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Lactamomethylation of Phenols: Synthesis, in silico Study of Reactivity and Possible Applications †

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Abstract: Lactamomethylation of phenols with various substituents was provided by pyrrolidone, valerolactam, caprolactam and 4-phenylpyrrolidone derivatives. The structures of the target compounds were confirmed by IR and NMR study. The behavior of alkylphenols (2,4-di-tert-butyl- and thymol), diphenols (catechol and hydroquinone), formylphenol (vanillin) and hydroxybenzoic acids (salicylic and resorcylic) in this reaction was compared by quantum-chemical calculations. For several compounds, the energy of dissociation of ArO-H bond was calculated by quantum-chemical method to reveal their possible antioxidant activity. In addition, the ability of synthesized compounds to destruct cumene hydroperoxide was studied. It was estimated that 1-(4-hydroxy-5-isopropil-2-methylbenzyl)azepan-2-one and 1-(4-hydroxy-5-isopropil-2-methylbenzyl)pyrrolidin-2-one possess the best antioxidant effect, comparable to the one of industrial additive BHT.

Keywords: organic synthesis; phenolic derivatives; lactams; quantum-chemical calculations; antioxidant activity

1. Introduction

The struggle against materials' oxidation plays an important role in food, pharmaceutical and oil industrials. Oxidation is known to be a radical chain process that can be interrupted by antioxidants [1]. One of the best-known class of antioxidants is phenols, especially sterically hindered alkylphenols, which demonstrate high efficiency [2–4]. Though not being the sterically hindered, thymol (2-isopropyl-5-methylphenol) also possesses antioxidant and biological activity [5–8]. Previously it was shown that alkylphenols with heterocyclic fragments demonstrate high antioxidant potential as well [9–12]. In addition, heterocyclic moieties in these compounds can reveal anti-inflammatory and analgetic effects [13,14].

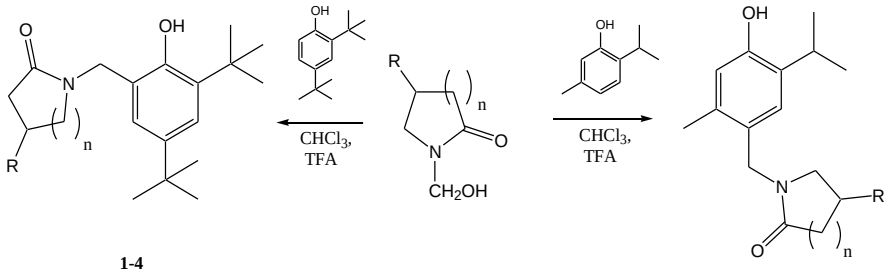
Basing on these works, we decided to synthesize several organic compounds with such heterocyclic substituents as lactams. Lactams and their derivatives are well known for their wide spectra of biological activity, such as nootropic and neuropsychotropic activities [15,16], anticonvulsant and anxiolytic effects [17,18].

As a result, we have successfully synthesized alkylphenols derivatives (of 2,4-di-tert-butylphenol and thymol) with the fragments of pyrrolidone, valerolactam, caprolactam and 4-phenylpyrrolidone [19]. In addition, we have obtained similar compounds for polyphenolic compounds, such as catechol and hydroquinone [20], and resorcinol, pyrogallol and phenolic acids [21].

In this work we discuss the selectivity of phenolic ring's substitution and some possible applications of the novel compounds.

2. Results and Discussion

As it was mentioned above, we have synthesized [19] eight compounds (1–8, Scheme 1) according to the method supposed in the work [22]. However, we also found that decreasing of the amounts of trifluoroacetic acid (TFA) used in this synthesis, in comparison to original method, led to the improvement of the target compounds' yields.



1-4

1: n=1, R= -H (53%);
2: n=2, R= -H (45%);
3: n=3, R= -H (61%);
4: n=1, R= -Ph (52%).

5-8

5: n=1, R= -H (50%);
6: n=2, R= -H (44%);
7: n=3, R= -H (65%);
8: n=1, R= -Ph (57%).

Scheme 1. Lactamomethylation of 2,4-di-tert-butylphenol and thymol.

Target compounds were obtained with acceptable yields. Their structure was confirmed by IR- and NMR study, and by elemental analysis. For the 2,4-di-tert-butylphenol there is only one possible path of substitution due to the steric factor. However, for thymol there are two expected ways of substitution—in *ortho*—or *para*- positions (the sixth and the fourth ones, respectively, in started compound) to the hydroxyl group. For the compounds 5 there are two peaks observed (6.70, 6.96 ppm) of aromatic protons in ^{1}H-spectrum (Figure 1), the both are singlets, which indicates that the *para*-substitution took place (otherwise, the AB-system of doublets should be expected). The same multiplicity of aromatic protons' signals reveals the same reaction's path for the other thymol derivatives 6–8.

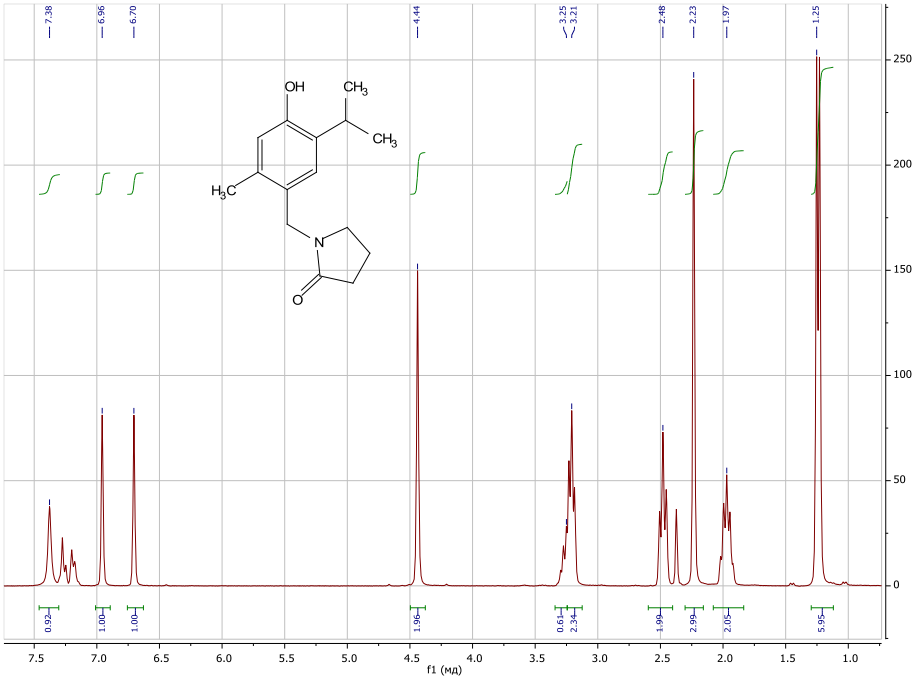


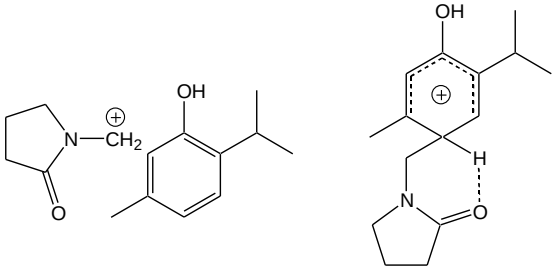
Figure 1. ^{1}H-NMR spectrum of the compound 5.

It is known from literature [23,24] that thymol can form products of Mannich reaction either of *ortho*- or *para*- substitution, but there is no systematical study of the factors influencing on the way of

the reaction. Only one explanation was given [24] that it depends on the structure of aminomethyl fragment. Noteworthy, that the conditions of aminomethylation reaction were the same in this work, although various products were obtained, so we can suppose that solvation doesn't play an important role in the orientation of the electrophile's attack.

We decided to prove our suggestion that the way of the reaction depends on the stability of the forming intermediate σ-complex. Thus, a stable, low-energy σ-complex results in a high reaction rate, while a high-energy σ-complex represents a low reaction rate (according to Hammond's posulate).

Quantum-chemical calculations for compound 5 showed, that the complex with the electrophile, formed in the fourth position (*para-*) is more stable than one in the sixth (*ortho-*), as its energy is 6.5 kJ/mol lower (Scheme 2). Noteworthy, that the minimum of energy for the intermediate 5a (for the *ortho-* substitution) corresponds not to the σ-complex, but to the π- one, which doesn't lead to the formation of the σ-bond, and, thus, to the formation of the product. We can assume that the energy of the appropriate σ-complex is even higher. The complex 5b is also stabilized by intramolecular hydrogen bond, as it is shown on the scheme:

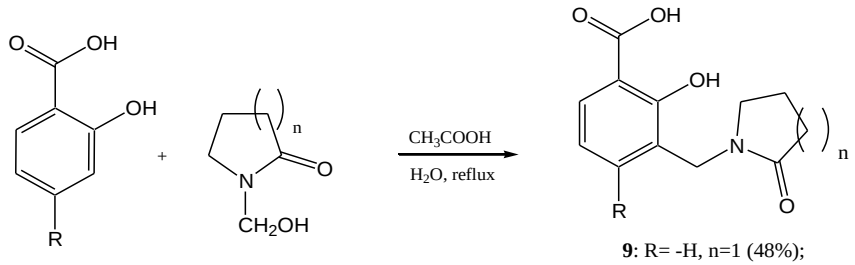


5a **5b**

E= -789.373412 E = -789.375873

Scheme 2. The structure of the two possible intermediates, 5a and 5b. The free energy ΔG values (E, a.u.) are shown for each particle.

The similar situation is observed for a range of our compounds. Thus, for salicylic and β-resorcylic acids there are several possible isomeric products. It was shown [21] that in case of these acids the lactamomethylation reaction took place in the third position (Scheme 3).

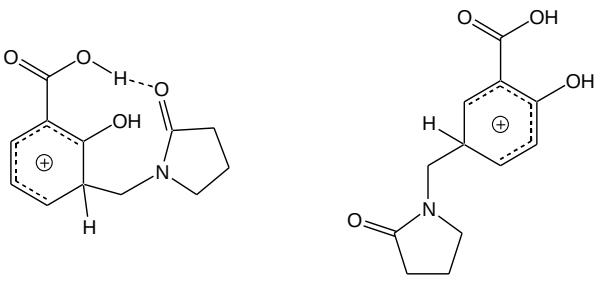


9: R= -H, n=1 (48%);
10: R= -OH, n=1 (62%);
11: R= -OH, n=3 (41%).

Scheme 3. Lactamomethylation of salicylic and resorcylic acids.

As expected, the quantum-chemical calculations are in agreement with the experimental data (Scheme 4). For salicylic acid complex with electrophile in the third position is more preferable than one in the fifth, as the latter has the energy 6.5 kJ/mol higher. In case of resorcylic acid, the difference in energies is even more significant, as the complex in the third position has the energy 16.2 kJ/mol lower than other possible isomer.

Both acids form hydrogen bonds in case of substitution in the third position, as it can be seen on the scheme:

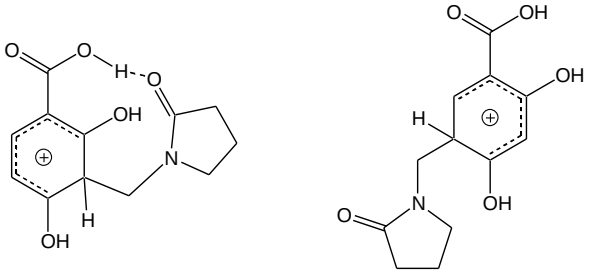


9a

E= -820.792221

9b

E= -820.789754



10a

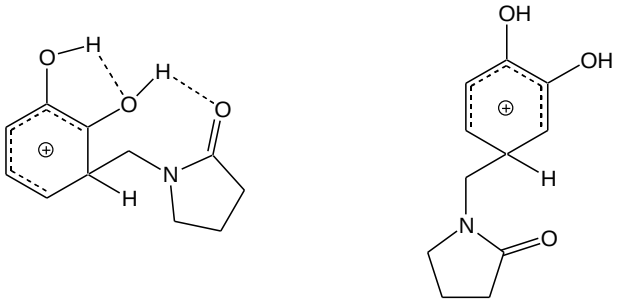
E= -896.025973

10b

E= -896.019805

Scheme 4. The structure of the pairs of possible intermediates **9a** and **9b**, **10a** and **10b**. The free energy ΔG values (E, a.u.) are shown for each particle.

The same observations were made for catechol derivatives [20] (Scheme 5). Hydrogens in intermediate 11a forms strong hydrogen bonds with nearby oxygens. It decreases the energy, and this intermediate is more stable, as its energy gain is equal 60.1 kJ/mol.



11a

E= -707.480898

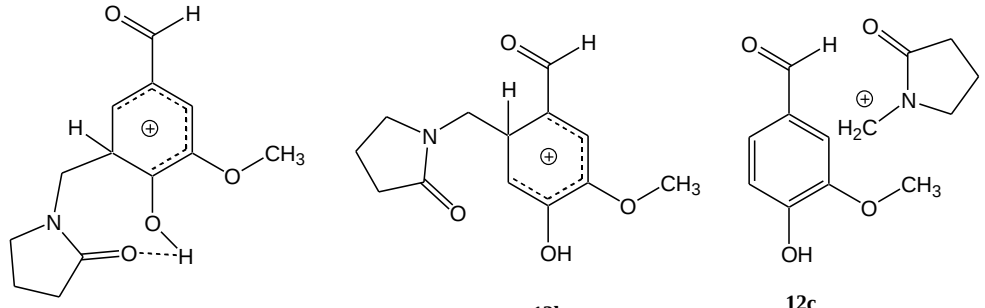
11b

E= -707.457994

Scheme 5. The structure of the possible intermediates **11a** and **11b**. The free energy ΔG values (E, a.u.) are shown for each particle.

We also decided to predict the way of substitution for a phenolic compound and then to provide lactamomethylation. We chose vanillin because of its commercial availability and because of presence of several substituents in its ring. Although the fifth position was expected to be substituted by lactamomethyl moiety, the non-cooperative orientational interaction of formyl-, hydroxyl- and methoxy- groups could give surprising result.

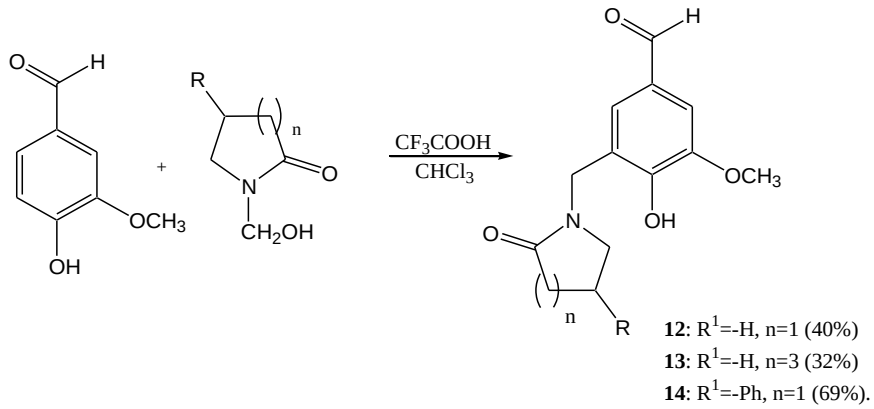
Quantum-chemical calculations demonstrate that the most stable is the complex 12a formed if the substitution in the fifth position take place (Scheme 6). Two other intermediates 12b and 12c both have higher energies (24.5 kJ/mol and 27.5 kJ/mol, respectively). The first complex is stabilized by strong hydrogen bond (about 1 Å). In case of intermediate 12c we can see that the energy minimum corresponds to the π-complex.



12a E = -860.036412 **12b** E = -860.027090 **12c** E = -860.025956

Scheme 6. The structure of the possible intermediates **12a, 12b** and **12c**. The free energy ΔG values (E, a.u.) are shown for each particle.

We succeeded in further synthesis of several vanillin derivatives (Scheme 7). Three compounds have been obtained, their structures were confirmed by IR and NMR investigations. In the ^{1}H-spectrum of the compound 13 AB-system of doublets is observed for aromatic protons. The value of the coupling constant (about 1.6 Hz) proves that it corresponds to the protons separated with four bonds (^{4}J).



12: R^1=-H, n=1 (40%)
13: R^1=-H, n=3 (32%)
14: R^1=-Ph, n=1 (69%).

Scheme 7. Lactamomethylation of vanillin.

To demonstrate the antioxidant activity of several synthesized compounds, we primary had performed quantum-chemical calculation [19] to evaluate the dissociation energy of the ArO-H bond in alkylphenols, according to the work [25]. The results are shown in the Table 1.

Table 1. Dissociation energy (D) of the ArO-H bond in phenols.

Compound	D(ArO-H), kcal/mol
Thymol	82.0
2,4-di-tert-butylphenol	82.5
1	82.8
2	83.2
3	88.9
4	82.6
5	78.8
6	78.5
7	78.7
8	78.9
BHT	75.4

The lower the energy is, the higher is the antioxidant potential, as the bond demonstrates the ability to break. As we can see, our compounds can demonstrate the antioxidant activity comparable to the industrial additive BHT (butylated hydroxytoluene). These results can be proved by experimental evaluation of the antioxidant activity, which has been performed [26] by the investigation of the ability of target compounds to destruct cumene's hydroperoxide. We found, that compounds 5 and 7 demonstrate the highest antioxidant activity among the studied compounds, decreasing the concentration of hydroperoxide almost thrice in four hours. It is comparable with the result shown by BHT. This data are in agreement with the calculations results, so we can infer that this method is suitable for predicting of antioxidant activity of phenols.

3. Materials and Methods

3.1. Quantum-Chemical Calculations

All quantum-chemical calculation were performed with the help of Gaussian09 software [27]. To evaluate the stability of intermediates in lactamomethylation reaction the functional M06-2X was chosen with the 6-311G(d,p) basic set. Gibbs energies are given in hartree units, which can be converted to kJ/mol by multiplying them on 2625.5. The calculations of the intermediates' stability were made only for complexes with pyrrolidone derivative to reduce the computation time.

Dissociation energy of the ArO-H bond were performed by using semi-empirical method PM6.

3.2. Synthesis of the Target Compounds

The reagents and solvents were commercial products (Acros and Sigma-Aldrich). 1-hydroxymethylpyrrolidin-2-one, 1-hydroxymethylazepan-2-one, 1-hydroxymethyl-4-phenylpyrrolidin-2-one, used as the starting compounds were synthesized as described previously [19,20]. The synthesis of 2,4-di-tert-butylphenol and thymol derivatives have been also described previously [19].

The melting points were determined on a Stuart SMP30 instrument. The IR spectra were recorded on a Agilent Carry 600 spectrometer equipped with an attenuated total reflectance (ATR) device. The ^{1}H and ^{13}C NMR spectra were measured at room temperature on Bruker Avance II 300 spectrometers (^{1}H, 300 MHz; ^{13}C, 75 MHz) in $CDCl_3$; Me_4Si was used as the internal standard. Elemental analysis was performed using Vario MicroCube apparatus.

Synthesis of lactamomethyl derivatives of vanillin (general procedure). A solution of vanillin (1.52 g, 0.01 mol), lactamomethylating reagent (N-hydroxymethyllactam, 0.01 mol), and trifluoroacetic acid (8 mL) in chloroform (20 mL) was refluxed for 48 h. Then the reaction mixture was cooled and poured into toluene (75 mL). The resulting solution was washed with an aqueous sodium bicarbonate solution to neutral pH. The organic layer was separated using a separatory funnel, dried over calcinated magnesium sulfate, and rotary evaporated. The residue was dissolved in ethylacetate and the product was isolated by column chromatography (eluent ethylacetate or the mixture of ethylacetate:hexane = 2:1). Eluent was rotary evaporated, crude product was filtered off and recrystallized from acetonitrile.

3.2.1. 4-Hydroxy-3-Methoxy-5-[(2-Oxopyrrolidin-1-yl)Methyl]Benzaldehyde 12

After column chromatography (ethylacetate) on silicagel 1,01 g (40%) of brown crystals was obtained. M.p. 144 °C (acetonitrile). IR ν/cm^{-1}: 1686, 1650 (C=O).

^{1}H NMR ($CDCl_3$, δ, ppm, $^{3}J_{HH}$, Hz): 1.92 (p, 2H, 4-CH_2 in lactam, J = 7.45); 2.28 (t, 2H, 3-CH2 in lactam, J = 8.20); 3.28 (t, 2H, 5-CH2 in lactam, J = 6.71); 3.87 (s, 3H, OCH_3); 4.37 (s, 2H, $ArCH_2$); 7.28 (s, 1H, Ar); 7.36 (s, 1H, Ar); 9.77 (bs, 1H, OH); 10.09 (bs, 1H, −CHO).

^{13}C NMR ($CDCl_3$, δ, ppm): 17.94 (4-CH_2 in lactam); 30.69 (C(O)$\underline{C}H_2$); 40.94 (Ar$\underline{C}H_2$N); 47.22 (N$\underline{C}H_2$ in lactam); 56.46 (ArO$\underline{C}H_3$); 110.16; 124.26; 125.58; 128.57; 148.44; 151.10 (6 Ar); 174.90; 191.68 (2 C=O).

Calc., %: C 62.64, H 6.07, N 5.62. Found, %: C 61.10, H 6.00, N 5.45. $C_{13}H_{15}NO_4$.

3.2.2. 4-Hydroxy-3-Methoxy-5-[(2-Oxoazepan-1-yl)Methyl]Benzaldehyde 13

After column chromatography (ethylacetate:hexane = 2:1) on silicagel 0,89 g (32%) of white powder was obtained. M.p. 113 °C (acetonitrile). IR ν/cm^{-1}: 1678, 1601 (C=O).

^{1}H NMR ($CDCl_3$, δ, ppm, $^{3}J_{HH}$, Hz): 1.48–1.70 (m, 6H, 4,5,6-CH_2 in lactam); 2.51 (m, 2H, 3-CH_2 in lactam); 3.40 (m, 2H, 7-CH_2 in lactam); 3.87 (s, 3H, OCH_3); 4.46 (s, 2H, $ArCH_2$); 7.25 (d, 1H, $^{4}J_{HH}$ = 1.68, Ar); 7.31 (d, 1H, $^{4}J_{HH}$ = 1.68, Ar); 9.73 (bs, 1H, OH); 10.33 (bs, 1H, COH).

^{13}C NMR ($CDCl_3$, δ, ppm): 22.98; 27.61; 29.74; 36.36; 48.97 (Ar$\underline{CH_2}$N); 50.11 (N$\underline{CH_2}$ in lactam); 56.16 (ArO$\underline{CH_3}$); 110.81; 123.13; 127.20; 128.44; 149.47; 152.19 (6 Ar); 178.51; 190.54 (2 C=O).

Calc., %: C 60.97, H 6.91, N 5.05. Found, %: C 60.79, H 7.039, N 4.68. $C_{15}H_{19}NO_4$.

3.2.3. 4-Hydroxy-3-Methoxy-5-[(2-oxo-4-Phenylpyrrolidin-1-yl)Methyl]Benzaldehyde 14

After column chromatography (ethylacetate:hexane = 2:1) on silicagel 2,26 g (69%) of yellow powder was obtained. M.p. 148 °C (acetonitrile). IR ν/cm^{-1}: 1662, 1591.

^{1}H NMR ($CDCl_3$, δ, ppm, $^{3}J_{HH}$, Hz): 2.59–2.93 (AB-system of doublets with $^{2}J_{HH}$ = 17.02, in which each line gives a doublet because of coupling $^{3}J_{HH}$ = 8.97, 2H, 3-C CH_2 in lactam); 3.42–3.86 (m, 3H, 4,5-C in lactam); 3.95 (s, 3H, OCH_3); 4.55 (s, 2H, $ArCH_2$); 7.15–7.38 (m, 7H, Ar); 8.51 (bs, 1H, OH); 9.79 (bs, 1H, -CHO).

^{13}C NMR ($CDCl_3$, δ, ppm): 37.38 (4-CH_2 in lactam); 38.40 (C(O)$\underline{CH_2}$); 42.17 (Ar$\underline{CH_2}$N); 54.79 (N$\underline{CH_2}$ in lactam); 56.26 (ArO$\underline{CH_3}$); 109.66; 122.33; 126.62; 127.24; 127.42; 128.92; 129.02; 141.73; 148.69; 150.97 (12 Ar); 175.24; 190.53 (2 C=O).

Calc., %: C 70.14, H 5.89, N 4.31. Found, %: C 69.54, H 6.431, N 4.29. $C_{19}H_{19}NO_4$.

4. Conclusions

The ability to predict the possible reaction's way in electrophilic substitution of phenols by quantum-chemical calculations was shown. The accuracy of described method was confirmed by the synthesis of three novel vanillin derivatives. Their structures were investigated by IR and NMR analyses. Also, we have demonstrated that quantum-chemical calculations are suitable for prediction of the antioxidant activity of the phenolic compounds, as experimental data, obtained from the test on destruction of cumene's hydroperoxide were in agreement with the calculations results.

Author Contributions: S.V., concept, performing chemical synthesis and purification, spectroscopy experiments and quantum-chemical calculations, analyzing spectroscopy data, writing manuscript. O.P., performing antioxidant activity experiment, analyzing data. V.K., concept, supervision, writing manuscript. All authors have read and agreed to the published version of the manuscript.

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