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Research article

Novel synthesis of oxoacetamides *via* reaction of salicylaldehyde and isocyanide under mild reaction condition

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ABSTRACT

A convenient procedure for the formation of oxoacetamides derivatives is reported *via* the reaction of salicylaldehyde and alkyl isocyanide in a simple process without the use of any catalyst or metal promoters in DCM at room temperature. The structure of all obtained derivatives were determined by elemental and spectral analyses. In this reaction, 1,3-dioxine-4,4-dicarboxamide was obtained as minor product. This process offers considerable advantages such as the simplicity of reaction, regioselectivity, and the use of commercially available materials.

1. Introduction

α-Ketoamides, as structurally privileged moieties, are widely distributed in many natural compounds including the immunosuppressant drugs FK-506 and rapamycin [1, 2] and the α-ketoamide groups have been evaluated as a pharmacophore in many clinically important drugs and drug candidates due to their various biological, pharmacological and therapeutic properties including anti-viral [3], anti-HIV [4], anti-tumor [5], anti-inflammatory [6], anti-bacterial [7] (Figure 1). Furthermore, the α-ketoamide scaffolds have polyfunctional groups and represent two potential nucleophilic reaction centers, as well as two electrophilic centers allowing for selection of specific activation modes (Figure 2) [2,8]. Accordingly, these moieties also used as useful synthetic intermediates and synthons in functional group conversion and different synthetic methods for the formation of diverse heterocyclic scaffolds including indoles, oxindoles, β-lactams, and quinolones, etc [9, 10, 11]. In addition, the great electrophilicity property of the α-keto group provides exceptional adducting opportunities for the synthesis of a hemiketal or hemithioketal products contain the –OH or –SH group present in the proteolytic enzymes such as serine or cysteine protease, respectively and in result makes the inhibition of proteases possible [12]. The synthesis of these types of products could result in preparation of therapeutic potentially novel drugs for the therapy of different diseases [13].

Due to the chemical and biological value of α-ketoamides, various synthetic methods have been introduced and reported for the synthesis of this class of products over the past decades [2, 14, 15, 16]. The methods that have been introduced so far for the synthesis of this valuable scaffold describe as following and an overview of the newest and important methods is outlined in Scheme 1. In 2003, Chen et al. described a one-pot microwave-assisted condensation between acyl chloride and isonitrile followed by $CaCO_3$-mediated hydrolysis to produce α-ketoamides [13]. In 2010, Mossetti et al. reported the synthesis of α-ketoamides in good efficiencies *via* the reaction of acyl chlorides and α-isocyanoacetamides in dichloromethane using triethylamine to acquire 2-acyl-5-aminooxazoles that followed by acid hydrolysis leads to the final product [12]. In 2014, Guin et al. reported the formation of *N*-monosubstituted α-ketoamides *via* decarboxylation of α-oxocarboxylic acids undergoes a palladium-catalyzed chemoselective insertion into organic cyanamides [17]. In 2015, Du et al. developed a method for the synthesis of desired α-ketoamides in high yields with excellent chemoselectivity based on Pd-catalyzed double carbonylation of aryl iodides with secondary or primary amines under atmospheric CO pressure condition. This reaction performed successfully even at room temperature conditions without the use of ligands and additives [18]. In 2015, Zhang and coworkers developed a novel synthetic procedure for the formation of α-ketoamides *via* coupling reactions between *N*,*N*-dialkylformamides and phenylacetic acids catalyzed by Cu_2O [19]. In 2016, Ramanathan et al. reported a solvent- and metal-free process for the synthesis of α-ketoamides *via* in situ formation of aryl ketones from easily accessible ethylarenes that in the next step amidation occurs with various amines. This sequential

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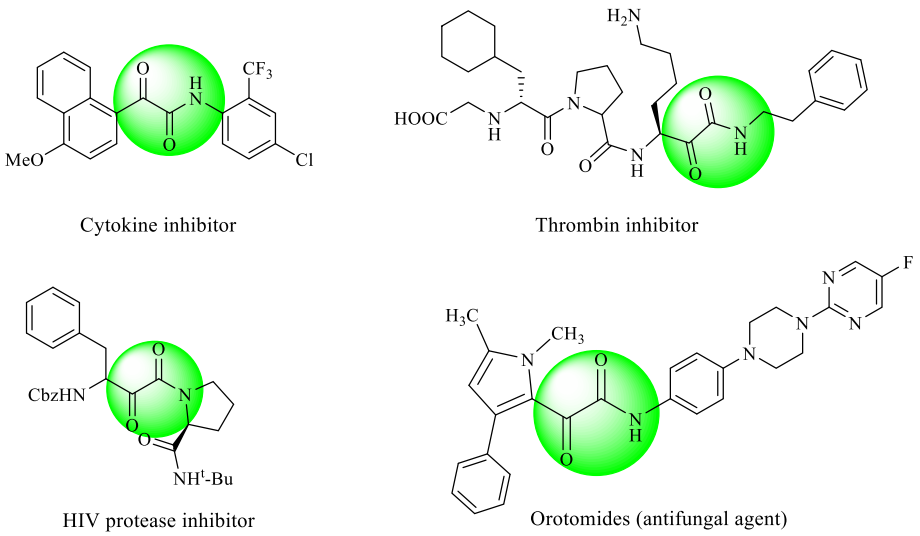


Figure 1. Structure of some biologically active compounds containing α-ketoamide framework.

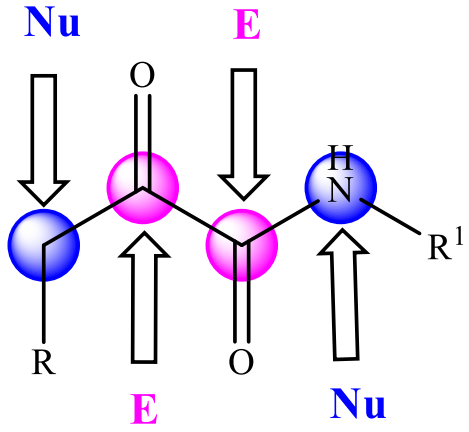


Figure 2. Potential reaction centers in α-ketoamides (Nu = nucleophile, E = electrophile).

oxidation protocol includes catalytic I_2–pyridine–TBHP (*t*-butyl hydroperoxide) mediated oxidative benzylic carbonylation followed by NaI–TBHP mediated oxidative amidation [20]. In 2017, Wang et al. reported the synthesis of a class of primary-, secondary-, and tertiary-α-ketoamides through the reaction of methyl ketones and inexpensive readily available amine/ammonium salts using non-metal catalyst nBu_4NI. These reactions performed smoothly under mild conditions and TBHP was applied as an oxidant [21]. In 2019, Zhang and Wang showed that β-ketonitriles and primary amines readily react together *via* an oxidative decyanation amidation process leads to the formation of α-ketoamides. This reaction proceeds by applying hydrogen peroxide sodium carbonate adduct ($Na_2CO_3.1.5H_2O_2$), K_2CO_3, and 1,4-dioxane without using any catalyst [22]. In 2019, Zhou and coworkers described a new and efficient visible light-promoted procedure for selective synthesis of α-ketoamides under mild reaction conditions through the reaction between primary amines and benzoylacetonitrile. In this protocol different anilines and benzoyl acetonitrile were used in order to increase structural diversity of products, and reaction performed through visible-light-induced electron transfer and oxidative coupling [23].

Although, published papers in recent years show various protocols for the synthesis of products with analogous structures but introduce of an efficient and practical procedure for the synthesis of these pharmaceutical compounds from commercial chemicals is still seems essential. In the following of our research interests in isocyanide reactions [24, 25], we would like to report here a new and atomic economic process for the synthesis of oxoacetamides *via* reaction of salicylaldehyde and isocyanide under mild reaction condition.

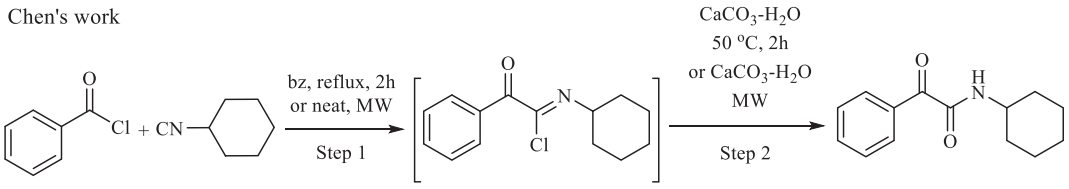
2. Results and discussion

In the view of above-mentioned chemical and biological importance of α-ketoamides, we were interested to synthesize oxoacetamides core in a molecular framework by the reaction of salicylaldehyde **1** and isocyanide **2** as a novel methodology. Due to this, a new class of *N*-cyclohexyl-2-(2-hydroxyphenyl)-2-oxoacetamides **3** were prepared in 57–72% yields instead of the expected 2-(cyclohexylamino) benzofuran-3-ol **5**. The reaction carried out in dichloromethane (DCM) as an organic solvent and at ambient temperature without any energy consumption and without the use of any catalyst (Scheme 2).

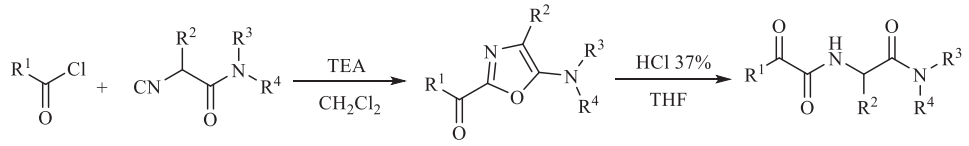
On the basis of the chemistry of α-addition of aldehyde and water to isocyanide [25, 26] a possible mechanism for the synthesis of the products **3a-g** is proposed in Schemes 3. In the first step, it is reasonable to assume that the formation of intermediate **6** happens *via* the addition of salicylaldehyde **1** to isocyanide **2**. The intermediate **6** is converted into **7** by attack the H_2O to nitrilium ion. Then protonation by the H-shift occurs, and the keto-enol tautomerization followed by oxidation which results in desired product **3** (Scheme 3). It is expected that oxygen in the airflow or one of the substances in the reaction act as an oxidizer, but based on the previous works [25, 26] the hydroxy group on aromatic moiety is likely to be effective in oxidizing of benzylic hydroxyl group. Apparently, the hydroxy group in the oxidation process, by transferring electrons to ortho-carbon, enriches the electron cloud of the benzyl position and facilitates the process of oxidation of the benzylic hydrogen. It is also noteworthy that we performed the process under argon as an inert gas and we obtained α-ketoamide product, which confirms the role of the hydroxy group in the oxidation process. Furthermore, based on the previous papers [25, 26], we expect that the Keto-enol tautomerization occurs prior to its oxidation and the tautomerization process has been done similar to Mumm rearrangement.

But in the case of the formation of minor product 4, the synthesis of this heterocycle can occur *via* the different process (Scheme 4). After the formation of the product **3** similar to the mechanism illustrated in Scheme 3, the intermediate **9** forms through the addition of another molecule of isocyanide **2** to product **3**, which undergoes a hydrolysis in presence of H_2O produce intermediate **10**. In the following, acetal formation occurs by condensation of diols of intermediate **10** with ketone of another molecule of salicylaldehyde **1** (Scheme 4).

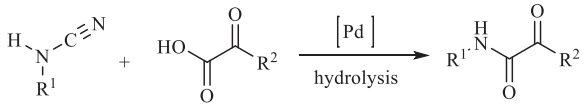
Chen's work



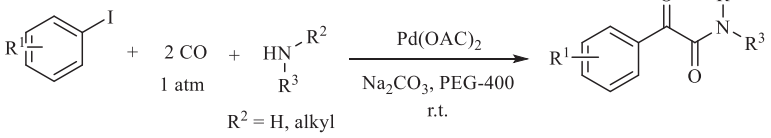
Mossetti's work



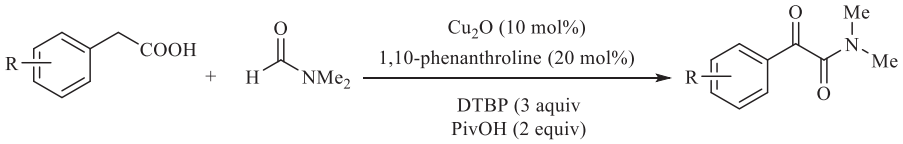
Guin's work



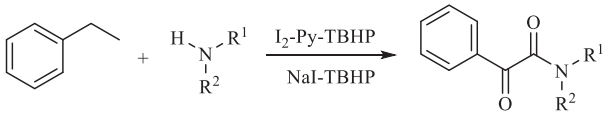
Du's work



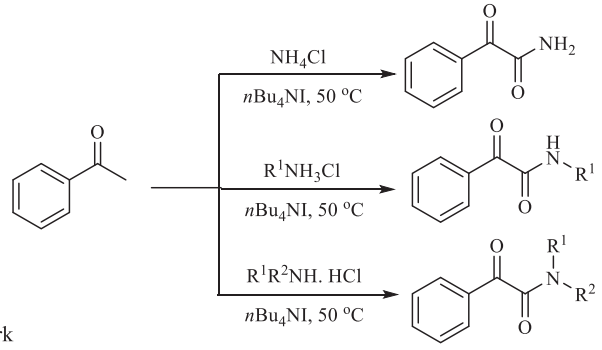
Zhang's work



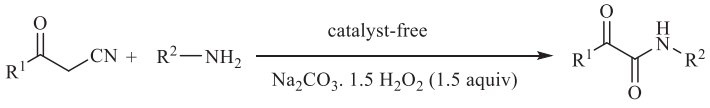
Ramanathan's work



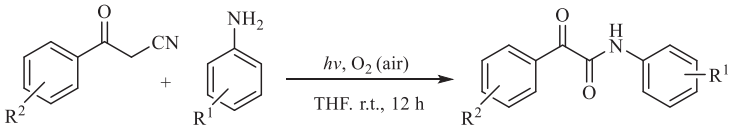
Wang's work



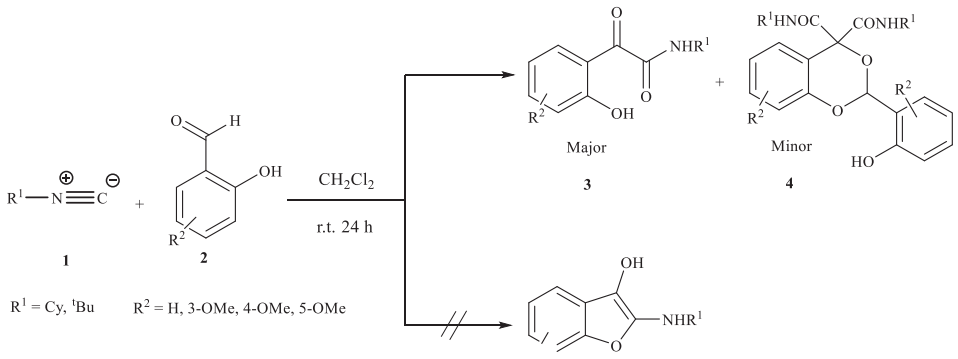
Zhang and Wang's work



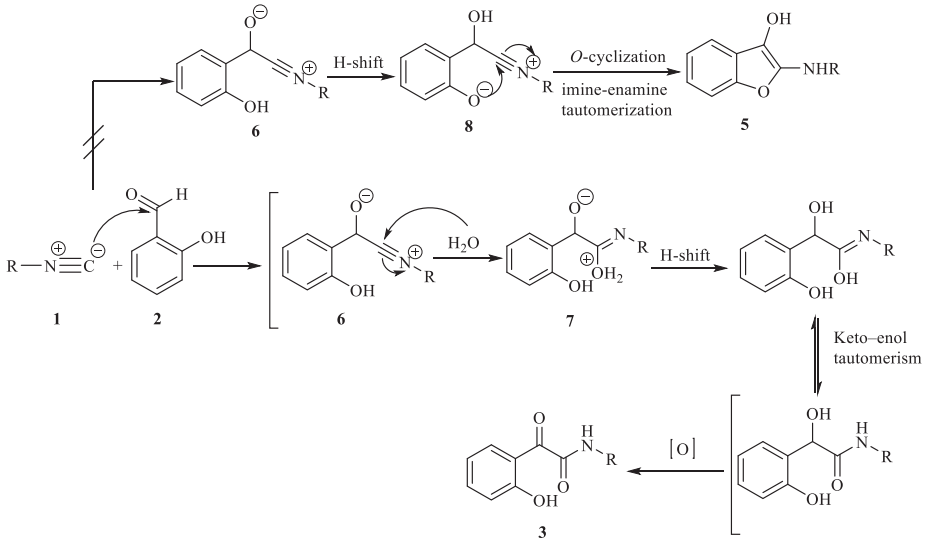
Zhou's work



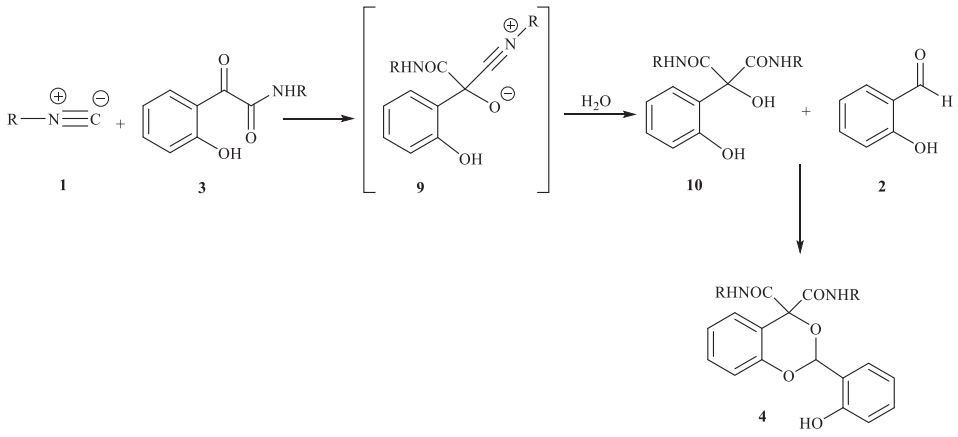
Scheme 1. Previous approaches to the synthesis of α-ketoamides.



Scheme 2. General scheme for the synthesis of products **3** (Major) and **4** (Minor).



Scheme 3. Proposed mechanism for the synthesis of **3**.



Scheme 4. Proposed mechanism for the synthesis of **4**.

As illustrated in Figure 3, various functional groups exist in aryl moiety such as methoxy group in *ortho*, *meta* and *para* positions, and in isocyanide scaffold which result in structural diversity of product and almost all of them did work well with various efficiency.

The structures of the separated crude compounds were clearly confirmed by their IR, ^{1}H, ^{13}C NMR, mass spectra and elemental analyses. The mass spectra of derivative **3d** indicated molecular ion peak at *m/z* 247 value, which matches to the offered structure of the product. The ^{1}H NMR spectrum of **3a** demonstrated one multiplet for methylene protons (δ 1.48–2.01 ppm), one singlet for methyl protons (δ 3.80 ppm), one multiplet for methine proton (δ 3.84–3.90 ppm), aromatic range of the spectrum (δ 6.93, 6.99, 8.10 ppm) for the aromatic core, broad line for NH group (δ 7.02 ppm), and one singlet for OH (δ 11.90 ppm). The ^{1}H-decoupled ^{13}C NMR spectrum of **3d** displayed 13 separated peaks. One signal at 188.7 ppm, which was specified as one carbonyl group, 161.3 ppm for carbonyl group in amide moiety, and the characteristic signals of C–OH and CH–N were observed at 158.7 and 48.9 ppm respectively which verified the selective synthesis of **3d** (Figure 4).

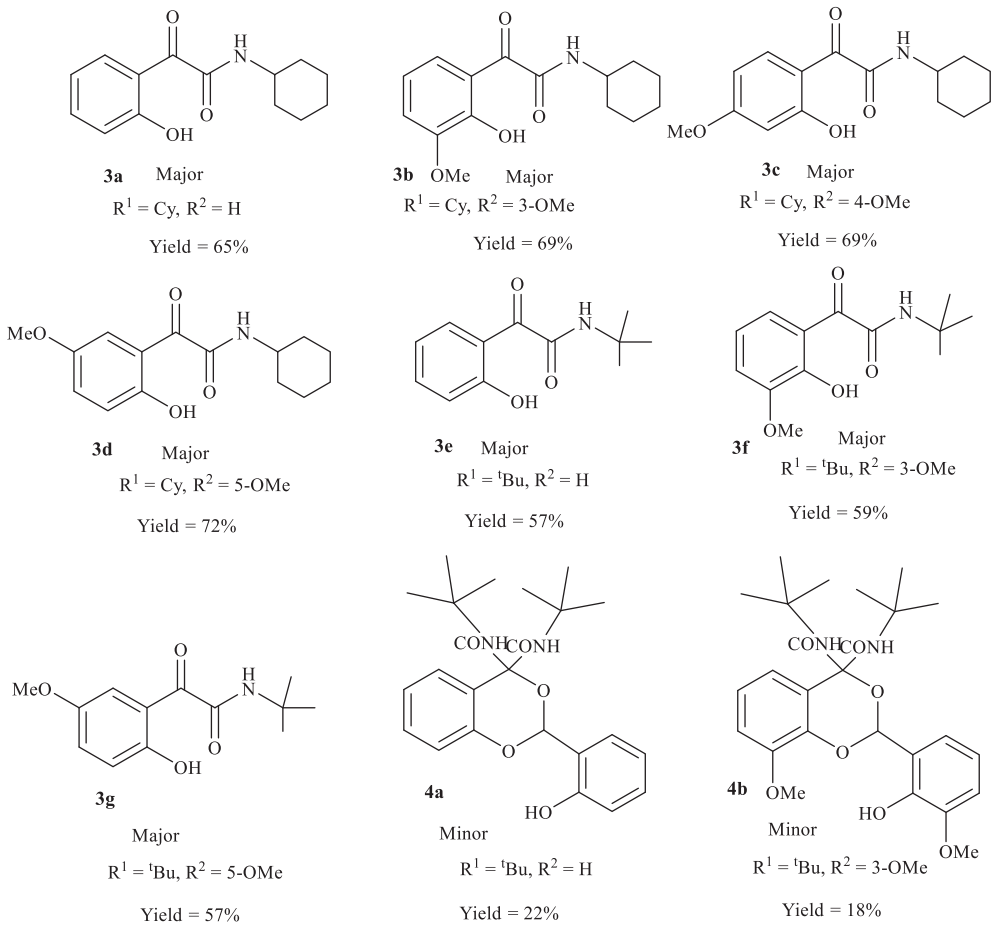


Figure 3. Substrate scope study of oxoacetamide (major product) and dicarboxamide (minor product).

3. Conclusion

The synthesis of a series of *N*-cyclohexyl-2-(2-hydroxyphenyl)-2-oxoacetamide by the coupling of salicylaldehyde with isocyanide in DCM solvent under ambient temperature condition is presented. Indeed, this paper reports a straightforward procedure with considerable characteristics for the synthesis of drug-like structure molecules and useful synthons in the synthesis of heterocycles with functional group diversity. The selectivity synthesis of *N*-cyclohexyl-2-(2-hydroxyphenyl)-2-oxoacetamide is confirmed from the fact that the other product 2-(cyclohexylamino)benzofuran-3-ol is not obtained even in traces during the process.

4. Experimental

4.1. General

The 2-hydroxybenzaldehyde derivatives, isocyanide derivatives and solvents were purchased from Sigma Aldrich and used without further purification. IR spectra were measured with, Bruker Tensor 27 spectrometer. NMR spectra were recorded with a Bruker DRX-300 Avance instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) with $CDCl_3$ as solvent. Chemical shifts are expressed in parts per million (ppm), and coupling constant (*J*) are reported in hertz (Hz). Mass spectra were recorded with an Agilent 5975C VL MSD with Triple-Axis detector operating at an ionization potential of 70 eV. Elemental analyses for C, H and N were performed using a Heraeus CHNO-Rapid analyzer. Melting points were measured with an electrotherma1 9100 apparatus.

4.2. General procedure for the synthesis of N-cyclohexyl-2-(2-hydroxyphenyl)-2-oxoacetamide 3a

To a magnetically stirred 2-hydroxybenzaldehyde (0.122 g, 1 mmol) in DCM (8 mL) in a 100 mL round-bottomed flask, cyclohexyl isocyanide (124 μL, 1 mmol) was added *via* a micropipette at laboratory ambient temperature. The reaction flask was placed on a magnetic stirrer for an overnight, and after completion, it was controlled by TLC, then the solvent was evaporated under reduced pressure conditions, and the residual oily material was purified by silica gel column chromatography using a mixture of hexane-EtOAc solvents as eluent. The product **3** and **4** as a major product in the form of yellow solid and a minor product in the form of yellow oil were obtained respectively.

4.3. Supplementary material

General remarks, structure of all products, copies of ^{1}H, ^{13}C NMR spectrum, IR spectra, and Mass spectra of selected products are provided.

***N*-cyclohexyl-2-(2-hydroxyphenyl)-2-oxoacetamide (3a)**: Yellow powder: m.p.: 73–77 °C, yield 0.160 g (65%); IR (KBr) ($\bar{\upsilon}_{max}$): 3300 (OH), 3200 (NH), 1634 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, CDCl3): δ = 1.20–2.01 (10H, m, $5CH_2$), 3.81(1H, m, CNH), 6.88–7.00 (2H, m, Ar–H), 7.06 (1H, br s, NH), 7.49–7.55 (1H, m, Ar–H), 8.48–8.51 (1H, m, Ar–H), 12.02 (1H, s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.7 ($2CH_2$), 25.3 (CH_2), 32.5 ($2CH_2$), 48.8 (CNH, 118.7, 119.5, 133.6), 138.0 (CH_{arom}), 161.4 (C–O), 163.4 (C=O), 190.1 (C=O); MS (EI, 70 eV): *m/z* (%) = 247 (15) [$M^{\cdot+}$], 135 (90), 121 (100). Anal. Calcd for $C_{14}H_{17}NO_3$ (247.12): C, 68.00; H, 6.93; N, 5.66. Found C, 68.38; H, 6.87; N, 5.45.

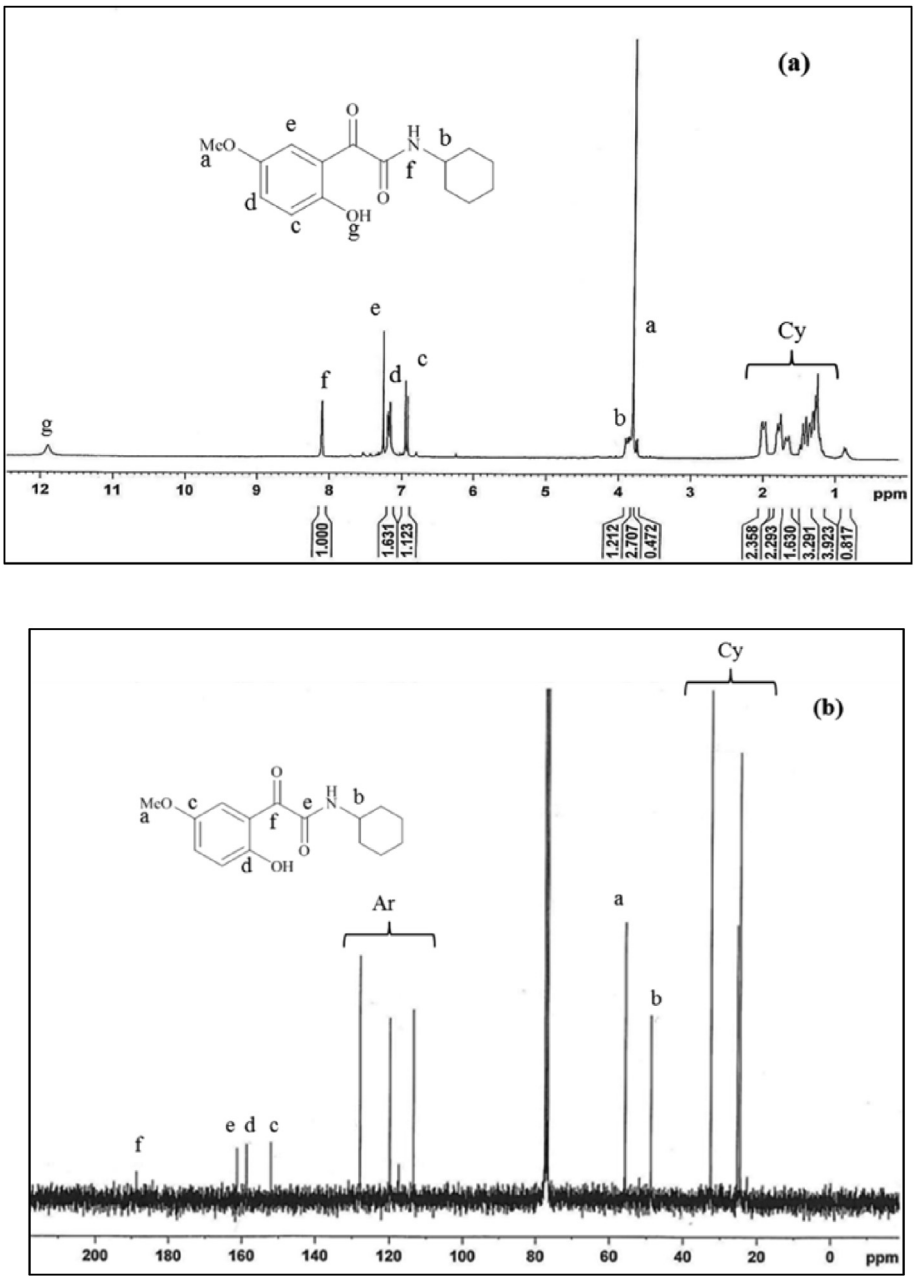


Figure 4. (a) The ^{1}H NMR spectrum of 3d and, (b) ^{13}C NMR spectrum of 3d.

***N*-cyclohexyl-2-(2-hydroxy-3-methoxyphenyl)-2-oxoacetamide (3b):** Red powder: m.p.: 95–99 °C, yield 0.191 g (69%); IR (KBr) ($\bar{\upsilon}_{max}$): 3400 (OH), 1642 (C=O), 1437 (C=C), 1255 (C–O, C–N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.97 (10H, m, 5CH_2), 3.88 (1H, m, CNH), 3.91 (3H, s, OMe), 7.1 (1H, br s, NH), 7.23 (1H, t, $^{3}J_{HH}$ = 8.3 Hz, Ar–H), 7.74 (1H, d, $^{3}J_{HH}$ = 8.1 Hz, Ar–H), 7.94 (1H, d, $^{3}J_{HH}$ = 8.39 Hz, Ar–H), 11.92 (1H, br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.08 (2CH_2), 29.7 (CH_2), 34.1 (2CH_2), 53.0 (CNH), 56.3 (OMe), 114.0, 118.0, 123.9 (CH_{arom}), 118.0, 145.0, 152.9 (3C), 175.6 (C=O), 191.3 (C=O). Anal. Calcd for $C_{15}H_{19}NO_4$ (277.13): C, 64.97; H, 6.91; N, 5.05. Found C, 64.69; H, 6.70; N, 5.34.

***N*-cyclohexyl-2-(2-hydroxy-4-methoxyphenyl)-2-oxoacetamide (3c):** Pale yellow powder: m.p.: 97–100 °C, yield 0.190 g (69%); IR (KBr) ($\bar{\upsilon}_{max}$): 3300 (OH), 3200 (NH), 1640 (C=O), 1215 (C–O, C–N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47–1.99 (10H, m, 5CH_2), 3.76 (1H, m, CNH), 3.83 (3H, s, OMe), 6.41–6.49 (2H, m, Ar–H), 7.11 (1H, br s, NH), 8.62 (1H, d, $^{3}J_{HH}$ = 9 Hz, Ar–H), 12.52 (1H, br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.7 (2CH_2), 25.4 (CH_2), 32.6 (2CH_2), 48.6 (CNH), 55.7 (OMe), 100.8, 108.8, 115.0 (CH_{arom}), 167.7 (C=O). Anal. Calcd for $C_{15}H_{19}NO_4$ (277.13): C, 64.97; H, 6.91; N, 5.05. Found C, 65.12; H, 6.98; N, 5.30.

***N*-cyclohexyl-2-(2-hydroxy-5-methoxyphenyl)-2-oxoacetamide (3d):** Yellow powder; m.p: 88–91 °C, yield 0.199 g (72%); IR (KBr) ($\bar{\upsilon}_{max}$): 3400 (OH), 3290 (NH), 3000 (=CH), 1657 (C=O), 1165 (C–O, C–N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48–2.01 (10H, m, 5CH_2), 3.80 (3H, s, OMe), 3.84–3.90 (1H, m, CNH), 6.93 (1H, d, $^{3}J_{HH}$ = 8.9 Hz, Ar–H), 6.99 (1H, s, Ar–H), 7.02 (1H, br s, NH), 8,10 (1H, d, $^{3}J_{HH}$ = 2.3 Hz, Ar–H), 11.9 (1H, br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.7 (2CH_2), 25.3 (CH_2), 32.6 (2CH_2), 48.9 (CNH), 55.8 (OMe), 113.5, 119.9, 127.9 (CH_{arom}), 117.5, 152.0, 158.7 (3C), 161.3 (C=O), 188.7 (C=O); MS (EI, 70eV): *m/z* (%) = 277 (20) [M$^{\cdot+}$], 151 (100), 123 (15). Anal. Calcd for $C_{15}H_{19}NO_4$ (277.13): C, 64.97; H, 6.91; N, 5.05. Found C, 65.07; H, 6.95; N, 5.19.

***N*-tert-butyl-2-(2-hydroxyphenyl)-2-oxoacetamide (3e):** Yellow oil; yield 0.125 g (57%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.33–1.49$ (9H, *m*, $3CH_3$), 6.88–6.98 (2H, *m*, CH_{arom}), 7.008 (1H, br s, NH), 7.49–7.55 (1H, m, Ar–H), 8.47 (1H, dd, $^3J_{HH} = 9.0$ Hz, $^4J_{HH} = 1.8$ Hz, Ar–H), 12.03 (1H, br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 28.31$ ($3CH_3$), 52.15 (CNH), 118.74, 119.41, 133.67, 137.90 (CH_{arom}), 118.02, 161.68 (2C), 163.35 (C=O), 190.51 (C=O). Anal. Calcd for $C_{12}H_{15}NO_3$ (221.11): C, 65.14; H, 6.83; N, 6.33. Found C, 65.41; H, 6.75; N, 5.98.

***N*-tert-butyl-2-(2-hydroxy-3-methoxyphenyl)-2-oxoacetamide (3f):** Pale yellow oil; yield 0.148 g (59%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.35–1.60 (9H, m, $3CH_3$), 3.88 (3H, s, OMe), 6.92–7.20 (2H, m, Ar–H), 8.28 (1H, d, $^3J_{HH} = 5.7$ Hz, Ar–H), 7.17 (1H, br s, NH), 12.3 (1H, br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 28.5$ ($3CH_3$), 51.6 (CNH), 56.2 (OMe), 117.9, 119.6, 124.5 (CH_{arom}), 118.3 (C), 167.4 (C=O), 196.7 (C=O). Anal. Calcd for $C_{13}H_{17}NO_4$ (251.12): C, 62.14; H, 6.82; N, 5.57. Found C, 61.86; H, 6.55; N, 5.23.

***N*-tert-butyl-2-(2-hydroxy-5-methoxyphenyl)-2-oxoacetamide (3g):** Orange oil; yield 0.143 g (57%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.24–1.45 (9H, m, $3CH_3$), 3.80 (3H, s, OMe), 6.90–6.93 (1H, m, Ar–H), 7.11–7.17 (1H, m, Ar–H), 7.13 (1H, br s, NH), 7.98 (1H, d, $^3J_{HH} = 3.0$ Hz, Ar–H), 11.92 (1H, br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 28.3$ ($3CH_3$), 52.1 (CNH), 55.9 (OMe), 115.1, 118.7, 125.3 (CH_{arom}), 117.6, 152.0, 156.0 (3C), 161.6 (C=O), 196.1 (C=O). Anal. Calcd for $C_{13}H_{17}NO_4$ (251.12): C, 62.14; H, 6.82; N, 5.57. Found C, 61.97; H, 6.89; N, 5.80.

***N*,*N*′-di-tert-butyl-2-(2-hydroxyphenyl)-4*H*-benzo[*d*][1,3]dioxine-4,4-dicarboxamide (4a):** Yellow oil; yield 0.093 g (22%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28–1.46$ (18H, *m*, $6CH_3$), 6.48 (1H, s, CH), 6.84 (1H, br s, NH), 6.91–7.86 (8H, m, $2C_6H_4$), 8.34 (1H, br s, NH), 9.55(1H, br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 28.2$, 28.47 (CMe_3), 51.76, 52.31 (CMe_3), 79.64 (C), 94.99 (CH), 117.06, 117.93, 119.10, 122.53, 125.56, 126.54, 129.49, 131.01 (CH_{arom}), 120.17, 120,88 (C), 153.27, 155.85 (C–O). Anal. Calcd for $C_{24}H_{30}N_2O_5$ (426.22): C, 67.59; H, 7.09; N, 6.57. Found C, 67.96; H, 6.63; N, 6.02.

***N*,*N*′-di-tert-butyl-2-(2-hydroxy-3-methoxyphenyl)-8-methoxy-4*H*-benzo[*d*][1,3]dioxine-4,4-dicarboxamide (4b):** Yellow oil; yield 0.087 g (18%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35–1.59$ (18H, m, $6CH_3$), 3.92 (3H, s, OMe), 3.95 (3H, s, OMe), 6.53 (1H, s, CH), 6.58 (1H, br s, NH), 6.87–7.43 (6H, m, 2C6H3), 8.70 (1H, br s, NH), 9.92 (1H, br s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 28.2$, 28.3 (CMe_3), 51.6, 52.0 (CMe_3), 56.2, 56.3 (OMe), 78.0 (C), 95.4 (CH), 111.4, 117.9, 118.2, 119.6, 121.7, 124.5 (CH_{arom}), 119.2, 121.5 (C), 167.4, 168.0 (C=O). Anal. Calcd for $C_{26}H_{34}N_2O_7$ (486.24): C, 64.18; H, 7.04; N, 5.76. Found C, 63.74; H, 6.59; N, 6.12.

Declarations

Author contribution statement

Mohammad Bayat: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Shima Nasri: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Rahman Alivisi: Contributed reagents, materials, analysis tools or data.

Azadeh Jani: Performed the experiments.

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