

# SYNTHESIS OF NOVEL ALDEHYDES SUITABLE FOR BIOCONJUGATION BY INTRODUCTION OF A CARBOXYL GROUP VIA ALKYLATION OF HYDROXYBENZALDEHYDES WITH CHLOROACETIC ACID

Natalia M. Fedosova<sup>a,b</sup>, Victor Ya. Chernii<sup>a\*</sup>, Iryna M. Tretyakova<sup>a,b</sup>, Vladyslava B. Kovalska<sup>a</sup>, Victor Ciornea<sup>c</sup>, Alexandru Rotaru<sup>d</sup>

<sup>a</sup>*V.I. Vernadsky Institute of General and Inorganic Chemistry, 32/34 Palladin Ave, 03-142 Kyiv, Ukraine*

<sup>b</sup>*Innovation development center ABN, 2/37 Pirogov Street, 01030 Kyiv, Ukraine*

<sup>c</sup>*“Ion Creanga” State Pedagogical University, Faculty of Biology and Chemistry, 1 Ion Creangă Street, MD-2069 Chisinau, Moldova*

<sup>d</sup>*“Petru Poni” Institute of Macromolecular Chemistry, Romanian Academy, Centre of Advanced Research in Bionanoconjugates and Biopolymers, Gligore Ghica Voda Alley 41 A, 700487 Iasi, Romania*

**Abstract:** The communication focuses on the alkylation of hydroxybenzaldehydes by chloroacetic acid to introduce a carboxyl group, and investigates the reactivity of the resulting compounds with semicarbazide and malonodinitrile under acidic or alkaline conditions. Successful alkylation of some hydroxybenzaldehydes with chloroacetic acid was carried out with yields 20-67%. The work demonstrates an effective approach to modifying existing aldehydes to introduce new functional groups, with potential applications in the synthesis of aromatic and heterocyclic compounds for use in various industries.

**Keywords:** hydroxybenzaldehydes, alkylation, semicarbazide, malonodinitrile.

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\* Victor Chernii, e-mail: v.chernii@gmail.com

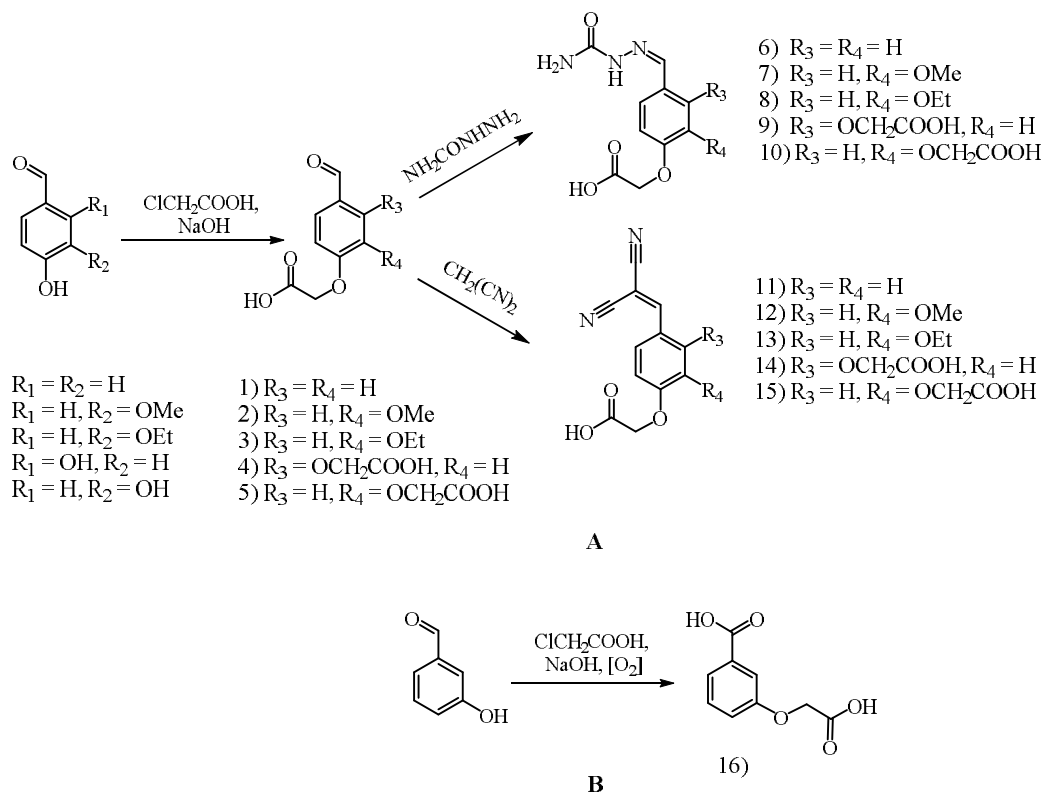
## Introduction

Aldehydes as starting materials are widely used for the synthesis of new aromatic and aliphatic compounds in organic, medical, inorganic, analytical and other fields of chemistry.<sup>1-3</sup> Particularly, aldehydes are used in synthesis of many aromatic and aliphatic compounds,<sup>4,5</sup> pharmaceuticals,<sup>6,7</sup> cosmetics,<sup>8</sup> or dyes.<sup>9,10</sup> Their chemical behavior is useful in studies of the mechanisms of organic reactions, as they participate in oxidation and reduction reactions,<sup>11-14</sup> condensations,<sup>15,17</sup> heterocyclization,<sup>18-20</sup> and many other reactions. Numerous methods to prepare aldehydes have been reported to date, including direct formylation (for example, Vilsmeier's reaction),<sup>21,22</sup> alcohol oxidation,<sup>23,24</sup> reduction of carboxylic acids,<sup>25,26</sup> or modification of compounds that already contain an aldehyde moiety. In this work, we have focused on the latter approach, performing alkylation of a number of hydroxybenzaldehydes by chloroacetic acid in order to introduce a carboxyl fragment, and investigated the reactivity of the obtained compounds with semicarbazide and malonodinitrile in the presence of acidic or alkaline catalysts. The reaction conditions were optimized for each new hydroxybenzaldehyde derivative, and the yields of the final products were determined. Overall, this work demonstrates a useful approach to the synthesis of aldehydes, where existing aldehydes are modified to introduce new functional groups. By optimizing the reaction conditions for each derivative, it was possible to achieve high yields of the final products. This method has potential applications in the synthesis of aromatic and heterocyclic compounds, which can have important applications in the pharmaceutical, agrochemical, and materials industries.

## Results and Discussion

In previous works, we investigated the synthesis and optical properties of fluorescent condensed derivatives of dehydroacetic acid with aldehydes,<sup>27</sup> the products of the opening of the pyran ring of these condensed derivatives<sup>28-30</sup> and corresponding phthalocyanine complexes of zirconium and hafnium.<sup>31</sup> All these compounds are well soluble in standard organic solvents, but are low soluble or practically insoluble in water and do not have functional groups for covalent bioconjugation. This significantly reduces the possibility of their practical application. Therefore, the goal of this work was to obtain a number of water-soluble benzaldehydes containing carboxylate groups (Figure 1A). To achieve this goal, the alkylation reaction of a series of hydroxybenzaldehydes with chloroacetic acid was chosen. Typically, dry aprotic solvents such as DMF, acetone and some others are used for this type of reaction in the presence of potassium or sodium carbonate.<sup>32,33</sup> However, chloroacetic acid is a rather strong alkylating agent, making it possible to carry out alkylation of hydroxybenzaldehydes in an aqueous medium in the presence of alkali. In this case, two (and in the case of dihydroxybenzaldehydes three) equivalents are needed to give a quantitative yield of the reaction. The first equivalent is used to neutralize chloroacetic acid, while the others to obtain phenolate anion. We succeeded in preparation of corresponding alkylated aldehydes with fairly high yields, about 45-67%, with the exception of 2,4-dihydroxybenzaldehyde (20%). The prepared compounds (**1-5**) have high solubility in aqueous-alkaline solutions. Interestingly, under similar conditions, 3-hydroxybenzaldehyde reacted with chloroacetic acid with the formation of the corresponding alkylated benzoic acid (**16**) with a yield of about 50% (Figure 1 B). This is probably due to the fact that

3-hydroxybenzaldehyde is quite easily oxidized under the applied oxidizing conditions of the reaction.



**Figure 1.** (A) Synthesis of aldehydes **1-5**, semicarbazones **6-10**, malonodinitrile derivatives **11-15**; (B) alkylation of 3-hydroxybenzaldehyde with chloroacetic acid to form 3-(carboxymethoxy)benzoic acid **16**.

To study the reactivity of aldehyde groups of newly synthesized compounds **1-5**, two reactions characteristic to aldehydes were chosen: interaction with semicarbazide hydrochloride (acidic conditions) to yield compounds **6-10** and condensation of the methylene active component with malonodinitrile (alkaline conditions) in the presence of piperidine as a catalyst to yield compounds **11-15** (Figure 1). In both investigated cases, the corresponding condensed derivatives were obtained in yields ranging from 80 to 33%.

## Experimental

### *Materials*

All reagents (Fluka, Aldrich) and solvents were used without additional purification.

### *Equipment and methods*

<sup>1</sup>H-NMR spectra were recorded on a "Varian" NMR spectrometer operating at 400 MHz. Tetramethylsilane was used as an internal standard.

### *General procedure for alkylation of hydroxybenzaldehydes.*

To a solution of 200 mmol (18.9 g) of chloroacetic acid dissolved in 50 mL of water, 100 mmol of the corresponding aldehyde was added under continuous stirring and cooling. Next, 300 mmol (12.0 g) of a concentrated aqueous solution of sodium hydroxide was gradually added to the resulting suspension, leading to a transparent solution. In the case of dihydroxybenzaldehydes the amount of sodium hydroxide was increased to 400 mmol. The mixture was stirred for several more minutes and heated to boiling, then refluxed until the pH became close to neutral. To adjust the pH to around 12, more sodium hydroxide solution was added gradually until the reaction mixture pH stabilized. The total reaction time ranged from 3 to 5 hours. Afterward, the reaction mixture was cooled gradually to 70°C and neutralized with concentrated hydrochloric acid until it became strongly acidic. The mixture was then cooled to room temperature, and the precipitate was washed with distilled water until the reaction became neutral. Recrystallization of aldehydes **1** and **5** was carried out using distilled water, while the reaction mixtures of compounds **2** and **3** were boiled with water and filtered hot, discarding the water fraction. Aldehyde **4** was recrystallized from a 1:1 aqueous solution of DMF, filtered, and washed with cold water. The resulting products were dried under reduced pressure at 50°C for 12 hours.

*2-(4-formylphenoxy)acetic acid (1)*. Yield 12.1 g (67.2%).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.96 (s, 1H), 9.87 (s, 1H), 7.86 (d,  $J = 8.7$  Hz, 2H), 7.11 (d,  $J = 8.8$  Hz, 2H), 4.83 (s, 2H).

*2-(4-formyl-2-methoxyphenoxy)acetic acid (2)*. Yield 13.8 g (65.7%).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.70 (s, 1H), 9.83 (s, 1H), 7.51 (d,  $J = 8.2$  Hz, 1H), 7.41 (s, 1H), 7.05 (d,  $J = 8.2$  Hz, 1H), 4.82 (s, 2H), 3.84 (s, 3H).

*2-(2-ethoxy-4-formylphenoxy)acetic acid (3)*. Yield 10.2g (45.5%).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  13.06 (s, 1H), 9.81 (s, 1H), 7.48 (d,  $J = 8.3$  Hz, 1H), 7.39 (s, 1H), 7.02 (d,  $J = 8.3$  Hz, 1H), 4.82 (s, 2H), 4.09 (q,  $J = 6.9$  Hz, 2H), 1.34 (t,  $J = 6.9$  Hz, 3H).

*2,2'-((4-formyl-1,3-phenylene)bis(oxy))diacetic acid (4)*. Yield 5.1 g (20.1%).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.84 (s, 2H), 10.26 (s, 1H), 7.67 (d,  $J = 8.5$  Hz, 1H), 6.69 (s, 1H), 6.65 (d,  $J = 9.0$  Hz, 1H), 4.89 (s, 2H), 4.81 (s, 2H).

*2,2'-((4-formyl-1,2-phenylene)bis(oxy))diacetic acid (5)*. Yield 14.4 g (56.7%).  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  9.79 (s, 1H), 7.51 (d,  $J = 8.2$  Hz, 1H), 7.29 (s, 1H), 7.06 (d,  $J = 8.2$  Hz, 1H), 4.81 (s, 2H), 4.75 (s, 2H), 3.71 (s, 2H+ $\text{H}_2\text{O}$ ).

*General procedure for the reaction of aldehydes 1-5 with semicarbazide hydrochloride.*

1 Mmol of aldehydes **1-5** was dissolved while heating in 3 mL of isopropanol:water (3:1). Then, a solution containing 100 mg of semicarbazide hydrochloride in 2 mL of water was added. The reaction mixture was stirred on a magnetic stirrer at 80°C for 30 minutes, followed by cooling to room temperature. The resulting precipitate was filtered off, washed three times with 5 mL of distilled water, and dried at 70°C for 12 hours.

*2-(4-((2-carbamoylhydrazineylidene)methyl)phenoxy)acetic acid (6)*. Yield 194 mg (81.9%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.93 (s, 1H), 10.08 (s, 1H), 7.77 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.40 (s, 2H), 4.70 (s, 2H).

*2-(4-((2-carbamoylhydrazineylidene)methyl)-2-methoxyphenoxy)acetic acid (7)*. Yield 170 mg (63.7%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.79 (s, 1H), 10.09 (s, 1H), 7.74 (s, 1H), 7.43 (s, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.48 (s, 2H), 4.67 (s, 2H), 3.82 (s, 3H).

*2-(4-((2-carbamoylhydrazineylidene)methyl)-2-ethoxyphenoxy)acetic acid (8)*. Yield 190mg (67.6%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.95 (s, 1H), 10.08 (s, 1H), 7.73 (s, 1H), 7.41 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.47 (s, 2H), 4.69 (s, 2H), 4.09 (q, *J* = 6.6 Hz, 2H), 1.34 (t, *J* = 6.4 Hz, 3H).

*2,2'-((4-((2-carbamoylhydrazineylidene)methyl)-1,3-phenylene)bis(oxy))diacetic acid (9)*. Yield 106 mg (34.1%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.05 (s, 2H), 10.13 (s, 1H), 8.12 (s, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 6.52 (s, 2H), 6.38 (s, 2H), 4.76 (s, 2H), 4.69 (s, 2H).

*2,2'-((4-((2-carbamoylhydrazineylidene)methyl)-1,2-phenylene)bis(oxy))diacetic acid (10)*. Yield 260 mg (83.6%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.00 (s, 2H), 10.11 (s, 1H), 7.72 (s, 1H), 7.35 (s, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.47 (s, 2H), 4.76 (s, 2H), 4.71 (s, 2H).

*General procedure for the reaction of aldehydes 1-5 with malonodinitrile.*

1 Mmol of aldehydes **1-5** was dissolved while heating in 5 mL of isopropanol: water (5:1). Then, 1 mmol (80 mg) of malonodinitrile and 1 drop of piperidine were added to the mixture. The reaction was refluxed for 30 minutes before 1-2 mL of distilled water was added. The solution was then cooled to room temperature, and the resulting precipitate was filtered off. The filtered precipitate was washed twice with 5 mL of a 50% aqueous

methanol solution and three times with 5 mL of distilled water. The products were then dried at 50°C for 12 hours under reduced pressure.

*2-(4-(2,2-dicyanovinyl)phenoxy)acetic acid (11)*. Yield 123 mg (53.9%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.11 (s, 1H), 8.36 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 4.62 (s, 2H).

*2-(4-(2,2-dicyanovinyl)-2-methoxyphenoxy)acetic acid (12)*. Yield 155 mg (60.0%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.13 (s, 1H), 8.35 (s, 1H), 7.66 (s, 1H), 7.55 (d, *J* = 1.0 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 4.94 – 4.80 (m, 2H), 3.82 (s, 3H).

*2-(4-(2,2-dicyanovinyl)-2-ethoxyphenoxy)acetic acid (13)*. Yield 100 mg (36.7%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.32 (s, 1H), 7.64 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 4.71 (s, 2H), 4.06 (q, *J* = 7.2, 6.3 Hz, 2H), 3.45 (s, 1H+H<sub>2</sub>O), 1.37 (s, 3H).

*2,2'-((4-(2,2-dicyanovinyl)-1,3-phenylene)bis(oxy))diacetic acid (14)*. Yield 100 mg (33.2%). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 6.1 Hz, 1H), 6.65 (s, 1H), 4.75 (s, 2H), 4.66 (s, 2H), 3.51 (s, 2H+H<sub>2</sub>O).

*2,2'-((4-(2,2-dicyanovinyl)-1,2-phenylene)bis(oxy))diacetic acid (15)*. Yield 80 mg (39.6%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.32 (s, 1H), 7.68 – 7.36 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 1H), 4.80 (s, 2H), 4.67 (s, 2H), 3.75 (s, 2H+H<sub>2</sub>O).

#### *Alkylation of 3-hydroxybenzaldehyde.*

The reaction is carried out under the same conditions as in the general procedure for alkylation of hydroxybenzaldehydes (synthesis of compounds **1-5**).

*3-(carboxymethoxy)benzoic acid (16)*. Yield 9.5 g (49.6%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.04 (s, 2H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.18 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.74 (s, 2H).

## Conclusions

Successful alkylation of a number of hydroxybenzaldehydes with chloroacetic acid was carried out in order to introduce a functional carboxyl group into the molecule with yields of up to 67%. The resulting aldehyde derivatives were then subjected to further investigation by reacting them with semicarbazide and malonodinitrile in the presence of acidic and alkaline catalysts. The results showed that the obtained compounds mostly behave like classical arylaldehydes, forming corresponding condensation compounds. Notable exception was observed in the case of 3-hydroxybenzaldehyde, where the reaction with chloroacetic acid resulted in the formation of an alkylated benzoic acid instead of the corresponding aldehyde. This was attributed to the oxidation conditions of the reaction.

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