 80.1, 102.1, 125.9, 126.9, 127.5, 128.1, 128.2, 128.9, 132.0, 138.6, 138.8, 139.9, 198.3.

14) ^{1}H-NMR ($CDCl_3$) δ 0.8-1.8 (m, 7H), 4.40-4.75 (m, 2H), 5.62(d, 1H, J=10 Hz), 6.01(s, 1H), 7.2-7.7 (m, 13H), 7.8-8.0 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 13.7, 18.8, 29.1, 52.7, 73.9, 76.4, 93.8, 126.2, 127.8, 128.0, 128.2, 128.9, 133.6, 136.3, 138.3, 139.9, 198.2.

15) Products, 3a, 3b, and 4, gave satisfactory elemental analyses.

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