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Selective Oxidation of Alkyl Benzenes Using CrO_3 Combined with $Ce(SO_4)_2$

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A novel system of oxidant-CrO_3 combined with $Ce(SO_4)_2$, has been demonstrated to be an effective and economic oxidant for the oxidation of alkyl benzenes to ketones or aldehydes with little by-products and high yields. Including 1-(2,4-diethylphenyl)ethanone (**3**), seven alkyl benzenes have been studied, the products have been characterized by the elemental analyses, ^1H, ^{13}C NMR and EI-MS. The possible mechanisms of this oxidation reaction were also proposed. The obtained 5-acetyl-3-methylisobenzofuran-1(3*H*)-one (**5**), the by-product of **3** was also confirmed by the crystal structure.

Key Words: Oxidation, $Ce(SO_4)_2$, CrO_3, 2D NMR, Crystal structure, 5-Acetyl-3-methyliso-benzofuran-1(3*H*)-one.

INTRODUCTION

The oxidation of alkyl benzenes is a fundamental synthetic transformation, which converts alkyl benzenes to alcohols, aldehydes, ketones or carboxylic acids depending on the oxidants and conditions. Among these conversions, the transformation of methylene to ketones or aldehydes is particularly important, deserving continued research and development. During the past years, a wide variety of oxidants have been developed and tested. Potassium permanganate[1] was often used to oxidize methylene in neutral condition with low yields and many by-products. Zhu[2] reported a modified method with little by-products while the yields were relatively poor (24-27 %). Noureldin[3] described a procedure by using permanganate adsorbed on either copper sulphate pentahydrate or moist alumina to oxidize methylene with good yield (85-98 %), but the reaction time was quite long (67-328 h) and the adsorbed permanganate was not easily obtained. Molecular oxygen[4], as an oxidant, represents a critical technology and usually needs an efficient catalyst. Recently metal oxide, particularly Ce(IV) compounds, have become more and more dominant in the oxidation of aliphatic side chain. Kenneth[5] used $Ce(OTf)_4$ as reagent to oxidize methylene to ketone but the mode of preparation of the $Ce(OTf)_4$ and the content of water in the sample have a distinct influence on the oxidation ability. Tandon[6] reported an improved method using $Ce(SO_4)_2$ to oxidize ethylbenzene under the catalysis of $IrCl_3$ with only 44 % yield, moreover the mainly Ce(IV) reagents are very expensive than other oxidants. Other oxidants such as H_2O_2[7], $K_2Cr_2O_7$[8], Fe(III)[9], $Na_2Cr_2O_7$[10]

and CrO_3[11] are also studied. In them, CrO_3 is an important reagent, which can oxidize methylene to ketone or aldehyde, but the lower yield[12] and more by-products limited the application of this oxidation. Herein, we reported a novel and economic system-CrO_3 combined with $Ce(SO_4)_2$, which can obviously reduce the dosage of Ce(IV) in the oxidization of methylene to ketones or aldehydes with high yields and little by-products. The detailed NMR spectral characterization of the 2-ethyl-1,4-diacetylbenzene (**4**), as well as the crystal structure of 5-acetyl-3-methylisobenzofuran-1(3*H*)-one (**5**) are presented first time.

EXPERIMENTAL

All the chemicals were purchased from commercial sources and used without further treatment. Reactions were monitored by gas chromatography.

General procedure: A four-necked 500 mL round-bottom flask equipped with a thermometer, a mechanical stirrer and a condenser, was arranged for external cooling with ice-water, 0.15 mol methylene compound, 160 mL CH_3COOH and 1 g $Ce(SO_4)_2$ were placed in the flask. The mixture was stirred vigorously and the solution temperature was controlled at 5-10 ºC. 35 g CrO_3 was added over a period of 2 h, keeping the reaction temperature below 50 ºC. Stirring was then continued at 50 ºC for an additional 3 h. During this period the reaction mixture became quite thick and GC monitored the progress of the reaction. The mixture was put into a 2000 mL beaker and diluted with 1000 mL water. The solution was extracted with chloroform. The organic layer was washed with ice water, dried with anhydrous sodium sulphate and then concentrated under reduced pressure to give a crude product.

Detection method: ^1H and ^{13}C NMR spectra were recorded at 500 MHz or at 300 MHz, using $CDCl_3$ as solvent on a Bruker NMR spectrometer. Gas chromatographic analysis was made on a Perkin-Elmer auto system instrument using a 25 m capillary column of 25QC2/BPX5 and helium as carrier gas with a flux of 0.9 mL/min. Electron impact (EI) mass spectrometry was investigated on an AutoSpec Premier instrument with isobutene as carrier gas. The elemental analyses were performed with a Vario El III elemental analyzer.

Crystal growth and crystal structure determination: Crystallization of **5** from acetone yields large colourless plate. The crystal of compound **5** was obtained by dissolving 0.1 g of compound **5** in 5 mL acetone and this solution was allowed to evaporate at room temperature over 5 days. Single-crystal X-ray diffraction data was collected at 298 K with a Nonius CAD-4 diffractometer using MoK_α radiation (λ = 0.71073 Å). The software programs used for data collection and reduction were CAD-4 software[13] and XCAD-4 software[14], for structure solution and refinement SHELXS-97 and SHELXL-97[21]. The crystal structure data of compound **5** is provided in the supporting information and are deposited in the Cambridge Crystallographic Data Center.

Acetophenone (2a): Colourless liquid, yield (%) 61.1, b.p. 204-206 ºC/756 mmHg (Lit.[15] b.p. 204-205 ºC/760 mmHg). ^1H NMR ($CDCl_3$): δ 7.94 (d, 2H, *J* =

7.50 Hz, Ar-H), 7.53 (dd, 1H, *J* = 7.50 Hz, *J* = 7.65 Hz, Ar-H), 7.38 (d, 2H, *J* = 7.65 Hz, Ar-H), 2.59 (s, 3H, $-CH_3$).

1-(4-Chlorophenyl)ethanone (2b): White solid, yield (%) 43.9, m.p. 22-23 ºC (Lit.[16] m.p. 23 ºC). ^{1}H NMR ($CDCl_3$): δ 7.93 (d, 2H, *J* = 8.55 Hz, Ar-H), 7.47 (d, 2H, *J* = 8.55 Hz, Ar-H), 2.57 (s, 3H, $-CH_3$).

1-(4-Ethylphenyl)ethanone (2c): Colourless liquid, yield (%) 89.0, b.p. 109-113 ºC/10 mmHg (Lit.[17] b.p. 116-117 ºC/15 mmHg). ^{1}H NMR ($CDCl_3$): δ 7.88 (dd, 2H, *J* = 6.50 Hz, *J* = 1.80 Hz, Ar-H), 7.27 (d, 2H, *J* = 6.50 Hz, Ar-H), 2.64 (q, 2H, *J* = 7.60 Hz, $-CH_2$), 2.56 (s, 3H, $-CH_3$), 1.25 (t, 3H, *J* = 7.60 Hz, $-CH_3$).

1-(3-Ethylphenyl)ethanone (2d): Colourless liquid, yield (%) 64.0, b.p. 114-116 ºC/14 mmHg (Lit.[18] b.p. 113-116 ºC/14 mmHg). ^{1}H NMR ($CDCl_3$): δ 7.38 (m, 2H, Ar-H), 7.77 (m, 2H, Ar-H), 2.71(q, 2H, *J* = 7.02 Hz, $-CH_2$), 2.59 (s, 3H, $-CH_3$), 1.26 (t, 3H, *J* = 7.02 Hz, $-CH_3$).

1-(2,4-diethylphenyl)ethanone (3): Colourless liquid, yield (%) 85.2, b.p. 114-115 ºC/14-16 mmHg (Lit.[19] b.p. 118-120 ºC/20 mmHg). ^{1}H NMR ($CDCl_3$): δ 7.59 (d, 1H, *J* = 7.82 Hz, Ar-H), 7.08 (d, 1H, *J* = 7.82 Hz, Ar-H), 7.06 (s, 1H, Ar-H), 2.89 (q, 2H, *J* = 7.60 Hz, $-CH_2$), 2.65 (q, 2H, *J* = 7.60 Hz, $-CH_2$), 2.55 (s, 3H, $-CH_3$), 1.23 (m, 6H, $-CH_3$).

2-Ethyl-1,4-diacetylbenzene (4): Colourless liquid, yield (%) 68.2, ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, *J* = 1.72 Hz, Ar-H), 7.81 (dd, 1H, *J* = 1.72 Hz, *J* = 6.22 Hz, Ar-H), 7.64 (d, 1H, *J* = 6.22 Hz, Ar-H), 2.88 (q, 2H, *J* = 7.50 Hz, $-CH_2$), 2.62 (s, 3H, $-CH_3$), 2.60 (s, 3H, $-CH_3$), 1.24 (t, 3H, *J* = 7.50 Hz, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ 202.0, 197.4, 143.8, 141.9, 138.6, 129.8, 128.3, 125.4, 30.0, 26.7, 26.5, 15.6; Anal. calcd. (%) for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found. (%): C, 75.58; H, 7.39.

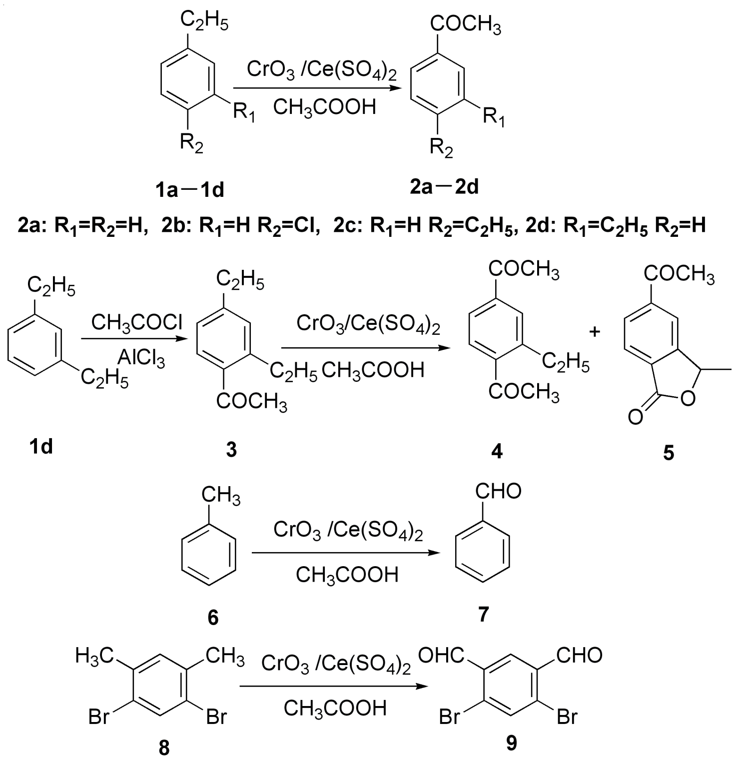
5-Acetyl-3-methylisobenzofuran-1(3*H*)-one (5): White powder, yield (%) 3.2, m.p. 120-123 ºC. ^{1}H NMR ($CDCl_3$): δ 8.08 (d, 1H, *J* = 7.50 Hz, Ar-H), 8.02 (s, 1H, Ar-H), 7.98 (d, 1H, *J* = 7.50 Hz, Ar-H), 5.63 (q, 1H, *J* = 6.70 Hz, -CH), 2.70 (s, 3H, $-CH_3$), 1.68 (d, 3H, *J* = 6.70 Hz, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ 196.9, 169.2, 151.3, 141.6, 129.3, 129.2, 126.0, 121.3, 77.9, 27.0, 20.3; MS (EI): m/z 190 (M^+), 175, 119, 147, 103, 58; Anal. calcd. (%) for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found. (%): C, 69.58; H, 5.28.

Benzaldehyde (7): Colourless liquid, yield (%) 70.1, b.p. 180-183 ºC/756 mmHg (Lit.[15] b.p. 180-182 ºC/760 mmHg). ^{1}H NMR ($CDCl_3$): δ 10.02 (s, 2H), 7.87 (d, 2H, *J* = 6.75 Hz, Ar-H), 7.64 (m, 1H, Ar-H), 7.56 (d, 2H, *J* = 6.75 Hz, Ar-H).

4,6-Dibromoisophthalaldehyde (9): White powder, yield (%) 80.2, m.p. 192-192 ºC (Lit.[20] m.p. 192-193 ºC). ^{1}H NMR ($CDCl_3$): δ 10.32 (s, 2H), 8.32 (s, 1H), 8.04 (s, 1H).

RESULTS AND DISCUSSION

Scheme-I illustrates the oxidation of methylene to ketones or aldehydes, the compound **3** was synthesized according to literature[19]. Two alkyl benzenes have been converted to aldehydes and 5 alkyl benzenes have been transformed to



Scheme-I: Oxidation of methylene to ketones or aldehydes

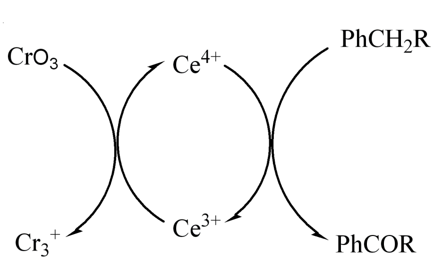
ketones, the yield of them was varied from 43.9-89.0 %. The results are listed in Table-1. This result shows that the new system can used to oxidize aliphatic side chains to aldehydes as well as ketones.

TABLE-1
OXIDATION OF METHYLENE BENZENES

No	R_1	R_2	Yield (%)
2a	H	H	61.1
2b	H	Cl	43.9
2c	H	C_2H_5	89.0
2d	C_2H_5	H	64.0
7			70.1
9			80.2

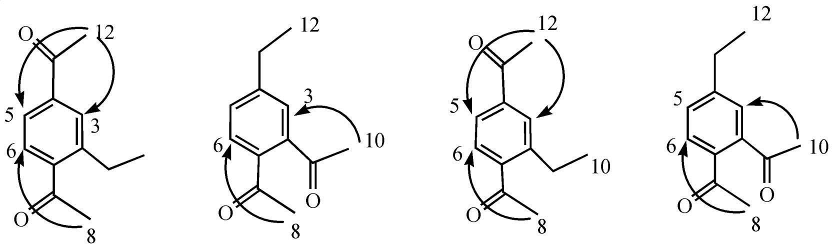
In order to determine to how the temperature influences on the oxidation of **1d**, we performed the reaction at different temperatures, all the reactions were controlled at certain temperature for addition 3 h, GC monitored the reaction progress. At room temperature (25 ºC), no 1-(3-ethylphenyl) ethanone (**2d**) was obtained, which means that the oxidation of **1d** was not occurred. When the temperature kept at 50 ºC, the yield of **2d** was 64 %. However when the reaction temperature was maintained at 80 °C, two by-products, isophthalic acid and 3-acetyl benzoic acid were formed and the yield of **2d** was only 50 %. Considering the yield and the cost of separation, we controlled all of the oxidation reaction temperature at 50 °C.

The reaction is studied at 50 °C using only CrO_3 as the oxidant so as to determine the influence of cerium salt, if there is no $Ce(SO_4)_2$ the yield of **2d** was reduced from 64-54 %. This suggests that cerium salt appeared to have a beneficial effect, which can partly confirmed by Allen[10], who reported a procedure using $Na_2Cr_2O_7$ to oxidize acenaphthene to acenaphthenequinone under the catalysis of ceric acetate. We tentatively put forward that the $Ce(SO_4)_2$ acted as a catalyst. The **Scheme-II** outlined the catalysis of the $Ce(SO_4)_2$, the H^+ and H_2O have been omitted.



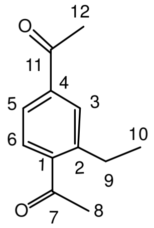
Scheme-II: Proposed mechanism for the oxidation of alkyl benzene

Compounds **3, 4** and **5** have been obtained by column chromatography. To our surprise, there was no 4-ethyl-1,2-diacetylbenzene, which showed that the *p*-ethyl of acetyl group was easier to be oxidized than the *o*-ethyl. In order to make sure the structure of 2-ethyl-1,4-diacetylbenzene (**4**), the compound was confirmed through detailed analysis by 1D and 2D NMR experiments such as ^1H-^{13}C HMBC, ^1H-^1H ROESY and ^{13}C-^1H HSQC. The low-temperature ROESY spectrum brought important information for confirmation of the signals as well as the flipping of the molecule. In the NMR spectrum, from the ^1H, ^{13}C NMR and ^{13}C-^1H HSQC we can easily make sure that there are two acetyls in the compound. We make the methyl of acetyls as an example to illustrate the difference between ^1H-^1H ROESY and ^1H-^{13}C HMBC of **4** and 4-ethyl-1,2-diacetylbenzene in **Scheme-III**. All the ^1H and ^{13}C chemical shifts and coupling constants for **4** are given in Table-2, along with the ^1H-^{13}C HMBC, ^1H-^1H ROESY and ^{13}C-^1H HSQC.



Scheme-III: ROESY and HMBC difference of compound 4 and 4-ethyl-1,2-diacetylbenzene

TABLE-2
NMR-SPECTRAL DATA OF COMPOUND **4**

Structure	C*	H**	ROESY	HSQC	HMBC
	1(141.9)				3, 5, 9, 8
	2(143.6)				10, 6, 9
	3(129.8)	3(7.85, d, J = 1.72)	9, 12	3-3	5, 9
	4(138.6)				6, 12
	5(125.4)	5(7.81, dd, J_1 = 1.72, J_2 = 6.22)	12	5-5	3
	6(128.3)	6(7.64, d, J = 6.22)	8	6-6	
	7(202.0)				6, 8
	8(30.0)	8(2.60)	6	8-8	
	9(26.7)	9(2.88, q, J = 7.50,)	3	9-9	3, 10
	10(15.6)	10(1.24, t, J = 7.50)		10-10	9
	11(197.4)				3, 5, 12
	12(26.5)	12(2.62, s)	3, 5	12-12	

*Carbons coupled to the corresponding H atom. **Chemical shifts in ppm (multiplicity, J in Hz).

For the first report of compound **5**, the crystal structure were determined and reported. Crystal of compound **5** was obtained by slowly evaporation of acetonic solution of compound **5**. Details of crystallographic data collection, crystal structure determination and refinement for **5** are given in Table-3. All the non-hydrogen atoms of the inclusion compound were refined with anisotropic displacement parameters. The unit cell parameters of a = 10.069(2) Å, b = 7.4850(15) Å, c = 13.218(3) Å, α = 90.00°, β = 111.04(3)° and γ = 90.00° compound for **5** are reported for the molecule. The space group was $P2_1/C$, respectively. Structure was refined to final residuals for

TABLE-3
CRYSTAL DATA OF COMPOUND **5** (CCDC-624074)

Empirical formula	$C_{11}H_{10}O_3$	Index ranges	$-12 \leq h \leq 11$, $0 \leq k \leq 9$, $0 \leq l \leq 16$
Formula weight	190.19	Z	4
Temperature	298(2) K	F(000)	400
Wavelength	0.71073 Å	θ range for data collection	2.17-26.01°
Color	Colorless	Reflections collected	1289
Crystal size/mm^3	0.40, 0.20, 0.10	Independent reflections	1242 [R(int) = 0.397]
Description	Plate	Data/restraints/parameters	1289/0/128
Crystal system	Monoclinic	Final R indices [I>2σ(I)]	R^a= 0.0528, wR^b = 0.1184
Space group	$P2_1/C$	Goodness of fit on F_2	1.105
Unit cell dimensions	a = 10.069(2) Å, α = 90.00° b = 7.4850(15) Å, β = 111.04(3)° c = 13.218(3) Å, γ = 90.00°	Largest diff. peak and hole	0.140 and -0.170 e Å^{-3}
Volume	929.8(3) Å^3		

$^a R = \Sigma|Fo|-|Fc|/\Sigma|Fo|$, $^b wR = [\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2]^{1/2}$.

R^a = 5.28 %. Molecular structure of compound **5** is presented in Fig. 1. The crystal structure of the compound **5** was determined by X-ray diffraction. The hydrogen bond patterns and the molecular packing of compound **5** are shown in Fig. 2. Details of hydrogen bond of compound **5** are presented in Table-4. Molecules of compound **5** are linked with each other by strong intermolecular C-H···O hydrogen bonds, forming a three dimensional framework, which may be effective in the stabilization of the crystal structure.

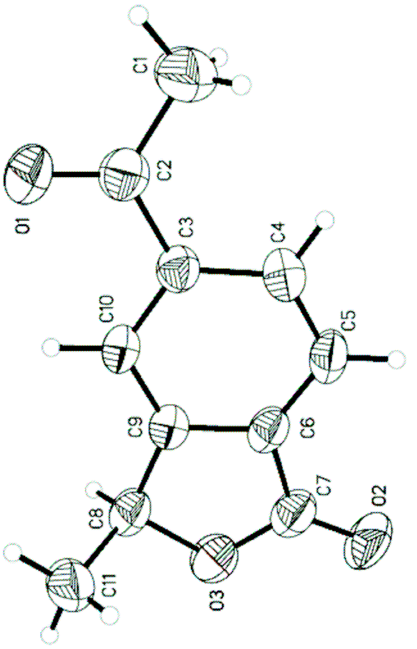


Fig. 1. Molecular structure of compound **5**

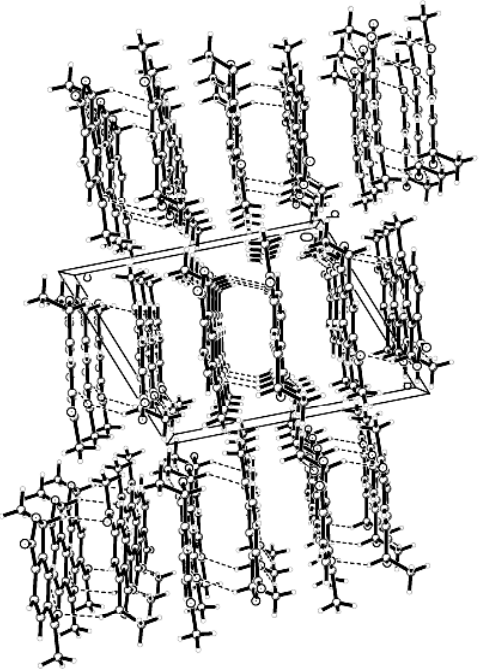


Fig. 2. Crystal structures of compound **5**

TABLE-4
HYDROGEN BOND OF COMPOUND **5**

D-H···A	d(D-H) (Å)	d(H···A) (Å)	d(D···A) (Å)	∠D-H···A (deg)
C5-H5A···O1	0.9300	2.4800	3.327(3)	152.00
C8-H8A···O1	0.9800	2.5600	3.421(3)	147.00
C11-H11B···O2	0.9600	2.5300	3.473(3)	166.00

Conclusion

In conclusion, this work described the function of a new oxidant system-CrO_3 combined with $Ce(SO_4)_2$ in the oxidation of methylene to ketone or aldehyde. The 1D and 2D spectra such as ^1H-^{13}C HMBC, ^1H-^1H ROESY, ^{13}C-^1H HSQC of 2-ethyl-1,4-diacetyl benzene are reported. Besides, it is the first time to report the crystal structure of 5-acetyl-3-methylisobenzofuran-1(3*H*)-one.

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