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

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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 synths 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 adding opportunities for the synthesis of a hemiketal or hemiaminal product [12]. In 2014, Guin et al. reported the formation of α-ketoamides via decarboxylation of α-oxoacrylic 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 Cu2O [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
oxidation protocol includes catalytic I2–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 nBu4NI. 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 (Na2CO3.1.5H2O2), K2CO3, 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 benzylocetonitrile. In this protocol different amines 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 another molecule 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) benzo[3-c]fluoran-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 H2O to nitroilum. 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 H2O 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

\[
\text{PhCl} + \text{CN} \xrightarrow{\text{bz, reflux, 2h, or neat, MW}} \text{PhCN} \xrightarrow{\text{CaCO}_3 \cdot \text{H}_2\text{O}, 50 \degree \text{C, 2h, or CaCO}_3 \cdot \text{H}_2\text{O}, MW}} \text{PhCONHPh}
\]

Mossetti's work

\[
\text{R}_1^1\text{Cl} + \text{CN} + \text{R}_2^1\text{N} \xrightarrow{\text{TEA, CH}_2\text{Cl}_2} \text{N} \xrightarrow{\text{HCl, 37%, THF}} \text{R}_2^1\text{CO} \xrightarrow{\text{Pd[hydrolysis]}} \text{R}_2^1\text{CONR}_2^1\text{R}_3^1\text{R}_4^1
\]

Guin's work

\[
\text{H}_2\text{N}-\text{C} \xrightarrow{\text{R}_1^1} \text{O} + \text{HO} \xrightarrow{\text{Pd}} \text{R}_1^1\text{CONR}_1^1\text{R}_2^1\text{R}_3^1\text{R}_4^1
\]

Du's work

\[
\text{Ph} \xrightarrow{2\text{CO}, 1\text{ atm}} \text{HN} \xrightarrow{\text{R}_2^1, \text{R}_3^1, \text{R}_4^1, \text{R}_5^1} \text{Pd(OAC)}_2 \xrightarrow{\text{N}_2\text{CO}_3, \text{PEG-400}, \text{r.t.}} \text{R}_1^1\text{CONR}_2^1\text{R}_3^1\text{R}_4^1
\]

Zhang's work

\[
\text{R}_1^1\text{COOH} + \text{H} \xrightarrow{\text{Cu}_2\text{O} (10 \text{ mol%), 1,10-phenanthroline (20 mol%)}, \text{DTBP (3 equiv), PivOH (2 equiv)}} \text{R}_1^1\text{CONMe}_2\text{Me}
\]

Ramanathan's work

\[
\text{Ph} + \text{NH}_2 \xrightarrow{\text{I}_2\text{-Py-TBHP, Nal-TBHP}} \text{R}_1^1\text{CONR}_1^1\text{R}_2^1\text{R}_3^1\text{R}_4^1
\]

Wang's work

\[
\text{PhCO} \xrightarrow{\text{NH}_4\text{Cl, } \text{nBu}_3\text{NH}, 50 \degree \text{C}} \text{PhCONH}_2 \xrightarrow{\text{R}_1^1\text{NH}_2\text{Cl, } \text{nBu}_3\text{NH}, 50 \degree \text{C}} \text{R}_1^1\text{CONR}_1^1\text{R}_2^1\text{R}_3^1\text{R}_4^1 \xrightarrow{\text{R}_1^1\text{R}_2^1\text{NH}_2\text{HCl, } \text{nBu}_3\text{NH}, 50 \degree \text{C}} \text{R}_1^1\text{CONR}_1^1\text{R}_2^1\text{R}_3^1\text{R}_4^1
\]

Zhang and Wang's work

\[
\text{R}_1^1\text{CN} + \text{R}_2^1\text{NH}_2 \xrightarrow{\text{catalyst-free, } \text{Na}_2\text{CO}_3, 1.5 \text{H}_2\text{O}_2 (1.5 equiv)}} \text{R}_1^1\text{CONR}_1^1\text{R}_2^1\text{R}_3^1\text{R}_4^1
\]

Zhou's work

\[
\text{PhCO} \xrightarrow{\text{CN, NH}_2} \xrightarrow{\text{hv, O}_2 (\text{air}), \text{THF, r.t., 12 h}}} \text{PhCONHPh}
\]

**Scheme 1.** Previous approaches to the synthesis of α-ketoamides.
As illustrated in Figure 3, various functional groups exist in aryl moiety such as methoxy group in ortho, meta and para positions, and in isocyano 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, 1H, 13C 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 1H 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 1H-decoupled 13C 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=O and CH=NR were observed at 158.7 and 48.9 ppm respectively which verified the selective synthesis of 3d (Figure 4).
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 synths 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 electrothermal 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 \(\mu\)L, 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) (\(\tilde{\nu}_{max}\)): 3300 (OH), 3200 (NH), 1634 (\(\text{C} = \text{O}\)) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.20–2.01\) (10H, m, \(5\text{CH}_2\)), \(3.81\) (1H, m, \(\text{CNH}\)), \(6.88–7.00\) (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\(_3\)): \(\delta = 24.7\) (\(2\text{CH}_2\)), \(32.5\) (\(2\text{CH}_2\)), \(48.8\) (CNH), \(118.7, 119.5, 133.6\), \(138.0\) (CHarom), \(161.4\) (C-O), \(163.4\) (C=O), 190.1 (C=C=O); MS (EI, 70 eV): \(m/z\) (%) = 247 (15) [\(\text{M}^+\)], 135 (90), 121 (100). Anal. Calcd for \(\text{C}_{14}\text{H}_{17}\text{NO}_3\): C, 68.00; H, 6.93; N, 5.66. Found C, 68.38; H, 6.87; N, 5.45.
N-cyclohexyl-2-(2-hydroxy-3-methoxyphenyl)-2-oxoacetamide (3b): Red powder; m.p.: 95–99 °C, yield 0.191 g (69%); IR (KBr) (υmax): 3400 (OH), 1642 (C=O), 1437 (C=C), 1255 (C-O, C-N) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.22–1.97 (10H, m, 5CH₂), 3.88 (1H, m, CNH), 3.91 (3H, s, OMe), 7.1 (1H, br s, NH), 7.23 (1H, t, JHH = 8.3 Hz, Ar-H), 7.74 (1H, d, JHH = 8.1 Hz, Ar-H), 7.94 (1H, d, JHH = 8.39 Hz, Ar-H), 11.92 (1H, br s, OH); ¹³C NMR (75.4 MHz, CDCl₃): δ = 24.08 (2CH₂), 29.7 (CH₂), 34.1 (2CH₂), 53.0 (OMe), 114.0, 118.0, 123.9 (CHarom), 118.0, 145.0, 152.9 (3C), 175.6 (C=O), 191.3 (C=O). Anal. Calcd for C₁₅H₁₉NO₄ (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) (υmax): 3400 (OH), 1640 (C=O), 1215 (C-O, C-N) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.47–1.99 (10H, m, 5CH₂), 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, JHH = 9 Hz, Ar-H), 12.52 (1H, br s, OH); ¹³C NMR (75.4 MHz, CDCl₃): δ = 24.7 (2CH₂), 25.4 (CH₂), 32.6 (CH₂), 48.6 (CH₃), 55.7 (OMe), 100.8, 108.8, 115.0 (CHarom), 167.7 (C=O). Anal. Calcd for C₁₅H₁₉NO₄ (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) (υmax): 3400 (OH), 1657 (C=O), 1165 (C-O, C-N) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.48–2.01 (10H, m, 5CH₂), 3.80 (3H, s, OMe), 3.84–3.90 (1H, m, CNH), 6.93 (1H, d, JHH = 8.9 Hz, Ar-H), 6.99 (1H, s, Ar-H), 7.02 (1H, br s, NH), 8.10 (1H, d, JHH = 2.3 Hz, Ar-H), 11.9 (1H, br s, OH); ¹³C NMR (75.4 MHz, CDCl₃): δ = 24.7 (2CH₂), 25.3 (CH₂), 32.6 (CH₂), 48.9 (CH₃), 55.8 (OMe), 113.5, 119.9, 127.9 (CHarom), 117.5, 152.0, 158.7 (3C), 161.3 (C=O), 188.7 (C=O); MS (EI, 70eV): m/z (%) = 277 (20[M⁺]), 151 (100), 123 (15). Anal. Calcd for C₁₅H₁₉NO₄ (277.13): C, 64.97; H, 6.91; N, 5.05. Found C, 65.07; H, 6.95; N, 5.19.

Figure 4. (a) The ¹H NMR spectrum of 3d and, (b) ¹³C NMR spectrum of 3d.
**Additional information**

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2020.e04076.

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