

## Chromate Oxidation of $\alpha$ -Nitro Alcohols to $\alpha$ -Nitro Ketones: Significant Improvements to a Classic Method

Tarek Abou Elmaaty and Lyle W. Castle \*

Department of Chemistry, Idaho State University, Campus Box 8023, Pocatello Idaho, 83209 USA.  
Fax: +(1) 208-282-4373.

\* Author to whom correspondence should be addressed. Email: castlyle@isu.edu

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**Abstract:** A series of eight alkyl and aryl  $\alpha$ -nitro ketones were prepared by the potassium dichromate oxidation of the corresponding nitro alcohols. Short reaction times allowed for the easy isolation of pure nitro ketones that are devoid of starting materials and/or other oxidation side products.

**Keywords:** Nitroalcohols, nitroketones, chromate oxidation.

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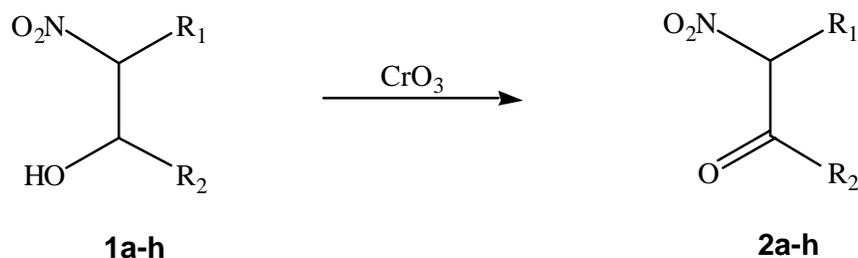
### Introduction

Our interest in  $\alpha$ -nitro ketones stems from their usefulness in the synthesis of alkyl substituted pyrazines [1]. A literature search revealed a limited number of procedures for their preparation.  $\alpha$ -Nitro ketones have been prepared in a one pot procedure by a solvent free nitroaldol (Henry reaction) reaction followed by oxidation to the corresponding ketone using wet-alumina supported chromium(VI) oxide [2], by the base catalyzed nitroaldol reaction using alumina supported potassium fluoride, followed by oxidation using  $\text{CrO}_3$  along with the addition of montmorillonite K 10 [3], or by the sodium dichromate oxidation of  $\alpha$ -nitro alcohols [4] formed from the Henry reaction [5]. Other general methods for the oxidation of primary and secondary alcohols have been reported and these include the use of PCC [6] and the Swern [7] oxidation reactions. Finally  $\alpha$ -nitro ketones can be prepared through the reaction of acyl imidazoles with nitroalkanes in the presence of lithium hydride in dimethyl sulfoxide [8].

## Results and Discussion

This series of compounds reported here was prepared by a modified version of the sodium dichromate oxidation [4]. In the method used by Hurd and Nilson [4] the sulfuric acid solution was added to a mixture of the alcohols and sodium dichromate over a period of six hours, followed by long mixing periods (2–72 hours), depending on the nitro ketone prepared. In our modification of the procedure (given below), the nitro alcohol was gradually added to the potassium dichromate solution followed by a ten-minute stirring period, then the drop-wise addition of the sulfuric acid solution over a period of one hour. After the sulfuric acid addition is complete, the reaction is terminated by the addition of water, followed by extraction and purification.

This method led to yields between 85–95%, with minimal purification, as compared to literature yields of 68–86% [2], 76–90% [3] and 39–74% [4], which required more time and, in some cases, complex methods. It should be noted that NMR spectral analysis of the crude material (prior to Kugelrohr distillation) showed the compounds to be very pure, and thus they can be used directly in most applications.



| Entry #   | R <sub>1</sub>                | R <sub>2</sub>                                    | Yield % of 2* |
|-----------|-------------------------------|---|---------------|
| <b>2a</b> | CH <sub>3</sub>               | CH <sub>3</sub>                                   | 95            |
| <b>2b</b> | C <sub>2</sub> H <sub>5</sub> | CH <sub>3</sub>                                   | 95            |
| <b>2c</b> | CH <sub>3</sub>               | (CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>   | 93            |
| <b>2d</b> | CH <sub>3</sub>               | (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>   | 93            |
| <b>2e</b> | CH <sub>3</sub>               | (CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>   | 87            |
| <b>2f</b> | CH <sub>3</sub>               | (CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>   | 85            |
| <b>2g</b> | CH <sub>3</sub>               | CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> | 90            |
| <b>2h</b> | CH <sub>3</sub>               | C <sub>6</sub> H <sub>5</sub>                     | 95            |

\* Yield of 100% pure isolated product;

# Nitro alcohols **a-g** were prepared using the Henry reaction [9].

## Conclusions

We have presented a facile route for the formation of  $\alpha$ -nitroketones, useful intermediates in heterocyclic synthesis.

## Acknowledgements

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## Experimental

### General

All  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were recorded in  $\text{CDCl}_3$  on a Varian Mercury NMR spectrometer operating at 300 and 100 MHz, respectively. Chemical shifts are expressed in ppm relative to TMS as an internal standard.  $J$  values are given in hertz. Final products were purified by Kugelrohr distillation using a Büchi B-580 Glass Oven. Starting materials were purchased from Aldrich and used without further purification.

### General Procedure for the Oxidation Reaction.

Potassium dichromate (0.069 mol) and water (35 mL) were mixed with constant mechanical stirring in a 3-necked flask fitted with a condenser and an addition funnel. The corresponding nitro alcohol **1a-h** (0.13 mol) was gradually added to the cooled stirring solution and stirring was continued for another 10 minutes. A cooled solution of  $\text{H}_2\text{SO}_4$  (30 mL) and water (18 mL) was then added dropwise over a period of 1 hr., after which water (100 mL) was introduced into the reaction mixture. The mixture was extracted with dichloromethane (3 x 150 mL), followed by subsequent washing with water (200 mL) and 5% sodium carbonate (200 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered and the solvent evaporated *in vacuo*. The liquid obtained was distilled using a Kugelrohr apparatus to give the desired nitroketones **2a-2h**.

*3-Nitro-2-butanone (2a)* [4]:  $^1\text{H}$ -NMR  $\delta_{\text{H}}$ : 1.7 (d, 3H,  $\text{CH}_3$ ); 2.25 (s, 3H,  $\text{CH}_3$ ); 5.2-5.3 (q, 1H, CH).

*3-Nitro-2-pentanone (2b)* [4]:  $^1\text{H}$ -NMR  $\delta_{\text{H}}$ : 1.05 (t, 3H,  $\text{CH}_3$ ); 2.0-2.2 (m, 2H,  $\text{CH}_2$ , diastereotopic protons); 2.3 (s, 3H,  $\text{CH}_3$ ); 5.1 (dd, 1H, CH;  $J=6$ ,  $J=10$ );  $^{13}\text{C}$ -NMR  $\delta_{\text{C}}$ : 193.5 (CO); 93.0 (CH), 26.5, 10.0 (2  $\text{CH}_3$ ); 22.5 ( $\text{CH}_2$ ); COSY [10].

*2-Nitro-3-hexanone (2c)*:  $^1\text{H}$ -NMR  $\delta_{\text{H}}$ : 0.95 (t, 3H,  $\text{CH}_3$ ); 1.61 (m, 2H,  $\text{CH}_2$ ); 1.75 (d, 3H,  $\text{CH}_3$ ); 2.6 (t, 2H,  $\text{CH}_2$ ); 5.25 (q, 1H, CH);  $^{13}\text{C}$ -NMR  $\delta_{\text{C}}$ : 200.0 (CO); 89.5 (CH); 41.0, 17.0 ( $\text{CH}_2$ ), 13.0 ( $\text{CH}_3$ ).

*2-Nitro-3-heptanone (2d)*:  $^1\text{H}$ -NMR  $\delta_{\text{H}}$ : 0.95 (t, 3H,  $\text{CH}_3$ ); 1.35(m, 2H,  $\text{CH}_2$ ); 1.6 (m, 2H,  $\text{CH}_2$ ); 1.75 (d, 3H,  $\text{CH}_3$ ); 2.6 (t, 2H,  $\text{CH}_2$ ); 5.25 (q, 1H, CH);  $^{13}\text{C}$ -NMR  $\delta_{\text{C}}$ : 200.0 (CO); 89.5 (CH), 39.5, 26.0, 22.0 ( $\text{CH}_2$ ); 16.0, 14.0 ( $\text{CH}_3$ ).

2-Nitro-3-nonanone (**2e**):  $^1\text{H-NMR } \delta_{\text{H}}$ : 0.9 (t, 3H, CH<sub>3</sub>); 1.3 (m, 6H, 3CH<sub>2</sub>); 1.65 (m, 2H, CH<sub>2</sub>); 1.7 (d, 3H, CH<sub>3</sub>); 2.55 (t, 2H, CH<sub>2</sub>); 5.25 (q, 1H, CH);  $^{13}\text{C-NMR } \delta_{\text{C}}$ : 200.0 (CO); 89.5 (CH); 39.5, 31.0, 29.5, 22.0(CH<sub>2</sub>); 15.0, 14.0 (CH<sub>3</sub>).

2-Nitro-3-decanone (**2f**):  $^1\text{H-NMR } \delta_{\text{H}}$ : 0.8 (t, 3H, CH<sub>3</sub>); 1.3 (m, 6H, 3CH<sub>2</sub>); 1.52 (m, 2H, CH<sub>2</sub>); 1.65 (m, 2H, CH<sub>2</sub>); 1.7 (d, 3H, CH<sub>3</sub>); 2.6 (t, 2H, CH<sub>2</sub>); 5.25 (q, 1H, CH);  $^{13}\text{C-NMR } \delta_{\text{C}}$ : 200.0 (CO); 89.5 (CH); 39.7, 31.9, 29.1, 29.0, 23.6, 22.8 (CH<sub>2</sub>); 15.2, 114.2 (2CH<sub>3</sub>).

5-Methyl-2-nitro-3-hexanone (**2g**):  $^1\text{H-NMR } \delta_{\text{H}}$ : 0.8 (d, 6H, 2CH<sub>3</sub>), 1.55 (d, 3H, CH<sub>3</sub>), 2.06 (m, 1H, CH), 2.41 (d, 2H, CH<sub>2</sub>), 5.05 (q, 1H, CH-NO<sub>2</sub>);  $^{13}\text{C-NMR } \delta_{\text{C}}$ : 202.0 (CO), 95.3 (CH), 47.5 (CH<sub>2</sub>), 22.9 (CH), 22.0, 10.1(CH<sub>3</sub>).

2-Nitro-1-phenylpropanone (**2h**) [8]:  $^1\text{H-NMR } \delta_{\text{H}}$ : 1.8 (d, 3H, CH<sub>3</sub>); 6.2 (q, 1H, CH); 7.4-8.0 (m, 5H, arom-H);  $^{13}\text{C-NMR } \delta_{\text{C}}$ : 190.0 (CO); 136.0, 134.0, 129.0, 128.0 (arom); 84.5 (CH), 16.5 (CH<sub>3</sub>).

## References and Notes

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10. The  $^1\text{H-NMR}$  spectrum of **2b** is interesting in that the resonance at 5.1 ppm appears as a doublet of doublets. The connectivity of the  $-\text{CH}(\text{NO}_2)\text{CH}_2\text{CH}_3$  was verified by a COSY experiment: the dd at  $\delta$  5.1 correlates with the m at  $\delta$  2.1, which correlates with the t at  $\delta$  1.05. A simple rigid search of the rotation barrier about the C<sup>2</sup>-C<sup>3</sup> bond using CAChe molecular modeling software gave a rotational barrier of 82 kcal/mole. This indicates that the barrier to rotation is large and explains the observed dd at 5.1 ppm for **2b**.

*Sample Availability:* Available from the authors.