

Letter

Cerium complexes with acetato acylbis(pyrazolinone) ligands as an efficient catalyst for the oxidation of cresols by molecular oxygen

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Accepted 1 February 2002

Abstract

The catalytic use of cerium complexes with acetato *o*-phthaloylbis(1,3-dimethyl-2-pyrazolin-5-one) ligands produced an 88% yield of 3,5-dimethoxy-4-hydroxybenzaldehyde for the oxidation of 3,5-dimethoxycresols by molecular oxygen even in 25% methanolic aqueous solution. The desired compound was obtained up to a 94% yield by increasing the concentration of the substrate or using a 1-propanol aqueous solution.

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Keywords: Acylbis(pyrazolinone); Oxidation; Molecular oxygen; Cresols; Hydroxybenzaldehydes; Cerium complexes

1. Introduction

The oxidation by molecular oxygen of the anti-oxidizing cresols is a very interesting field for many industrial and pharmaceutical chemicals [1].

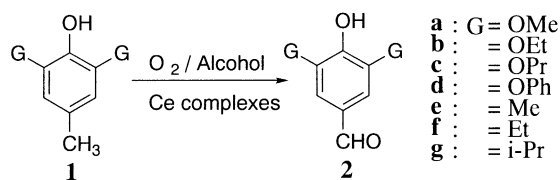
In general, the syntheses of disubstituted-hydroxybenzaldehyde **2** from disubstituted-cresol **1** by direct oxidation (as shown in Scheme 1) is difficult because the methyl group competes with a free hydroxy group [2–5]. Cerium triacetate in various metal compounds was found to give the desired compound **2a** with more than 82% yield from compound **1a** without the formation of a quinone [6] and dimers [7] when treated in anhydrous methanol [8].

However, even in the presence of a trace amount of water in methanol as the solvent, the yield of compound **2** drastically decreased. Therefore, a search was made to investigate the activity of complexes other than cerium triacetate. At the same time, the use of

aqueous solvents is necessary from the viewpoint of environment safety and economical cost. However, oxidation of organic compounds is very limited in aqueous solvent, because of their low solubility resulting in low yield of oxidation products. In previous studies [8], cerium complex with phenylmethylpyrazolinone was found to exhibit an activity superior to cerium triacetate in methanolic aqueous solution, while this complex and ligand are hardly soluble in methanolic aqueous solution.

A variety of complexes were tested in the hope of oxidizing cresols in alcoholic aqueous solution, as well as in anhydrous solvents. Oxidation research consequently arrived at ligands which contained a methyl group enhancing an affinity for water compared to a phenyl group on pyrazolinone.

This paper describes cerium complexes with dimethylpyrazolinone ligands showing higher activity for oxidation of cresol in comparison with hitherto reported complexes even in high water contents.



Scheme 1. The cerium complexes-catalyzed oxidation of cresols into hydroxybenzaldehyde.

2. Experiment

2.1. Ligands

Preparation of a typical ligand is as follows.

3d: *o*-Phthaloylbis(1,3-dimethyl-4-pyrazolin-5-one); 1,3-dimethyl-2-pyrazolin-5-one (3.36 g, 30.0 mmol) was placed in a three-necked flask (200 ml) with calcium hydroxide (Aldrich, 5 g) and distilled dioxane (20 ml) and the mixture was stirred at 70 °C for 30 min. The *o*-phthaloyldichloride (3.05 g, 15.0 mmol) was then dropwise added using a pump over 30 min. After the stirring for 30 min, an additional amount of *o*-phthaloyldichloride (0.55 g) was added and the stirring was continued for 10 h at 90 °C. After cooling to 50 °C, a 2 M HCl aqueous solution (100 ml) was added over 30 min. The solution was evaporated by an evaporator. The residue was treated with water (20 ml), filtered through G4 glass and dried in vacuo. The yellow precipitate was dissolved in MeOH, the desired layer was separated by chromatography and a yellow product (3.29 g) was obtained by evaporation in vacuo. ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 2.48 (6H, CH₃), 2.50 (6H, CH₃), 3.50 (2H, CH), 7.55–7.59 (2H, aromatics), 7.62–7.67 (2H, aromatics). ¹³C NMR (DMSO): δ: 38.67, 38.95, 39.23, 39.50, 39.78, 40.06, 40.33, 128.18, 130.57, 132.57, 168.43. Anal. Calcd. for C₁₈H₁₈N₄O₄: C, 61.04; H, 5.12; N, 15.81%. Found: C, 60.90; H, 5.33; N, 15.94%.

3a: Succinylbis(3-methyl-4-pyrazolin-5-one); ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 2.41 (6H, CH₃). ¹³C NMR (DMSO): δ: 28.74, 38.67, 38.67, 38.95, 39.22, 39.50, 39.78, 40.06, 40.33, 173.33. Anal. Calcd. for C₁₂H₁₄N₄O₄: C, 51.80; H, 5.07; N, 20.14%. Found: C, 51.89; H, 5.02; N, 20.21%.

3b: *o*-Phthaloylbis(3-methyl-4-pyrazolin-5-one); ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 2.48 (3H,

CH₃), 2.66(3H, CH₃), 5.88(2H, CH), 7.97–8.00 (2H, aromatic), 8.21–8.27(2H, aromatic). ¹³C NMR (DMSO): δ: 16.00, 38.67, 38.94, 39.22, 39.50, 39.77, 40.05, 40.33, 102.70, 127.71, 127.77, 129.24, 134.64, 152.56, 159.91. Anal. Calcd. for C₁₆H₁₄N₄O₄: C, 58.89; H, 4.32; N, 17.17%. Found: C, 58.95; H, 4.41; N, 17.09%.

3c: Succinylbis(1,3-dimethyl-4-pyrazolin-5-one); ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 2.41 (6H, CH₃), 2.49(6H, CH₃). ¹³C NMR (DMSO): δ: 28.75, 38.67, 38.95, 39.23, 39.50, 39.78, 40.06, 40.34, 173.34. Anal. Calcd. for C₁₄H₁₈N₄O₄: C, 54.89; H, 5.92; N, 18.29%. Found: C, 54.82; H, 6.11; N, 18.21%.

3k: Succinylbis(1-phenyl-2,3-dimethyl-4-pyrazolin-5-one); ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 2.42(6H, CH₃), 2.49(6H, CH₃), 7.33–7.36 (5H, aromatic), 7.47–7.50(5H, aromatic).

¹³C NMR (DMSO): δ: 28.75, 38.67, 38.95, 39.23, 39.50, 39.78, 40.06, 40.33, 178.34. Anal. Calcd. for C₂₆H₂₈N₄O₄: C, 67.81; H, 6.13; N, 12.17%. Found: C, 67.73; H, 6.04; N, 12.22%.

3l: *o*-Phthaloylbis(1-phenyl-2,3-dimethyl-4-pyrazolin-5-one); ¹H NMR (300 MHz, DMSO-*d*₆), δ (ppm): 2.48 (6H, CH₃), 2.49 (6H, CH₃), 7.32–7.35 (5H, aromatic), 7.46–7.48 (5H, aromatic), 7.55–7.59 (2H, aromatic), 7.62–7.67 (5H, aromatic). ¹³C NMR (DMSO): δ: 38.67, 38.94, 39.22, 39.50, 39.78, 40.05, 40.33, 128.21, 130.59, 132.75, 168.47. Anal. Calcd. for C₂₈H₂₈N₄O₄: C, 69.40; H, 5.82; N, 11.56%. Found: C, 69.49; H, 5.69; N, 11.63%.

3g: This ligand was synthesized by the previously reported method [9].

2.2. Complexes

Syntheses of a typical complex, [Ce(OAc)(**3d**)]: ligand **3d** (0.355 g, 1.00 mmol) was placed in a three-necked flask (100 ml) with sodium acetate buffer (20 ml) and the mixture was stirred for 30 min. Cerium triacetate hydrate (0.335 g, 1.0 mmol) was added to the red solution and the stirring was continued for 2 h at 70 °C. The resulting product was filtered through G4 glass and dried in vacuo. Anal. Calcd. for C₂₀H₁₉N₄O₆Ce: C, 43.56; H, 3.47; N, 10.16; Ce, 25.4%. Found: C, 43.33; H, 3.62; N, 10.01; Ce, 25.53%.

[Ce(OAc)(**3a**): Anal. Calcd. for C₁₄H₁₅N₄O₆Ce: C, 35.37; H, 3.18; N, 11.79; Ce, 29.47%. Found: C, 29.52; H, 3.09; N, 11.69; Ce, 29.55%.

[Ce(OAc)(**3b**): Anal. Calcd. for C₁₅H₁₇N₄O₆Ce: C, 36.81; H, 3.50; N, 11.45; Ce, 28.63%. Found: C, 36.73; H, 3.59; N, 11.48; Ce, 28.52%.

[Ce(OAc)(**3c**): Anal. Calcd. for C₁₆H₁₉N₄O₆Ce: C, 38.17; H, 3.80; N, 11.13; Ce, 27.83%. Found: C, 38.25; H, 3.69; N, 11.22; Ce, 27.76%.

[Ce(OAc)(**3k**): Anal. Calcd. for C₂₈H₂₉N₄O₆Ce: C, 51.13; H, 4.44; N, 8.52; Ce, 21.31%. Found: C, 51.21; H, 4.38; N, 8.56; Ce, 21.36%. [Ce(OAc)(**3l**): Anal. Calcd. for C₃₀H₂₉N₄O₆Ce: C, 52.86; H, 4.29; N, 8.22; Ce, 20.55%. Found: C, 52.91; H, 4.22; N, 8.31; Ce, 20.51%.

2.3. General procedure

The oxidation was carried out in a 50 ml autoclave equipped with a magnetic stirrer in a glass tube at a dioxygen pressure of 3 kg/cm² and 130 °C using anhydrous methanol or a methanolic aqueous solution (2 ml) of the substrate (0.06 mmol) and catalysts (0.005 mmol). After a fixed time (3 h), the mixture was evaporated using an evaporator to remove the solvents. The residue was diluted with dimethylsulfoxide and acetonitrile in a 20 ml volumetric flask containing an internal standard. The percentage yield of the products was measured by comparison with a blank, taking ethoxybenzoic acid as the internal standard, by HPLC in a mixed solution of acetonitrile (300 ml)/water (750)/phosphoric acid (0.6) using a reversed column (YMC-AM-312-ODS).

2.4. Computational method

The structures of [Ce(OAc)(**3f**)] was obtained with Chem3D as the graphics software from the Cambridge Soft Corporation. The value of the minimum restrict movement of selected atom (RMS) error and gradient is set to 0.10. Thermal ellipsoids are drawn at the 30% probability level.

3. Results and discussion

When used for the oxidation of cresols by molecular oxygen, cerium complexes with ligands such as

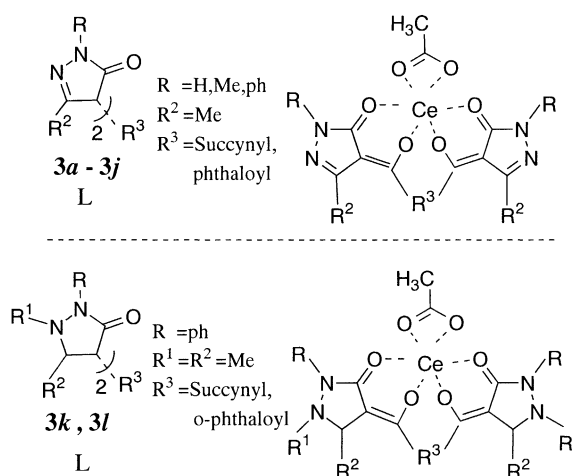


Fig. 1. Proposed molecular structure of ligand (L) and complex [Ce(OAc)(L)].

acac, bzac, dbm, dpm, acacen, salen and saltn give the compound **2** in the range of about 5–25% yield in anhydrous methanol. The ligands have a weak effect on the efficiency of the oxidation. The low yield may be correlated to the instability of the catalyst in an alcoholic aqueous solution.

A family of acylbis(pyrazolinone) ligands (L) was designed and synthesized to stabilize the complexes as a catalyst, in which two pyrazolinone subunits **3a–l** are linked with succinyl or phthaloyl as shown in Fig. 1. The cerium complexes [8] were synthesized by the reaction between cerium triacetate and a ligand (L) in acetate buffer solution as listed in Table 1. Cerium complex [Ce(OAc)(**3d**)] with acetate *o*-phthaloylbis(1,3-dimethyl-2-pyrazolin-5-one) gave the highest yield (88%) of compound **2a** for the oxidation in anhydrous methanol. The yield of compounds **2b–f** having a different substituent G was also kept at high levels of 87–82% yield for the oxidation of compound **1** obtained by replacing the methoxy group with an alkoxy **1a–c** (entry 4–6), phenoxy **1d** (entry 7) and alkyl **1e–g** (entry 8–10).

The catalytic activity of the geometrical isomers of R³ in the ligand (L) followed the order of *o*- > *p*- > *m*-phthaloyl for ligands with dimethyl (*R* = R²; **3d–f**; entries 4, 11, 12) and phenylmethyl (*R*, R²; **3h–j**) substituents (entries 14, 17, 18). The structure of the cerium complex with *p*-phthaloyl was presumed to be a dimer from a computerized graphical method with

Table 1

The oxidation of cresols by molecular oxygen using Ce(OAc)(L) complexes

Entry		Ligand (L) ^a				1	2
		R	R ¹	R ²	R ³		
1	3a	H	–	Me	C ₂ H ₄ (CO) ₂	a	58
2	3b	H	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	a	69
3	3c	Me	–	Me	C ₂ H ₄ (CO) ₂	a	79
4	3d	Me	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	a	88
5	3d	Me	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	b	85
6	3d	Me	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	c	84
7	3d	Me	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	d	84
8	3d	Me	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	e	87
9	3d	Me	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	f	85
10	3d	Me	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	g	82
11	3e	Me	–	Me	<i>m</i> -C ₆ H ₄ (CO) ₂	a	79
12	3f	Me	–	Me	<i>p</i> -C ₆ H ₄ (CO) ₂	a	84
13	3g^c	Ph	–	Me	C ₂ H ₄ (CO) ₂	a	72
14	3h	Ph	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	a	84 ^d
15	3h	Ph	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	b	81
16	3h	Ph	–	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	c	79
17	3i	Ph	–	Me	<i>m</i> -C ₆ H ₄ (CO) ₂	a	58
18	3j	Ph	–	Me	<i>p</i> -C ₆ H ₄ (CO) ₂	a	75
19	3k	Ph	Me	Me	C ₂ H ₄ (CO) ₂	a	40
20	3l	Ph	Me	Me	<i>o</i> -C ₆ H ₄ (CO) ₂	a	47

^a Characterized by NMR, IR, MS and elemental analysis.

^b The yield using an internal standard. Condition: substrate; 0.06 mmol, catalyst; 0.005 mmol, solvent; 2 ml, temperature; 130 °C, time; 3 h, O₂; 3 kg/cm².

^c Synthesized by the previously reported method [9].

^d Analogous to data given previously [8b].

three dimensions by setting the minimum RMS error and gradient as described in Section 2. The cerium complexes with a ligand having three substituents **3k** and **1** had a mild effect on the oxidation (entries 19, 20). The complex Na[Ce(OH)₂(**3d**)], obtained from complex [Ce(OAc)(**3d**)] by treatment with sodium hydroxide, had a mild effect providing a 65% yield of compound **2**.

In the oxidation by molecular oxygen using cerium triacetate, even in the presence of 2% water in the solvent, the yield of compound **2** drastically decreased to 4% from 82% in anhydrous methanol as shown in Fig. 2 [10].

On the other hand, a high yield of compound **2** was obtained using the complex [Ce(OAc)(**3d**)] as a catalyst in the broad range of 25–50% methanolic aqueous solution by overcoming the inactivation due to the chelation of cerium triacetate. The cerium complex [Ce(OAc)(**3h**)] (entry 14, [8]) had an activity followed

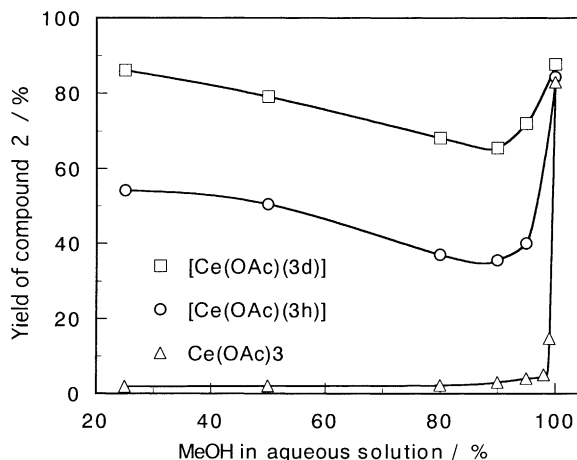


Fig. 2. Activity of cerium complexes in aqueous methanol solution. substrate: 0.06 mmols, catalyst: 0.005 mmol, solvent: 2 ml, 130 °C, 3 h. The complete data for [Ce(OAc)(**3h**)] are analogous to those given previously [8b].

by the complex [Ce(OAc)(**3d**)] (entry 4), which provided the highest yield even in methanolic aqueous solution.

The type of alcohol in the 25% aqueous solvent affected the yield of compound **2** in the reaction catalyzed by the complex [Ce(OAc)(**3d**)], in the order of 1-propanol (93%) > ethanol (89%) > methanol (86%) with increasing number of carbons, while 1-butanol and -pentanol and their geometric isomers gave a yield similar to methanol.

For the methanol and propanol solvents, the increasing concentration of the substrate significantly increased the yield of compound **2** in both the 25 and 90% aqueous solutions as shown in Fig. 3. The catalytic activity in 25% propanolic aqueous solution under conditions where the water content was kept at high levels in spite of the increase of concentration of substrate. 1-Propanol was well suited for methanol to elevate the yield of compound **2**. From the viewpoint of environment safety and economical cost, it is preferable to use the complex [Ce(OAc)(**3d**)] in 25% 1-propanolic aqueous solution. The yield in 1-propanol was higher than in the corresponding alcohols for all the substrate concentrations in aqueous solution.

One of the byproducts of the oxidation by molecular oxygen was found to be as carboxylic acid derived from alcohol used as a solvent, especially from

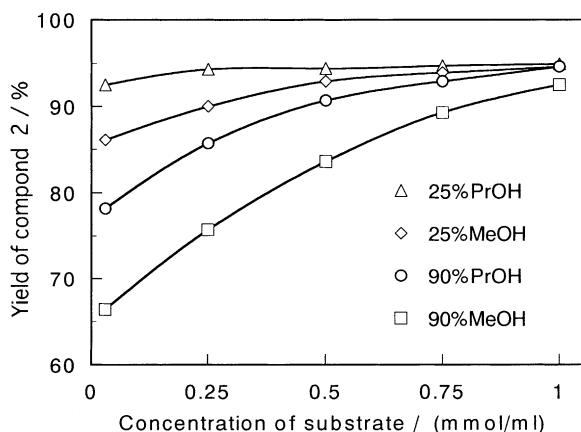


Fig. 3. The influence of the concentration in alcoholic aqueous solution. Catalyst/substrate = 0.083, solvent: 2 ml, 130 °C, 3 h.

methanol. Therefore, it was suggested that there was a competitive oxidation between the methyl group on cresol and the alcohol in oxidation by molecular oxygen [11]. Propanol is suitable for preventing an excessive oxidation of cresol by causing the intermolecular hydrogen bonding with the solvent [12].

4. Conclusion

The present study describes the cerium complexes with the acetato acylbis(pyrazolinone) ligand as catalyst for the oxidation of cresols by molecular oxygen that produced a high yield of disubstituted-hydroxybenzaldehydes even in 25% methanolic aqueous solution and in propanol. Several of complexes have been found to be even more effective catalysts for the oxidation of cresols by increasing the concentration of the substrate.

Acknowledgements

This work was partially supported by a Grant from the Excell Human Fukae Foundation and the Mitsubishi Chemical Corporation Fund.

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