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# One-pot oxidative bromination - esterification of aldehydes to 2-bromoesters using cerium(IV) ammonium nitrate and lithium bromide

Gennady I. Nikishin <sup>a</sup>, Nadezhda I. Kapustina <sup>a</sup>, Lyubov' L. Sokova <sup>a</sup>, Oleg V. Bityukov <sup>a</sup> and Alexander O. Terent'ev \* <sup>a,b</sup>

<sup>a</sup> N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect 47, Moscow, 119991, Russian Federation <sup>b</sup> D.I. Mendeleev University of Chemical Technology of Russia, 9 Miusskaya square, Moscow, 125047, Russian Federation

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### ABSTRACT

A two-step, one-pot reaction of aldehydes with the CAN/LiBr oxidation system under solventfree conditions followed by the addition of methanol affords methyl  $\alpha$ -bromocarboxylates. The oxidation of aldehydes with methanol using this system gives only methyl esters. A facile method, which does not require special equipment, was developed for the synthesis of 2bromoesters from aliphatic aldehydes with carbon chain lengths of 5 to 10 atoms.

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### Aldehydes Oxidation Esterification Bromination 2-Bromoesters Cerium(IV) ammonium nitrate (CAN)

### 1. Introduction

Oxidation of the aldehyde group to the carboxyl group is a reaction of fundamental importance in organic chemistry. In recent years the oxidation of aldehydes with alcohols giving carboxylic acid esters has been extensively developed. These reactions proceed under mild conditions, often selectively, with a wide range of oxidants. Initial studies in this area were performed at the end of the  $20^{\rm th}$  century using oxidation systems including O<sub>3</sub>/KOH,<sup>1</sup> NaClO/MeCOOH,<sup>2</sup> CrO<sub>3</sub>/pyridine,<sup>3</sup> pyridinium dichromate,<sup>4</sup> and *N*-iodosuccinimide/K<sub>2</sub>CO<sub>3</sub>.<sup>5</sup> In subsequent years, oxone,<sup>6</sup> *S*-SnO<sub>2</sub>/H<sub>2</sub>O<sub>2</sub>,<sup>7</sup> pyridinium hydrobromide perbromide,<sup>8</sup> CuBr/t-BuOOH,<sup>9</sup> PhI(OAc)<sub>2</sub>,<sup>10</sup> and Fe(II)/H<sub>2</sub>O<sub>2</sub><sup>11</sup> were also used as oxidants. In reactions with alcohols, aromatic aldehydes have been oxidized to aromatic acid esters in the presence of Ti(IV)/H<sub>2</sub>O<sub>2</sub>,<sup>12</sup> V<sub>2</sub>O<sub>3</sub>/H<sub>2</sub>O<sub>2</sub>,<sup>13</sup> TsNBr<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub>,<sup>14</sup> CaCl<sub>2</sub>/H<sub>2</sub>O<sub>2</sub>,<sup>15</sup> B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>/t-BuOOH,<sup>16</sup> and LiBr/NaIO<sub>4</sub>,<sup>17</sup> as well as other oxidation systems.

Apart from the oxidative esterification of aldehydes, attention has been given to the development of original approaches to the synthesis of esters based on oxidative homo- and crossesterification of aliphatic and benzylic alcohols. In the context of our study, this approach is particularly useful because the oxidation of alcohols proceeds through the formation of aldehydes and often with the involvement of bromide ions as the redox catalyst: PhIO/KBr,<sup>18</sup> NaBrO<sub>3</sub>/HBr,<sup>19</sup> H<sub>2</sub>O<sub>2</sub>/HBr,<sup>20</sup> oxone/NaBr, <sup>21</sup>  $H_2O_2/KBr/PhSO_3H$ , <sup>22</sup>  $PhI(OAc)_2/KBr$ , <sup>23</sup>  $H_2O_2/ZnBr_2$ , <sup>24</sup> and others.<sup>9,14</sup>

However, it should be emphasized that the formation of bromine-containing esters has not been reported in the above publications, despite the involvement of bromine in the oxidation process. Thus, the idea of aldehyde oxidation to give 2bromoesters has escaped the attention of organic chemists.

The first versatile method for the synthesis of 2-bromocarboxylic acids and 2-bromoesters, which is still frequently used, was based on the Hell-Volhard-Zelinsky (HVZ) reaction – the bromination of carboxylic acids with molecular bromine in the presence of red phosphorus or phosphorus tribromide, followed by treatment of the reaction mixture with water or alcohol.<sup>25</sup>

### 2. Results and Discussion

In the present work, we describe a new oxidative transformation of aldehydes accompanied by additional functionalization. The one-pot oxidation of aldehydes **1a-f** with the CAN/LiBr system can be used to furnish methyl 2-bromocarboxylates **2a-f** or bromine-free carboxylic acid esters **3a-f** depending on the reaction conditions (Scheme 1).

The reaction was performed under solvent-free conditions in the "solid-liquid" phase composed of cerium and lithium salts,

<sup>\*</sup> Corresponding author. Tel.: +7-916-385-4080; e-mail: terentev@ioc.ac.ru

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Scheme 1. Bromination-oxidation of aldehydes to methyl 2bromocarboxylates **2a-f** and methyl carboxylates **3a-f**. the aldehyde, and the esterifying alcohol. An important advantage of this method over the HVZ synthesis is that it does not require toxic liquid bromine as the starting reagent.

The reaction conditions for the synthesis of esters 2 were optimized using the oxidation of heptanal 1c to methyl 2-bromoheptanoate 2c. The influence of the reagent ratio, the temperature, and the reaction time on the yields of 2c and 3c were investigated (Table 1).

Table 1. Reaction optimization for the oxidation of heptanal 1c with CAN/LiBr to give methyl 2-bromoheptanoate 2c and methyl heptanoate 3c.

Entry <sup>a</sup>	Molar ratio 1c:CAN:LiBr:MeOH	Conversion 1c (%)	Yield $2c (\%)^{b}$	Yield $3c (\%)^{b}$
1	1:1:1:1	50	trace	45
2	1:2:1:1	80	3	66
3	1:2:1:2	93	trace	79
4	1:3:3:2	100	48	40
5	1:4:1:2	97	11	74
6	1:4:2:2	98	67	22
7	1:4:3:2	100	83	11
8 <sup>c</sup>	1:4:3:2	100	87	7
9	1:4:4:2	95	57	24
10	1:5:3:2	100	63	19
11 <sup>d</sup>	1:4:3:2	98	49	39
12 <sup>e</sup>	1:4:3:2	99	trace	77

<sup>a</sup>General reaction conditions: **1c** (1 mmol), 20 °C, 20 h. <sup>b</sup>Yield with respect to the starting aldehyde **1c** was determined by GC using methyl pentanoate and methyl decanoate as internal standards. <sup>c</sup>35-40 °C, 3.5-4 h. <sup>d</sup>NaBr. <sup>c</sup>NH<sub>4</sub>Br.

The best results were obtained using the reagents **1c**:CAN:LiBr:MeOH in a ratio of 1:4:3:2 at 20 °C for 20 h or 35-40 °C for 3.5 h (Table 1, entries 7 and 8). Under these conditions, ester **2c** was obtained in 83% and 87% yield, respectively. A decrease in the amount of CAN or LiBr led to decreased yields of ester **2c** (Entries 1-6). An increase in the amount of these reagents also, contrary to expectations, led to decreased yields of ester **2c** and the formation of ester **3c** (Entries 9 and 10). The use of NaBr instead of LiBr had an adverse effect, and esters **2c** and **3c** were produced in nearly equal yields (Entry 11). The reaction in the presence of NH<sub>4</sub>Br instead of LiBr gave only ester **3c** (Entry 12).

In the next step of the work, under the optimized conditions (Table 1, entries 7 and 8) all aldehydes underwent almost complete conversion to give the targeted products **2a-f** in moderate to high yields (Table 2). The yields for esters **2a-c** with carbon chain lengths of 5-7 atoms were 80-87% (Entries 1-5), while the yields for esters **2d-f** with increased carbon chain lengths of 8-10 atoms decreased to 39-71% (Entries 6-11). These differences can most likely be attributed to steric effects while electronic effects are not manifested. The yields of esters **3a-f** increased in the series of aldehydes from pentanal to decanal.

Table 2. Oxidation of aldehydes 1a-f with CAN/LiBr to give methyl 2-bromocarbox	ylate <b>2a-f</b> .	20
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Entry <sup>a</sup>	1a-f	$T(^{\circ}C)$	Time (h)	Conversion 1a-f (%)	Yield <b>2a-f</b> $(\%)^{b}$	Yield <b>3a-f</b> $(\%)^{b}$
1	1-pentanal (1a)	20	20	100	<b>2a,</b> 81 (77)	<b>3a,</b> 9
2	1-hexanal ( <b>1b</b> )	20	20	100	<b>2b,</b> 80 (78)	<b>3b,</b> 11
3	1b	35-40	3.5	98	<b>2b,</b> 84 (80)	<b>3b,</b> 10
4	1-heptanal (1c)	20	20	100	<b>2c,</b> 83 (78)	<b>3c,</b> 11
5	1c	35-40	3.5	100	<b>2c,</b> 87 (82)	<b>3c,</b> 7
6	1-octanal (1d)	20	20	98	<b>2d,</b> 58 (52)	<b>3d,</b> 30
7	1d	35-40	3.5	100	<b>2d</b> , 71 (70)	<b>3d,</b> 19
8	1-nonanal (1e)	20	20	94	<b>2e,</b> 39 (35)	<b>3e,</b> 48
9	1e	35-40	3.5	99	<b>2e,</b> 65 (60)	<b>3e,</b> 25
10	1-decanal (1f)	20	20	93	<b>2f,</b> 30 (27)	<b>3f,</b> 54
11	1f	35-40	3.5	98	<b>2f,</b> 59 (53)	<b>3f,</b> 29

<sup>a</sup>General reaction conditions: molar ratio **1a-f**:CAN:LiBr:MeOH = 1:4:3:2, **1a-f** (1 mmol). <sup>b</sup>Yield with respect to the starting aldehyde **1a-f** was determined by GC using methyl pentanoate and methyl decanoate as internal standards. Isolated yield in parenthesis.

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Based on the results obtained in Table 1, a procedure for the synthesis of esters **3a-f** was developed. The required changes include altering the sequence for the addition of reagents to the CAN/LiBr mixture: firstly, methanol was added, followed by the aldehyde (Table 3).

$1 \mathbf{a} \mathbf{b} \mathbf{c} \mathbf{c} \mathbf{c} \mathbf{c} \mathbf{c} \mathbf{c} \mathbf{c} c$	Table 3.	<b>Synthesis</b>	of methyl	esters 3a-f
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Entry <sup>a</sup>	1a-f	Yield <b>3a-f</b> $(\%)^{b}$
1	1-pentanal, 1a	<b>3a,</b> 78 (70)
2	1-hexanal, 1b	<b>3b,</b> 80 (73)
3	1-heptanal, 1c	<b>3c,</b> 81 (73)
4	1-octanal, 1d	<b>3d,</b> 81 (70)
5	1-nonanal, 1e	<b>3e</b> , 80 (76)
6	1-decanal, 1f	<b>3f</b> , 82 (74)

<sup>a</sup>General reaction conditions: molar ratio **1a-f**:CAN:LiBr:MeOH = 1:2:0.3: 2, **1a-f** (1 mmol), 35-40 °C, 3.5-4 h. <sup>b</sup>Yield with respect to the starting aldehyde **1a-f** was determined by GC using methyl pentanoate and methyl decanoate as internal standards. Isolated yield in parenthesis.

Under the optimal reaction conditions using the reagents **1**:CAN:LiBr:MeOH in a molar ratio of 1:2.1:0.3:2 at 35-40 °C for 3.5 h, esters **3a-f** were obtained in 78-82% yield (Entries 1-6). The oxidation proceeds without additional solvent, which makes it convenient for the synthesis of methyl esters.



Taking into account published data on the oxidative esterification of aldehydes and the oxidative bromination of ketones, two alternative mechanisms for the transformation of aldehydes **1a-f** to esters **2a-f** can be *a priori* envisaged (Scheme 2).

Mechanism A involves two key steps: successive bromination of the aldehyde group and the  $\alpha$ -CH<sub>2</sub> group followed by esterification of the resulting 2-bromoalkanoyl bromides with methanol. This interpretation is consistent with the results of Minisci and co-wokers.<sup>20</sup> It was proposed that the oxidation of aldehydes to esters in the presence of the H<sub>2</sub>O<sub>2</sub>/HBr system proceeds *via* bromination of the aldehyde group and alcoholysis of the resulting acid bromides.

Mechanism B differs only in the sequence of steps. Thus, the  $\alpha$ -CH<sub>2</sub> group is brominated first and is followed by bromination at the aldehyde group. This could be evidenced by the results for selective bromination of the  $\alpha$ -CH<sub>2</sub> group in aliphatic ketones using the CAN/LiBr system where 2-bromoketones were produced with high selectivity and high yield.<sup>27</sup>

That the reaction follows mechanism A is supported by the results presented in Table 1 (in particular, entries 1 and 2). According to these results, a decrease in the amount of oxidant (CAN) from 4 to 1-2 equiv. with respect to heptanal **1c**, results in bromination predominantly occurring at the aldehyde group, while the  $\alpha$ -CH<sub>2</sub> group remains virtually intact. Consequently, the transformation of alkanals to esters **2a-f** starts with bromination of the aldehyde group followed by bromination of the resulting

acid bromides at the  $\alpha$ -CH<sub>2</sub> group with formation of 2bromoalkanoyl bromides (mechanism A). It should be noted that esters **3a-f** cannot be transformed to esters **2a-f** under the experimental conditions given in Table 1. This was exemplified using methyl heptanoate **3c** as starting reagent, which was not converted into 2-bromocarboxylate **2c** (see ESI).

#### 3. Conclusion

In summary, a new method was developed for the synthesis of methyl 2-bromocarboxylates, based on the oxidative bromination-esterification of aliphatic aldehydes using the CAN/LiBr system. The reaction proceeds under mild conditions in the absence of solvent through successive steps: bromination of the aldehyde to form the carboxylic acid bromide and then to 2-bromocarboxylic acid bromide followed by alcoholysis of the latter with methanol. Methyl 2-bromoesters were produced in up to 87% yield. Additionally, a novel procedure was developed for the synthesis of methyl esters from aldehydes by the oxidation of the latter together with methanol using the same oxidation system.

### Acknowledgments

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### **Supplementary Material**

Supplementary data (experimental procedures, spectroscopic data for all of the synthesized compounds) associated with this article can be found, in the online version, at http://.....

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- 26. Table 2. Oxidation of aldehydes 1a-f with CAN/LiBr to methyl 2bromocarboxylate 2a-f. To a pear-shaped two-necked reactor (25 mL) equipped with a thermometer and reflux condenser, CAN (2.2 g, 4.0 mmol) and LiBr (261 mg, 3.0 mmol) were added and stirred. Next, aldehyde 1a-f (1 mmol) was added and the reaction mixture stirred for 10-15 min. Then MeOH (64 mg, 2.0 mmol) was added and the reaction

mixture stirred for 20 h at 20 °C (3.5 h at 35-40 °C). The reaction mixture was cooled, diluted with water (10-15 mL) and extracted with Et<sub>2</sub>O (3×10-15 mL). The combined organic phases were washed with aqueous NaHCO<sub>3</sub> (10 mL) and water (10 mL), then dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure (water bath temperature 25-28 °C). The conversion of 1a-f and the yields of 2a-f and **3a-f** were determined by GLC using methyl pentanoate and methyl decanoate as internal standards. The isolation of 2-bromoesters 2a-f was performed using gradient silica gel column chromatography with petroleum ether (b.p. 40-70 °C):chloroform (10-1:1), as eluent. Preparative yields of **2a-f** were 53-82%.

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### **Highlights**

- Accepter • Synthesis of α-bromoesters from aldehydes
  - Solvent free mild conditions