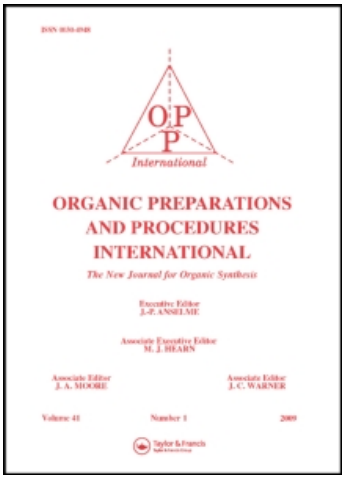

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Tamaki Jikyo[a]; Masashi Eto[a]; Toshikazu Matsuoka[a]; Kazunobu Harano[a]
[a] Faculty of Pharmaceutical Sciences, Kumamoto University, Kumamoto, JAPAN

To cite this Article Jikyo, Tamaki , Eto, Masashi , Matsuoka, Toshikazu and Harano, Kazunobu(1997) '*p*-CHLOROPHENOL AS A SOLVENT FOR CYCLOADDITION OF CYCLOPENTADIENONES WITH NON-ACTIVATED OLEFINS', Organic Preparations and Procedures International, 29: 4, 459 — 464
To link to this Article: DOI: 10.1080/00304949709355218
URL: http://dx.doi.org/10.1080/00304949709355218

ORGANIC PREPARATIONS AND PROCEDURES INT., 29 (4), 459-464 (1997)

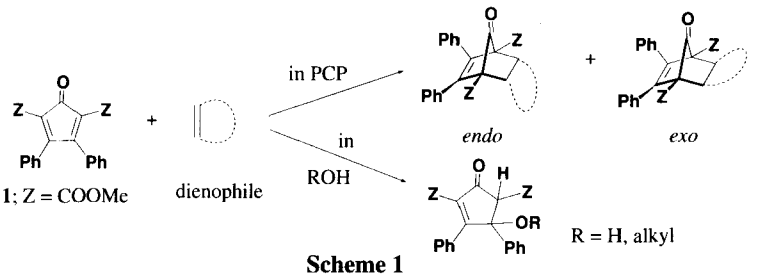
p-CHLOROPHENOL AS A SOLVENT FOR CYCLOADDITION OF CYCLOPENTADIENONES WITH NON-ACTIVATED OLEFINS

Tamaki Jikyo, Masashi Eto, Toshikazu Matsuoka and Kazunobu Harano*†

Faculty of Pharmaceutical Sciences, Kumamoto University
5-1 Oe-honmachi, Kumamoto 862, JAPAN

Cycloadditions in polar solvents have been considered to be unfavorable because of higher activation energies than those in nonpolar solvents due to additional desolvation energies of the addends.[1a] Recently, remarkable accelerations of some Diels-Alder (DA) reactions in aqueous solution have been reported, in which the hydrophobic effect is of principal importance.[1b] However, the "water effect" cannot be expected for dienes like cyclopentadienones because active cyclopentadienones react with hydroxylic solvent.[1c]

This paper describes the solvent effect of *p*-chlorophenol (PCP) on pericyclic reactions of cyclopentadienones with nonactivated olefins involving medium-ring polyenes.



Scheme 1

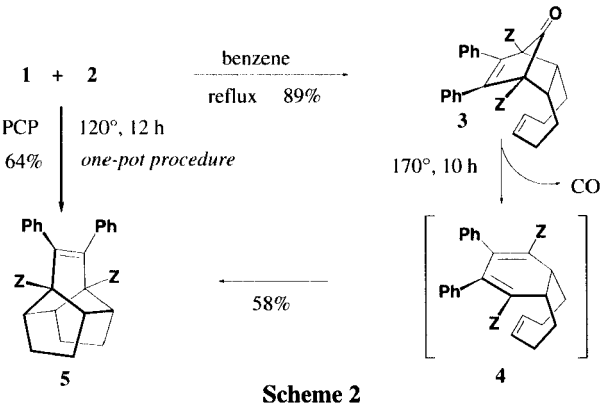
Table 1 shows the solvent effect of PCP on the cycloadditions of 2,5-*bis*(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1**) with several olefins which have no electron-withdrawing functional groups conjugated with dienophile. Table 1 shows significant rate enhancements.[2] With dienophiles like 1,5-cyclooctadiene (COD) and styrene,[3,4] an average of 5-fold rate enhancement was observed on changing the solvent from benzene to PCP. Cyclohexene which is known to be a very unreactive dienophile reacted with **1** in PCP at 80° to give the DA adducts; while no DA adduct was obtained in benzene (entry 8), the use of the dienophile as solvent gave the DA adduct under the same conditions (entry 7). In PCP, the yield the *exo* cycloadducts increased in comparison with those for benzene (see entries 1, 2, 7 and 8).

TABLE 1. Cycloaddition of **1** with Nonactivated Olefins in Benzene and PCP.

Entry	Olefin	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	styrene[a]	benzene	r.t.	6	96 (*endo*:*exo* = 11: 1)
2		PCP	r.t.	1	91 (*endo*:*exo* = 4: 1)
3	2,4-hexadiene	benzene	60	12	83
4		PCP	60	3	79
5	norbornadiene[a]	benzene	40	1	96
6		PCP	40	0.5	94
7	cyclohexene	none	80	48	61 (*endo*:*exo* = 2: 1)
8		PCP	80	72	88 (*endo*:*exo* = 1: 1)
9	1,5-cyclooctadiene (COD)[b]	benzene	80	8	86
10		PCP	80	3	95
11	cycloheptatriene (CHT)[c]	benzene	60	48	99
12		PCP	r.t	96	96

a) See ref. 4. b) see ref. 3. c) see ref. 6.

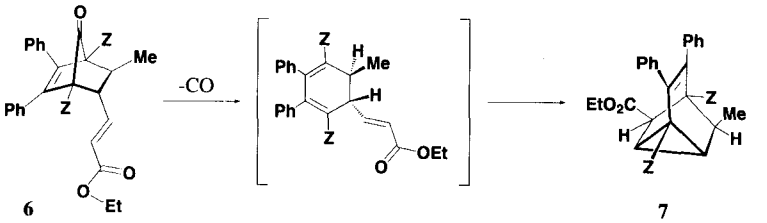
Thermolysis of the DA adduct (**3**) derived from **1** and COD (**2**) at 170° for 10 h gave the double Diels-Alder (DDA) adduct (**5**) *via* the decarbonylated DA adduct (**4**).[3] Heating a solution of **1** and COD in PCP at 120° for 12 h gave the DDA adduct (**5**) in a one-pot procedure *via* three-step sequential pericyclic reactions which involves intermolecular DA, decarbonylation and intramolecular DA reactions (Scheme 2). This reaction occurs at a temperature *ca.* 50° lower than that performed without solvent. A rough estimation of the decarbonylation rate based on the half-lives of **3** in PCP and *o*-dichlorobenzene indicates that the decarbonylation is over 30-fold faster in PCP than in *o*-dichlorobenzene.



Scheme 2

In the DA adduct (**6**) of **1** and ethyl sorbate, similar decarbonylation rate enhancement was observed, in which the DDA adduct **7** having a cyclopropane ring was isolated (Scheme 3). The structure of **7** was

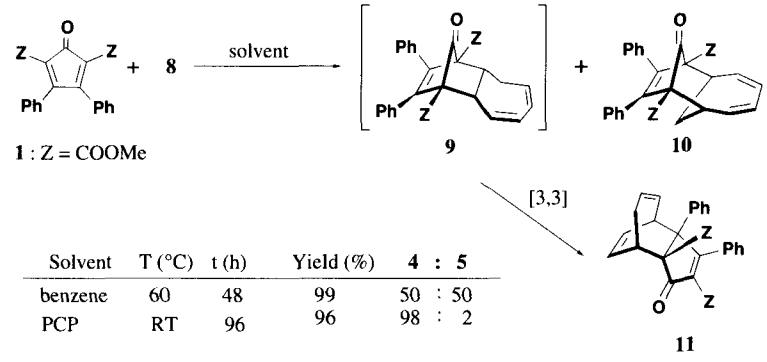
determined by comparison of the NMR spectral data with those of the structurally similar compounds.[5]



Solvent	T (°C)	t (h)	Yield (%)
none	170	8	64
PCP	120	9	53

Scheme 3

To clarify the effect of PCP on the reactivity and periselectivity of medium-ring polyenes, we examined the cycloaddition of **1** with cycloheptatriene (CHT, **8**).[6] The reaction of **1** with CHT in benzene at 60° afforded a 1:1 mixture of the *exo*[4+6] cycloadduct (**10**) and *endo*[2+4] cycloadduct (**11**) which derived from the [3,3]-sigmatropic rearrangement of the primary *endo*[4+2] cycloadduct (**9**). When this reaction was carried out in PCP, the reaction was about 15-fold faster than in benzene. The effect of PCP on the periselectivity is remarkable. At sufficiently high concentration of PCP, **9** virtually disappeared; the yield of *exo*[4+6]: *endo*[4+2] products in a ratio is 98:2 and 96% total yield.



Solvent	T (°C)	t (h)	Yield (%)	4 : 5
benzene	60	48	99	50 : 50
PCP	RT	96	96	98 : 2

Scheme 4

Of liquid phenols studied, PCP showed very interesting solvent effects on pericyclic reactions of various types. The solvent effect of PCP towards nonactivated olefins seems to be important from the synthetic point of view. Further studies are in progress on the solvation mechanism of PCP and the effect of phenols on the regioselectivity for the cycloaddition of unsymmetrical dienes.

EXPERIMENTAL SECTION

The IR spectra were taken with a Hitachi 270-30 spectrophotometer. The ^{1}H NMR spectra were taken with JEOL JNM-EX 270 (270 MHz), GX-400 (400 MHz) and JNM-A 500 (500 MHz) spectrometers using TMS as an internal standard and the chemical shifts are expressed in δ (ppm) values. The

coupling constants (*J*) are presented in Hz. High resolution mass spectra (HRMS) were taken with a JEOL JMS-DX303HF spectrometer.

Cycloadditions of 1 with Cyclohexene.- A solution of **1** (0.5 g, 1.44 mmol) in an excess cyclohexene (5.8 g, 70 mmol) was heated until the red color had disappeared. The excess cyclohexene removed under reduced pressure. The mixture was diluted with methanol. The solid was collected and recrystallized from EtOH to give 0.41 g (61%) of the *endo* DA adduct as colorless needles, mp. 170-171° ; IR (KBr): 1790 (bridge C=O), 1730 (ester >C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.54 (2H, br, methylene), 1.78 (4H, d, *J* = 8, methylene), 1.92 (2H, d, *J* = 12, methylene), 2.92 (2H, d, *J* = 11, methine), 3.63 (6H, s, -OMe), 7.04-7.34 (10H, m, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7 (methylene), 20.2 (methylene), 38.3 (methine), 52.0 (-OMe), 68.6 (quaternary carbon), 127.7, 128.2, 128.4 and 129.2 (aromatic CH), 134.3 and 138.6 (quaternary carbon), 167.9 (ester >C=O), 191.5 (bridge C=O); MS (m/z) 430 (M^+), 402 (M^+-CO).

Anal. Calcd. for $C_{27}H_{26}O_5$: C, 75.33, H, 6.09. Found: C, 75.39, H, 6.11

Inspection of the NMR spectrum of the oily crude product from the filtrate indicated the presence of the *exo* DA adduct beside the *endo* DA adduct. However, the *exo* DA adduct could not be isolated because of the cleavage of the strained ketonic bond during chromatography on silica gel.

Cycloadditions of 1 with 2,4-Hexadiene.- A solution of **1** (0.5 g, 1.44 mmol) in an excess 2,4-hexadiene (5.8 g, 70 mmol) in benzene was heated until the red color had disappeared. The excess 2,4-hexadiene was removed under reduced pressure. The mixture was diluted with methanol. The precipitated solid was collected and recrystallized from EtOH to give 0.50 g (83%) of the *endo* DA adduct as colorless prisms, mp. 79-82° ; IR (KBr): 1788 (bridge C=O), 1738 and 1712 (ester >C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, d, *J* = 7, methyl), 1.77 (3H, d, *J* = 7, methyl), 2.16 (1H, t, *J* = 6 and 12, methine), 2.99 (1H, q, *J* = 9 and 12, methine), 3.55 and 3.62 (6H, s, -OMe), 5.43 (1H, q, *J* = 9 and 15, olefin), 5.91 (1H, q, *J* = 15 and 7, olefin), 7.00-7.29 (10H, m, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6 (methyl), 18.0 (methyl), 41.6 (methine), 49.9 (methine), 51.7 and 52.1 (OMe), 68.1 and 68.8 (quaternary carbon), 127.6, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8 and 128.9 (aromatic CH), 128.9 and 129.5(olefin), 133.5, 133.6, 137.9 and 139.6 (quaternary carbon), 166.9 and 167.9 (ester >C=O), 191.6 (bridge C=O); MS (m/z) 430 (M^+).

Anal. Calcd. for $C_{27}H_{26}O_5$: C, 75.33, H, 6.09. Found: C, 75.45, H, 6.10

Cycloadditions of 1 with Some Dienophiles in PCP. General Procedure.- A solution of **1** (0.28-0.57 mmol) in an excess amount of diene (0.6-1.5 mmol) in PCP was stirred at given temperature until the red color had disappeared (see Scheme 2-9 for reaction condition). The mixture was diluted with benzene and washed three times with 10% sodium hydroxide. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The cycloadduct was isolated as a mixture of the stereoisomers and its formation ratio was determined by 270 MHz ^1H NMR spectroscopy.

Cycloadditions of 1 with 1,5-Cyclooctadiene (2) in PCP.- The procedure was similar to that described in the previous paper.[3] The known compound (**5**) was identified by comparison of the ^1H

NMR spectral data with those of authentic sample. A solution of **1** (0.50 g) and **2** (1.52 g) in PCP (2 mL) was stirred at 120° for 12 h. The mixture was diluted with benzene and washed three times with 10% sodium hydroxide. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The resulting oil was purified by chromatography on silica gel with AcOEt-benzene (1:20) to give **5** as colorless prisms: mp>200° (lit.[3] mp. 227-229°) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57-2.12 (8H, m, methylene), 2.47-2.74 (4H, brs, methine), 3.05 (6H, s, -OMe), 6.73-7.22 (10H, m, aromatic H).

Thermolyses of the DA Adduct (6). Formation of DDA Adduct (7).- The DA adduct (1.0 g, 2.05 mmol) was heated at 120° to give an oil with evolution of CO gas. The resulting oil was purified by chromatography on silica gel with AcOEt-benzene (1:20) to give **7** (0.604 g, 64%) as colorless prisms: mp. 102° ; IR (KBr): 1734 (>C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, d, J = 6.72, methyl), 1.25 (3H, t, J = 6.1, CH_2-CH_3), 2.23 (1H, dd, J = 4.88, 1.83, methine), 2.49 (2H, d, J = 4.88, methine), 3.23 and 3.26 (6H, s, -OMe), 3.42 (1H, d, J = 1.84, methine), 4.20 (2H, q, J = 6.71, methylene), 6.96-7.08 (10H, m, aromatic H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0 (methyl), 14.6 (-CH_2-CH_3), 28.7 (methine), 30.3 (methine), 33.1 (quaternary carbon), 39.1 (methine), 47.7 (methine), 51.8 and 52.1 (-OMe), 58.2 (quaternary carbon), 60.9 (methylene), 126.2, 126.3, 127.3, 127.6, 128.3, 128.7, 128.9, 129.0, 129.3 and 130.1 (aromatic CH), 134.3, 139.2 and 139.9 (quaternary carbon), 170.9, 171.6 and 172.4 (>C=O) ; MS (m/z) 488 (M^+), 387 (M^+-CO_2Et). HRMS Calcd for $C_{28}H_{28}O_6$ (M^+) 460.1842, Found 460.1886;

Anal. Calcd. for $C_{28}H_{28}O_6$: C, 73.03, H, 6.13. Found: C, 73.26, H, 6.16

Cycloadditions of 1 with Cycloheptatriene(8) in PCP.- A solution of **1** (0.20 g) and **8** (0.12 mL) in PCP (1 mL) was stirred at room temperature for 96 h. The mixture was diluted with benzene and washed three times with 10% sodium hydroxide. The organic layer was dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure to give a mixture of the cycloadducts **10** and **11**. The formation ratio of the cycloadducts was determined by 270 MHz ^{1}H NMR spectroscopy (**10** : **11**=98 : 2). The resulting solid was recrystallized from EtOH to give **10** as colorless prisms. : mp. 189-192° (lit.[6] mp. 189-193°) ; IR (KBr): 1781 (bridge C=O), 1735 (ester >C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (1H, d, J = 14, methylene), 2.60 (1H, m, methylene), 3.56 (6H, s, -OMe), 3.68 (2H, t, J = 5, 6, methine), 5.98 (2H, m, >CH-CH=C*H*), 6.30 (2H, m, >CH-C*H*=CH), 6.96-7.50 (10H, m, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9 (methylene), 41.6 (methine), 52.2 (-OMe), 71.6 (quaternary carbon), 126.6 (olefin), 128.2, 128.5, 128.8, 129.1 and 133.5 (aromatic CH), 133.6 (quaternary carbon), 136.9 (olefin), 168.4 (ester >C=O), 195.7 (bridge C=O).

The minor cycloadduct **11** was identified by comparison of the ^{1}H NMR spectral data with those of the adduct isolated in benzene: pale yellow powder; mp. 172-175° (lit.[6] mp. 172-177°); IR (KBr): 1798 (bridge C=O), 1736 (ester >C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67, 2.72 (2H, m, methylene), 3.54, 3.76 (6H, s, -OMe), 3.70 (2H, m, methine), 5.96-6.32 (4H, m, olefin), 6.82-7.40 (10H, m, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3 (methylene), 42.8 and 55.7 (methine), 51.9 and 52.3 (-OMe), 68.4 and 69.0 (quaternary carbon), 126.6 (olefin), 128.1, 128.2, 128.5, 128.8, 129.1 and

133.5 (aromatic CH), 134.9, 136.9, 138.4 and 139.4 (quaternary carbon), 167.5 and 167.2 (ester >C=O), 190.8 (bridge C=O).

Acknowledgement.- This work was supported in part by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture Government of Japan. We thank Mrs. K. Izumi (née Tanaka) and Miss H. Fukue for experimental assistance.

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E-mail harano@gpo.kumamoto-u.ac.jp

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2. The pseudo first-order rate constants (k x 10^5) for cycloadditions of **1** with some dienophiles in benzene and PCP are as follows: cycloheptatriene (CHT), 3.26 (benzene), 47.5 (PCP); cyclohexene 0.046 (benzene), 0.37 (PCP); 1,5-cyclooctadiene (COD), 0.372 (benzene), 2.07 (PCP); styrene 323.3 (benzene), 1453 (PCP).

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(Received August 26, 1996; in revised form March 24, 1997)