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Unexpected Metal-Free Dehydrogenation of a β-Ketoester to a Phenol Using a Recyclable Oxoammonium Salt

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Abstract: The conversion of ethyl 2-oxocyclohexanecarboxylate to ethyl salicylate using an oxoammonium salt is reported. The dehydrogenation reaction is operationally simple and compares favorably with previous literature examples for the same transformation and expands the scope of oxoammonium salts as reagents for oxidative functionalization processes.

Keywords: oxoammonium salt; dehydrogenation; phenol; recyclable; ketone

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1. Introduction

Oxoammonium salts are stable, metal-free oxidants that are recyclable and can be used under mild conditions. They and their nitroxide analogs have been employed extensively for the oxidation of alcohols to aldehydes, ketones, and carboxylic acids [1–7]. The most widely used oxoammonium salt is 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, **1** (Figure 1) [7]. Moving beyond simple alcohol oxidation, **1** can also be used as a reagent for a range of oxidative functionalization reactions [8–11]. These include oxidative esterification [12], amidation [13], and the preparation of nitriles from aldehydes [14]. It is also possible to couple **1** with visible-light photocatalysis in a dual catalytic system [15–22]. When using **1** in a stoichiometric perspective, one transformation of particular interest is the dehydrogenation of ketones (Scheme 1) [23,24].

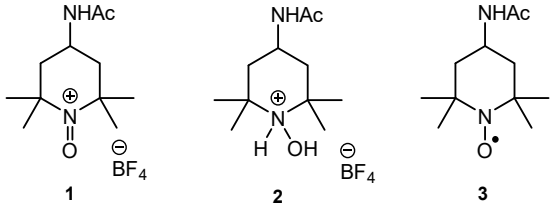
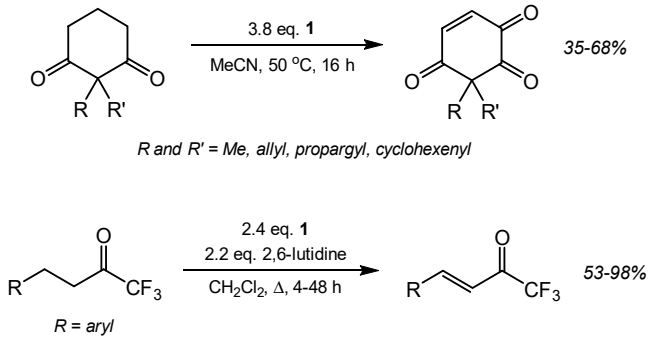


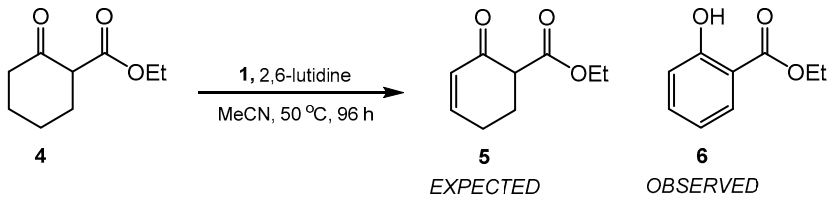
Figure 1. Oxoammonium salt **1** and its hydroxyammonium and nitroxide analogs **2**, and **3**.



Scheme 1. Dehydrogenation of ketones using oxoammonium salt **1**.

Ene-triketones have been prepared by oxidation of diketones [25], and perfluoroalkyl ketones can be converted to their α,β-unsaturated analogs [26]. Reactions are performed in the presence of a nitrogenous base such as pyridine or 2,6-dimethylpyridine (2,6-lutidine). A superstoichiometric quantity of the oxoammonium salt is required because, in the presence of a base, the hydroxyammonium byproduct, **2**, initially formed undergoes a comproportionation reaction with a further aliquot of **1** to generate two equivalents of nitroxide **3** [27,28]. Thus, a sacrificial equivalent of **1** is required in order to affect complete dehydrogenation of the substrate. The spent oxidant can be easily removed by filtration at the end of a reaction and converted back to **1** [29].

In an attempt to expand the scope of previous methodologies, we sought to use **1** for the dehydrogenation of a range of cyclohexanones. This transformation is traditionally performed using hypervalent iodine reagents [30] or by palladium catalysis [31]. We wanted to see if **1** could be used as an environmentally benign alternative. As a sharpening stone for probing this reaction, our attention focused on ethyl 2-oxocyclohexanecarboxylate, **4**, as a substrate. However, rather than obtaining ethyl 2-oxo-3-cyclohexene-1-carboxylate, **5**, as the product, we observed the formation of ethyl salicylate, **6,** a well-known phenolic compound (Scheme 2) [32–36]. We report this serendipitous discovery here.



Scheme 2. Conversion of β-ketoester **4** to phenol **6** rather than α,β-unsaturated β-ketoester **5**.

2. Results and Discussion

Our discovery arose when we performed the reaction of **4** with 3.6 eq. of **1**, using 5 eq. of 2,6-lutidine as a base. Heating an acetonitrile solution of the reagents at 50 °C for 96 h led to an almost equimolar ratio of phenol **6** and unreacted starting material **4** (Table 1, entry 1). Increasing the loading of **1** to 7.5 eq. and reducing the reaction time to 24 h, resulted in complete conversion to **6** (entry 2). Performing the reaction in absence of 2,6-lutidine was not successful, indicating the importance of the base (entry 3). Reducing the reaction temperature to 25 °C slowed the reaction considerably, it taking 72 h to reach completion (entries 4 and 5). Operating at 50 °C but reducing the oxoammonium salt loading to 5 eq. required extending the reaction time to 72 h (entry 6). Attempts to perform the reaction catalytically in **1** using a number of secondary oxidants were not successful. In order to improve the efficacy of the stoichiometric protocol, we wanted to reduce the reaction time. To achieve this, we turned to using microwave heating under sealed-vessel conditions as a tool. This way we were able to reach 100 °C simply and safely and could reduce the reaction time from 24 h to 30 min and obtain a near-quantitative conversion (entry 7). These became the optimal conditions for the protocol.

Our attention turned next to the isolation of the phenol from the product mixture. With an organic base and byproducts from the oxoammonium salt in the mixture, isolation of **6** involved a series of extractions. The product mixture was first diluted with water and then dilute hydrochloric acid added. An extraction with petroleum ether removed non-acidic byproducts. The organic layer was then washed with dilute sodium hydroxide in order to extract the product as the phenoxide anion into the aqueous phase and leaving organic byproducts, spent oxidant, and any unreacted starting material in the organic phase. Acidification of the aqueous extract with dilute hydrochloric acid liberated the phenol which was then extracted using petroleum ether. Removal of the solvent gave **6** in 40% isolated yield.

Table 1. Optimization of reaction conditions for the conversion of β-ketoester **4** to phenol **6** [a].

Entry	1 (eq.)	2,6-Lutidine (eq.)	Temperature (°C)	Time (h)	Conversion to 6 (%) [b]
1	3.6	5	50	96	51
2	7.5	5	50	24	100
3	7.5	0	50	24	0
4	7.5	5	25	72	53
5	7.5	5	25	72	95
6	5.0	5	50	72	92
7 [c]	7.5	5	100	0.5	100

[a] Reagents and conditions: ethyl 2-oxocyclohexanecarboxylate (**4**, 0.5 mmol, 1 eq.), acetonitrile (2 mL, 0.25 M in **4**), requisite quantity of **1** and 2,6-lutidine, stirred at the desired temperature in an oil bath for the allotted time. [b] Determined using GCMS. [c] Performed using microwave heating.

The fact that phenol **6** is formed in the reaction of **4** with **1** is noteworthy in light of the two other literature reports of this transformation. One employs an *o*-iodoxybenzoic acid derivative bearing a trimethylammonium group [30]. A comparable yield of **6** is obtained in the oxidative dehydrogenation of **4**. The other approach involves the use of 10 mol% of palladium chloride in conjunction with 2 eq. of chloranil as a terminal oxidant [31]. The phenol product is obtained in 95% yield after 18 h. Compared to these reports, our methodology has the advantage that it is metal-free and that the oxidant is cheaper, easier to use, recyclable, and non-toxic.

3. Materials and Methods

3.1. General

All microwave-heating reactions were performed using a CEM Discover SP microwave unit (CEM Corporation, Matthews, NC, USA), in closed-vessel configuration. Temperature was measured by means of an IR temperature sensor located below the reaction vessel. NMR spectra (^{1}H, ^{13}C) were obtained in deuterated chloroform at 300 K using a Brüker DRX-400 400 MHz spectrometer (Brüker, Billerica, MA, USA). ^{1}H-NMR spectra were referenced to residual $CHCl_3$ (7.26 ppm) in $CDCl_3$. ^{13}C-NMR spectra were referenced to $CDCl_3$ (77.16 ppm). Reactions were monitored by an Agilent Technologies (Santa Clara, CA, USA) 7820A Gas Chromatograph attached to a 5975 Mass Spectrometer.

3.2. Chemicals

Ethyl 2-oxocyclohexanecarboxylate [CAS 1655-07-8] was purchased from Acros Organics (Geel, Belgium). 2,6-lutidine [CAS 108-48-5] was purchased from Oakwood Chemical (Estill, SC, USA). Acetonitrile [CAS 75-05-8] was obtained from Sigma-Aldrich (St. Louis, MO, USA). Petroleum ether [CAS 8032-32-4] was purchased from Fisher Scientific (Hampton, NH, USA). Deuterated chloroform ($CDCl_3$) [CAS 865-49-6] was purchased from Cambridge Isotope Laboratories (Tewksbury, MA, USA). Oxoammonium salt, **1**, [CAS 219543-09-6] was prepared using a literature procedure [29].

3.3. Synthesis of Ethyl Salicylate (**6**) *[CAS 118-61-6]*

Ethyl 2-oxocyclohexanecarboxylate [CAS 1655-07-8] (**4**, 1 mmol, 1 eq), 2,6-lutidine [CAS 108-48-5] (5 mmol, 5 eq), 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1**, 7.5 mmol, 7.5 eq), acetonitrile (3 mL) and deionized water (1 mL) were added to a 40 mL-capacity glass tube equipped with a magnetic stir bar. The reaction mixture was sealed with a cap and placed into a CEM Discover SP microwave unit. The content of the vessel was heated to 100 °C and held at this temperature for 30 min, the microwave power automatically fluctuating to hold the reaction mixture at the desired temperature. The reaction mixture was stirred constantly. After the allotted time, the reaction mixture was allowed to cool to below 50 °C before taking the vessel out of the microwave unit. An intensely colored solution was obtained at this point. The product mixture was transferred from the glass tube to a separatory funnel whereupon water (2 mL) was added, followed by 1 M HCl (5 mL). An extraction with petroleum ether was

performed (5 × 10 mL) in order to remove non-acidic byproducts. The organic layer was then washed with 0.5 M NaOH (2 × 25 mL) in order to extract the product in phenoxide anion form. At this point the color of the solution changed from yellow to green. The two basic aqueous fractions were collected and acidified with 2 M HCl until a pH of less than 3 was reached (~30 mL acid). At this point the solution turned a cloudy yellow color. This solution was extracted with petroleum ether (3 × 30 mL). The combined organic extracts were washed with brine (~30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure by rotary evaporation affording pure phenol **6** as a yellow oil (66 mg, 40%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 10.84 (s, 1H), 7.85 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.45 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.88 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).^{13}C-NMR (101 MHz, $CDCl_3$): δ ppm 170.36, 161.83, 135.73, 130.05, 119.22, 117.70, 112.79, 77.48, 77.16, 76.84, 61.55, 14.33. GC-MS: (EI), *m*/*z* (relative intensity, %), 166 ([M]$^+$, 39), 121 (28), 120 (100), 92 (37), 65 (11). Spectral data for this compound are consistent with those previously reported [37,38] (Supplementary Materials).

4. Conclusions

In summary, we report the conversion of β-ketoester **4** to a phenol **6** using oxoammonium salt **1**. The reaction is operationally simple and compares favorably with previous literature examples for the same transformation. This serendipitous discovery opens the door to further exploration of the dehydrogenation of ketones to generate phenol products and work is currently underway in our laboratory to this end.

Supplementary Materials: The following are available online. ^{1}H- and ^{13}C-NMR, and GCMS spectra of product **6**.

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