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Reaction of α,β-unsaturated ketones using cerium (IV) sulfate tetrahydrate in acetic acid

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The reaction of α,β-unsaturated ketones with cerium (IV) sulfate tetrahydrate [$Ce(SO_4)_2 \cdot 4H_2O$, CS] in acetic acid gave the corresponding β-acetoxy ketones. In the case of 2-cyclohexen-1-one with CS in acetic acid, benzobicyclo[2.2.2]octen-2-one was obtained. The reaction mechanism also was proposed. Moreover, we report the aromatization and esterification of (*R*)-(−)-carvone by CS in acetic acid.

KEYWORDS: α,β-unsaturated ketones; cerium(IV) sulfate tetrahydrate; acetic acid; β-acetoxy ketones; benzobicyclo[2.2.2]octen-2-one

INTRODUCTION

β-Acetoxy ketones are generally used as intermediates for the synthesis of natural products. For example, 1-acetoxy-3-butanone was transformed into the vinylidene analogue of mevalonolactone by the addition of allyl Grignard and iodoetherification of the resultant diol- and DBN (1,5-diazabicyclo [4.3.0] non-5-ene)-mediated dehydrogenation.[1] It is known that β-acetoxy ketones can be prepared by acetylation of β-hydroxy ketones by cobalt(II) chloride–acetic anhydride or 4-dimethylaminopyridine (DMAP)-triethylamine–acetic anhydride,[2,3] oxidation of allyl acetates by palladium(II) chloride–copper(I) chloride–O_2 or palladium(II) chloride–*p*-benzoquinone,[4] and addition of α,β-unsaturated ketones in acetic acid by $PdCl_2(MeCN)_2$.[5]

We have investigated the development of some new reaction systems using cerium(IV) salts. Cerium(IV) salt has been utilized extensively for a variety of oxidative transformations. In the previous papers, we reported a synthesis of *trans*-iodohydrins from cycloalkenes using iodine-ammonium cerium(IV) nitrate (CAN) or CS,[6] the oxidative cleavage of 2-alkyl substituted cycloalkanones using CS in alcohols and acetic acid,[7] a synthesis of carboxylic esters from alkenes using CS in carboxylic acids,[8] a new one-pot synthesis of 3-acylisoxazoles using CAN,[9,10] a synthesis of 2-oxo- and 2-oxo-5-hydroxy derivatives using CS in carbonyl compounds-H_2O[11] and reaction of α,β-unsaturated ketones with cerium(IV) salts in alcohols.[12]

In this paper we report that the reaction of α,β-unsaturated ketones with CS in acetic acid gave the corresponding β-acetoxy ketones. In addition, the reaction of 2-cyclohexen-1-one with CS in acetic acid gave benzobicyclo[2.2.2]octen-2-one. The reaction mechanism is also proposed. Moreover, we report the aromatization and esterification of (*R*)-(−)-carvone as a monoterpene by CS in acetic acid.

RESULTS AND DISCUSSION

The reaction of α,β-unsaturated ketones with CS in acetic acid gave the corresponding β-acetoxy ketones (Scheme 1).

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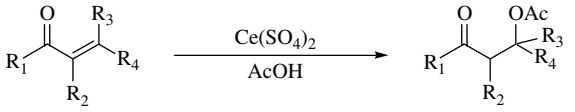
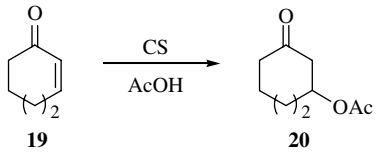
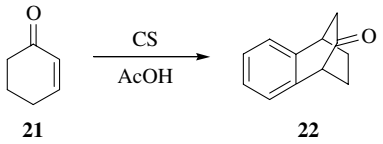


Scheme 1. Reaction of α, β-unsaturated ketones with CS in acetic acid.



Scheme 2. Reaction of 2-cyclohepten-1-one with CS in acetic acid.



Scheme 3. Reaction of 2-cyclohexen-1-one with CS in acetic acid.

These results are summarized in Table 1. In the case of ethyl vinyl ketone (**3**), under reaction conditions using 0.20 mmol CS at 50 °C for 12 h, 1-acetoxy-3-pentanone (**4**) was obtained in 84% GLC (Gas - Liquid Chromatography) yield (Table 1, run 8). However, the yields of the product were decreased under reaction conditions using 1.00 mmol CS (Table 1, run 12). It seems that the yield of the product was decreased by the oxidation of excess CS. From these results, this reaction must be carried out under reaction condition using 0.20 mmol CS. On the basis of these results, β-acetoxy ketones **10, 12** and **14** from 3-methyl-3-buten-2-one (**9**), 3-hepten-2-one (**11**) and 5-methyl-3-hexen-2-one (**13**) were obtained (Table 1, runs 13 and 15–18). Also, in the case of 3-methyl-3-penten-2-one (**15**) and 4-methyl-3-penten-2-one (**17**), the corresponding β-acetoxy ketones **16** and **18** were obtained (Table 1, runs 20 and 21). It seems that the formation of the product was affected by the bulk of the methyl group for the substrate.

We further examined the reaction of cyclic α,β-unsaturated ketones using CS in acetic acid (Schemes 2 and 3). The results are shown in Table 2. The reaction of 2-cyclohepten-1-one (**19**; 1.00 mmol) using CS (0.20 mmol) in acetic acid (5 ml) at 50 °C for 24 h gave 3-acetoxy-1-cycloheptanone (**20**) in 46% GLC yield (Table 2, run 1). On the other hand, in the case of 2-cyclohexen-1-one (**21**), however, the corresponding β-acetoxy

Table 1. Reaction of α, β-unsaturated ketones with CS in acetic acid

Run[a]	Substrate	R_1	R_2	R_3	R_4	CS (mol. equiv.)	Time (h)	Product (%)[c]
1	**1**	CH_3	H	H	H	0.2	12	**2** (36)
2[a,b]	**3**	C_2H_5	H	H	H	—	12	**4** (17, 29[d])
3[b]	**3**	C_2H_5	H	H	H	0.01	12	**4** (73[d])
4[b]	**3**	C_2H_5	H	H	H	0.05	12	**4** (77[d])
5[b]	**3**	C_2H_5	H	H	H	0.1	12	**4** (77[d])
6[b]	**3**	C_2H_5	H	H	H	0.2	3	**4** (79[d])
7[b]	**3**	C_2H_5	H	H	H	0.2	6	**4** (82[d])
8[a,b]	**3**	C_2H_5	H	H	H	0.2	12	**4** (77, 84[d])
9[b]	**3**	C_2H_5	H	H	H	0.2	15	**4** (84[d])
10[b]	**3**	C_2H_5	H	H	H	0.25	12	**4** (82[d])
11[b]	**3**	C_2H_5	H	H	H	0.5	12	**4** (75[d])
12[b]	**3**	C_2H_5	H	H	H	1.0	12	**4** (63[d])
13	**5**	C_2H_5	H	H	CH_3	0.2	12	**6** (54)
14	**7**	Ph	H	H	CH_3	0.2	12	**8** (22)
15	**9**	CH_3	CH_3	H	H	0.2	12	**10** (12)
16	**11**	CH_3	H	H	*n*-C_3H_7	0.2	12	**12** (19)
17	**13**	CH_3	H	H	*iso*-C_3H_7	0.05	12	**14** (11)
18	**13**	CH_3	H	H	*iso*-C_3H_7	0.1	12	**14** (15)
19	**13**	CH_3	H	H	*iso*-C_3H_7	0.2	12	**14** (trace)
20	**15**	CH_3	CH_3	H	CH_3	0.2	12	**16** (trace)
21	**17**	CH_3	H	CH_3	CH_3	0.2	12	**18** (trace)

[a] Substrate (2.55 mmol), CS (0.13–0.51 mmol) and acetic acid (10 ml) were employed at 50 °C. [b] Substrate (1.00 mmol), CS (0–1.00 mmol) and acetic acid (5 ml) were employed at 50 °C. [c] Determined by isolated yield. [d] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard.

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Table 2. Reaction of cyclic α, β-unsaturated ketones with CS in acetic acid

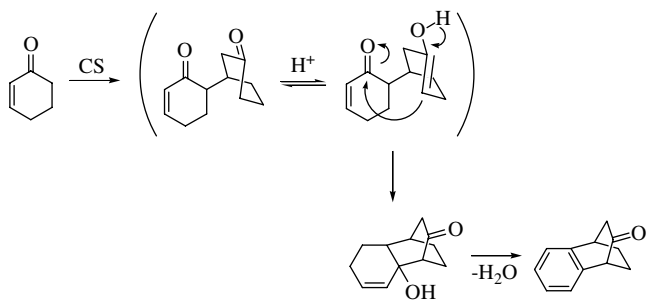
Run[a]	Substrate	CS (mol. equiv.)	Temp. (°C)	Product (%)
1	**19**	0.2	50	**20** (46)
2	**19**	0.2	80	**20** (33)
3	**19**	0.5	50	**20** (36)
4	**19**	1.0	50	**20** (23)
5	**21**	0.2	50	No reaction
6	**21**	0.2	110	**22** (15)
7	**21**	0.5	110	**22** (18)
8	**21**	1.0	110	**22** (16)
9	**21**	2.0	110	**22** (10)

[a] Substrate (1.00 mmol), CS (0.20–2.00 mmol) and acetic acid (5 ml) were employed for 24 h. [b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard.

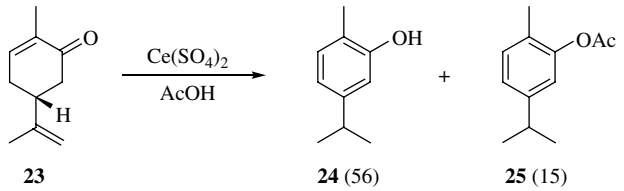
ketone was not afforded and benzobicyclo[2.2.2]octen-2-one (**22**) was obtained. The reaction of 2-cyclohexen-1-one (**21**; 1.00 mmol) with CS (0.50 mmol) at 110 °C for 24 h gave benzobicyclo[2.2.2]octen-2-one[13] (**22**) in 18% GLC yield (Table 2, run 7). From these results, it seems that this reaction is a new synthetic method for obtaining benzobicyclo[2.2.2]octen-2-one.

We propose the reaction mechanism shown in Scheme 4. First, the addition of 2-cyclohexen-1-one occurs to another 2-cyclohexen-1-one by CS. Then the keto form of the adduct was transformed into the cyclic intermediate by intermolucular cyclization. Finally, benzobicyclo[2.2.2]-octen-2-one was obtained by aromatization with dehydration of the cyclic intermediate.

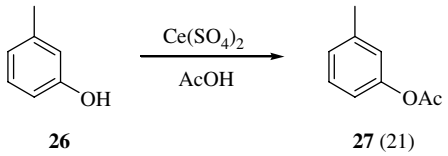
Moreover, we attempted to react (*R*)-(−)-carvone (**23**) as monoterpene using CS (Scheme 5). The reaction of (*R*)-(−)-carvone (**23**; 2.55 mmol) using CS (0.51 mmol) under reflux for 3 h gave 5-isopropyl-2-methylphenol (**24**) and 2-acetoxy-4-isopropyltoluene (**25**) in 56 and 15% yields, respectively. Also, the reaction of 3-methylphenol (**26**) using CS afforded 3-acetoxytoluene (**27**) in 21% yield (Scheme 6). From these results, it seems that in the reaction pathway the



Scheme 4. The mechanism for benzobicyclo [2.2.2.] octen-2-one from cyclohexenone.



Scheme 5. Reaction of (R)-carvone with CS in acetic acid. Reaction conditions: substrate (2.55 mmol), CS (0.51 mmol) and acetic acid (10 ml) were employed under reflux for 3 h. Determined by isolated yield.



Scheme 6. Reaction of 3-methylphenol with CS in acetic acid. Reaction conditions: substrate (2.55 mmol), CS (0.51 mmol) and acetic acid (10 ml) were employed under reflux for 10 h. Determined by isolated yield.

aromatization of (*R*)-(−)-carvone by CS afforded 5-isopropyl-2-methylphenol, followed by the esterification of 5-isopropyl-2-methylphenol to give 2-acetoxy-4-isopropyltoluene.

In conclusion, however, these reactions are non-stereoselective synthetic methods; they demonstrate the use of cerium (IV) sulfate tetrahydrate, and provide a new and simple synthetic method for benzobicyclo[2.2.2]octen-2-one.

EXPERIMENTAL

General

IR spectra were recorded on a Jasco FT-IR 230 spectrometer. Both ^{1}H and ^{13}C-NMR spectra were measured on a Jeol GSX-400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) spectrometer. Chemical shifts were reported on the δ scale (ppm) with solvent ($CHCl_3 = 7.26$) as an internal standard. The signal of the solvent ($CDCl_3 = 77.00$) was used as a standard for ^{13}C NMR spectra. The gas chromatographic analyses were perfomed using a Shimadzu GC-17A equipped with a GC-column (DB-1, 25 m). GC-MS (EI) analyses were performed on a Shimadze GCMS-QP5000 equipped with GC-column (DB-1, 60 m) and an ionizing energy of 70 eV. Analytical TLC was carried out on precoated TLC plates (Silica gel 60 F254, layer thickness 0.2 mm). Silica gel 60 (0.063–0.200 mm) was used for column chromatography. All chemicals were purchased from Tokyo Kasei Kogyo Corporation and Aldrich Chemical Company.

Typical procedures 1

A mixture of methyl vinyl ketone (**1**; 0.1787 g, 2.55 mmol) and CS (0.2062 g, 0.51 mmol) in acetic acid (10 ml) was stirred at 50 °C for 12 h. A white precipitate was filtered

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off and the solvent was removed under reduced pressure. The residue was poured into H_2O (20 ml) and extracted with ethyl acetate (50 ml). The solution was washed with saturated aqueous NaCl (2 × 10 ml), aqueous sodium hydrogencarbonate solution (2 × 5 ml), and water (2 × 5 ml). The extract was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ethyl acetate gave 1-acetoxy-3-butanone (**2**; 0.1200 g, 36%). The products were known and identified by ^{1}H-NMR, ^{13}C-NMR and GC-MS spectra by reference to the literature. Since the reference of 2-acetoxy-4-hexanone (**6**) was not found, the spectral data of **6** are shown below.

*1-Acetoxy-3-butanone (**2**)*

IR (NaCl) 1740 and 1718 cm^{-1}, ^{1}H-NMR ($CDCl_3$) $\delta = 4.32$ (t, $J = 5.5$ Hz, 2H), 2.78 (t, $J = 6.2$ Hz, 2H), 2.20(s, 3H) and 2.03 (s, 3H); ^{13}CNMR ($CDCl_3$) $\delta = 205.7$, 170.9, 59.3, 42.2, 30.2 and 20.8.

*2-Acetoxy-4-hexanone (**6**)*

IR (NaCl) 1736 and 1245 cm^{-1}, ^{1}H-NMR ($CDCl_3$) $\delta = 5.29$ (m, 1H), 2.79 (m, 2H), 2.56 (m, 2H), 2.445 (q, $J = 12.0$, 8.0 Hz, 2H), 2.01 (s, 3H), 1.27 (d, $J = 8.0$ Hz, 3H) and 1.05 (t, $J = 8.0$ Hz, 3H); ^{13}C-NMR ($CDCl_3$) $\delta = 208.2$, 170.3, 67.2, 48.2, 36.5, 21.2, 20.1 and 7.6; EIMS m/z 158 $[M]^+$ (0.05), 143 $[M - 143]^+$ (0.1), 129 $[M - CH_3CH_2]^+$ (1.60), 115 $[M - CH_3CO]^+$ (1.41), 99 $[M - CH_3COO]^+$ (0.38), 98 $[M - CH_3COOH]^+$ (2.07), 69 $[M - CH_3COOH\text{-}CH_3CH_2]^+$ (55.14), and 57 $[CH_3CH_2CO]^+$ (57.26), 43 $[CH_3CO]^+$ (100); HRMS found: m/z 158.0933 $[M]^+$. Calcd for $C_8H_{13}O_3$: M, 158.0943.

Typical procedures 2

A mixture of 2-cyclohexen-1-one (**21**; 0.9613 g, 10.0 mmol) and CS (2.0215 g, 5.00 mmol) in acetic acid (30 ml) was stirred at 110 °C for 24 h. A white precipitate was filtered off and the solvent was removed under reduced pressure. The residue was poured into H_2O (20 ml) and extracted with ethyl acetate (100 ml). The solution was washed with saturated aqueous NaCl (2 × 15 ml), aq sodium hydrogencarbonate solution (2 × 5 ml), and water (2 × 5 ml). The extract was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ethyl acetate gave benzobicyclo[2.2.2]octen-2-one (**22**). The product was known and identified by ^{1}H-NMR by reference to literature.

Benzobicyclo[2.2.2]octen-2-one[13] *(**22**)*

IR (NaCl) 1736 cm^{-1}, ^{1}H-NMR ($CDCl_3$) $\delta = 7.17$–7.27 (m, 4H), 3.61 (t, 1H), 3.42 (q, 1H) and 1.61–2.37 (m, 6H); ^{13}C-NMR ($CDCl_3$) $\delta = 212.0$, 142.9, 136.5, 127.3, 126.9, 125.5, 123.9, 52.6, 41.9, 36.5, 25.1 and 23.5; EIMS m/z 172 $[M]^+$ (16), 131 $[M - C_3H_5]^+$ (10), 130 $[M - C_2H_2O]^+$ (97), 129 $[M - C_3H_7]^+$ (91), 128 $[M - C_2H_4O]^+$ (100), 127 $[M - C_2H_5O]^+$ (18), 116 $[M - C_3H_4O]^+$ (13), 115 $[M - C_3H_5O]^+$ (52), 102 $[M - C_4H_7O]^+$ (7), 89 $[M - C_5H_7O]^+$ (8), 77 $[M - C_6H_7O]^+$ (8), and 42 $[M - C_{10}H_{10}]^+$ (33).

Typical procedures 3

A mixture of (*R*)-(−)-carvone (**23**; 0.3831 g, 2.55 mmol) and CS (0.2062 g, 0.51 mmol) in acetic acid (10 ml) was stirred under reflux for 3 h. A white precipitate was filtered off and the solvent was removed under reduced pressure. The residue was poured into H_2O (20 ml) and extracted with ethyl acetate (50 ml). The solution was washed with saturated aqueous NaCl (2 × 10 ml), aqueous sodium hydrogencarbonate solution (2 × 5 ml), and water (2 × 5 ml). The extract was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ethyl acetate gave 5-isopropyl-2-methylphenol (**24**; 0.2142 g, 56%) and 2-acetoxy-4-isopropyltoluene (**25**; 0.0734 g, 15%). The product was known and identified by ^{1}H-NMR, ^{13}C-NMR or GC-MS by reference to literature.

*5-Isopropyl-2-methylphenol (**24**)*[14]

IR (NaCl) 3100–3700 cm^{-1}, ^{1}H-NMR ($CDCl_3$) $\delta = 7.01$ (d, 1H), 6.70 (d, 1H), 6.61 (s, 1H), 5.55 (s, 1H), 2.77 (m, 1H), 2.19 (s, 3H) and 1.17 (d, 6H); ^{13}C-NMR ($CDCl_3$) $\delta = 153.5$, 148.4, 130.9, 121.2, 118.8, 113.1, 33.7, 24.0, 23.8 and 15.4

*2-Acetoxy-4-isopropyltoluene (**25**)*[15]

IR (NaCl) 1764 cm^{-1}, ^{1}H-NMR ($CDCl_3$) $\delta = 7.13$ (d, 1H), 7.00 (d, 1H), 6.85 (s, 1H), 2.86 (m, 1H), 2.29 (s, 3H), 2.13 (s, 3H) and 1.22 (d, 6H); ^{13}C-NMR ($CDCl_3$) $\delta = 169.3$, 149.3, 148.1, 130.9, 127.2, 124.2, 119.8, 33.6, 23.9, 21.3, 20.8 and 15.7.

Acknowledgements

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