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Selenium dioxide-mediated synthesis of α -ketoamides from arylglyoxals and secondary amines

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Abstract

A facile and expeditious synthetic approach to α -ketoamides **3** is described. A series of α -ketoamides **3** was synthesized via reaction of selenium dioxide-mediated oxidative amidation between arylglyoxals **1** and secondary amines **2**, and accelerated with microwave irradiation. Our findings indicate that constrained amines, such as piperazine and piperidine exhibit higher conversions for this transformation. This reaction was explored by synthesizing a series of α -ketoamides **3** from various arylglyoxals with cyclic and acyclic secondary amines.

Keywords

α -ketoamides; selenium dioxide; microwave-assisted; arylglyoxals

α -Ketoamides¹ are of great interest within the realms of medicinal chemistry, and this structural scaffold represents a key framework of many biologically active agents in natural products such as immunosuppressive drugs FK506 and rapamycin.² Moreover, α -ketoamides have been developed as serine or cysteine protease inhibitors,³ human cytosolic phospholipase A₂ (GIVA PLA₂) inhibitors,⁴ androgen and estrogen receptors antagonists,⁵ p38 inhibitors⁶ and cathepsin S inhibitors.⁷ Thanks to their pharmacological relevance, a variety of synthetic methodologies to access them have been developed, such as palladium-catalyzed amino(double) carbonylation of organic halides⁸ and reactions of carbamoylstannane and carbamoylsilane with acid chlorides.⁹ Indeed more recently, 2,2-dibromoacetophenone was reported to undergo oxidative amidation reaction with secondary amines via aerial oxidation with moderate to good yields.¹⁰ Through efforts to develop an expeditious and efficient protocol for the synthesis of α -ketoamides **3**, we herein utilize commercially available arylglyoxal **1**, an equal oxidative status of 2,2-dibromoacetophenone, to undergo oxidative amidation with secondary amines **2** mediated by selenium dioxide under microwave irradiation to give the desired α -ketoamides **3**, Scheme 1.

The feasibility of aerial oxidative amidation was initially investigated in Table 1 (Entries 1–3) and upon microwave irradiation of phenylglyoxal **1a** with 1-phenylpiperazine **2a** in the

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absence of oxidizing agent, no appreciable oxidative amidation product was found.¹⁰ Indeed when hydrogen peroxide was utilized as an oxidant (Entries 4, 5), no significant transformation was observed.¹¹ We further examined the oxidative amidation potential of pyridinium dichromate (PDC) which resulted in slight improvement with 11% conversion rate (Entry 6).¹² Subsequently, we turned our attention to employ selenium dioxide as the oxidizing agent, Table 1 (Entries 7–13). Encouragingly, the oxidative amidation product **3a** was significantly increased over all attempted aerial oxidations and moreover, results suggested reaction times were shortened at higher temperatures (Entries 10, 11). It was also noted that the reaction could be completed in DCM or DCM/1,4-dioxane (3/1) with comparable isolated yields (Entries 9, 10). Compared to the abovementioned oxidative amidation of 2,2-dibromoacetophenone that required 4 equiv. of secondary amines, this method dramatically reduced the amount of required secondary amine for successful SeO₂-mediated oxidative amidation.¹³

With optimized conditions in hand, a series of oxidative amidations of phenylglyoxal **1a** with various secondary amines **2a–2l** was thus carried out, Table 2. Results revealed that the desired α -ketoamides were obtained in moderate to good yields, the reactivity domain being broad including acyclic amines, five-membered, six-membered and seven-membered cyclic amines. Interestingly, acyclic secondary amines bearing flexible appendages such as **2b** (*N,N*-dicyclohexylamine), **2c** (*N*-methyl-benzylamine) and **2f** (*N,N*-dibenzylamine) displayed poor reactivity with isolated yields of 26, 47 and 0%, respectively.

Furthermore, arylglyoxals **1b–j** containing electron-donating and electron-withdrawing substituents and secondary amines **2a–p** were examined and exhibited good scope of reaction, Table 3. Most promising conversions were observed with substituted piperidines such as **2j** and **2o**, of which the α -ketoamide **3n** (Entry 2) was isolated in 85% yield. Highly noteworthy was the performance of primary amines in this sequence which failed to give any appreciable oxidized product. The generality and scope of the amine inputs were clearly confined to secondary amines.

The plausible mechanism of this selenium dioxide driven oxidative amidation is depicted in Figure 1. Upon nucleophilic addition of amine **2a** to phenylglyoxal **1a**, α -hydroxyacetophenone **4** is produced, which subsequently generates intermediate **5** upon reaction with SeO₂. Internal rearrangement of **6** via proton transfer affords the desired α -ketoamide **3a** with release of selenediol.

In summary, we have successfully demonstrated a facile synthesis of α -ketoamides via the oxidative amidation of arylglyoxals with secondary amines mediated by selenium dioxide and assisted by microwave irradiation in moderate to good yields. The application of this method to generate additional structural diversity will be disclosed in the due course.

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13. **General procedure for preparation of aryl α -ketoamide 3. 3a:** To a mixture of phenylglyoxal monohydrate **1a** (152 mg, 1.0 mmol), 1-phenylpiperazine **2a** (251 mg, 1.5 mmol) in DCM (3mL) and 1,4-dioxane (1mL), selenium dioxide (111 mg, 1.0 mmol) was added to the solution. The resulting mixture was heated at 100 °C for 20 min under microwave irradiation. The solution was diluted with DCM (5 mL), washed with NaHCO₃(sat) (10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, evaporated *in vacuo* to obtain the crude product **3a**. The crude residue **3a** was transferred to a pre-packed column (2.5 g) and was purified using the ISCOTM purification system (12g silica gel flash column; eluent, ethyl acetate: hexane = 0 to 40%). The fractions containing the product were collected and the solvent was evaporated under reduced pressure and dried under high-vacuum system to afford **3a** (176 mg, 60%). ¹H NMR (400 MHz, CDCl₃) δ 8.03 – 7.94 (m, 2H), 7.69 – 7.60 (m, 1H), 7.55 – 7.47 (m, 2H), 7.31 – 7.23 (m, 2H), 6.94 – 6.88 (m, 3H), 3.91 (dd, *J* = 6.0, 4.5 Hz, 2H), 3.54 – 3.48 (m, 2H), 3.30 – 3.25 (m, 2H), 3.13 (dd, *J* = 5.9, 4.4 Hz, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 191.33, 165.41, 150.74, 134.88, 133.17, 129.68, 129.28, 129.09, 120.90, 116.96, 49.89, 49.58, 45.81, 41.27 ppm. HRMS (ESI) Calcd for C₁₈H₁₉N₂O₂ (M+H)⁺ 295.1442, Found 295.1441.

Figure 1.
Plausible mechanism to generate aryl α -ketoamide **3a**.

Scheme 1.

Synthesis of α -ketoamides **3** via oxidative amidation.

Table 1

Synthesis of α -ketoamide **3a**^a

Entry	2a	oxidant	solvent	Temp (°C)	Time	Conversion (%) ^b 3a
1	1.0 eq	air	DCM	100	20	trace
2	1.5 eq	air	DCM	100	20	<5
3	2.0 eq	air	DCM	100	20	<5
4	1.5 eq	H ₂ O ₂	1,4-dioxane	100	20	<5
5	1.3 eq	H ₂ O ₂	-	80	120	ND ^c
6	1.5 eq	PDC	DCM	100	20	11
7	1.5 eq	SeO ₂	1,4-dioxane	100	20	(100) ^b (37) ^d
8	1.0 eq	SeO ₂	DCM/1,4-dioxane (3/1)	100	20	(100) ^b (51) ^d
9	1.5 eq	SeO ₂	DCM/1,4-dioxane (3/1)	100	20	(100) ^b (60) ^d
10	1.5 eq	SeO ₂	DCM	100	20	(100) ^b (60) ^d
11	1.5 eq	SeO ₂	DCM/1,4-dioxane (3/1)	120	10	(100) ^b (58) ^d
12	1.5 eq	SeO ₂	DCM/1,4-dioxane (3/1)	120	20	(100) ^b (60) ^d

^a All reactions were performed with phenylglyoxal **1a** (1 mmol), 1-phenylpiperazine **2a** in the absence and presence of oxidant (1 mmol) in the corresponding solvents (4 mL). All reactions were carried out under microwave irradiation.

^b The conversion rate was determined by LC-MS using Evaporative Light Scattering (ELS) detection.

^c Not detected from LC-MS analysis. The reaction performed in 1 mL of 50% hydrogen peroxide solution under conventional heating.

^d Isolated yield.

Table 2

Synthesis of α -ketoamides **3b–3l**.^a

Entry	2	Yield (%) ^b 3
1	1-phenylpiperazine (2a)	60 (3a)
2	<i>N,N</i> -dicyclohexylamine (2b)	26 (3b)
3	<i>N</i> -methylbenzylamine (2c)	47 (3c)
4	pyrrolidine (2d)	45 (3d)
5	1-(4-fluorophenyl)piperazine (2e)	80 (3e)
6	<i>N,N</i> -dibenzylamine (2f)	ND ^c (3f)
7	1-(2-furoyl)piperazine (2g)	62 (3g)
8	1-(pyrrolidinocarbonylmethyl)-piperazine (2h)	52 (3h)
9	<i>t</i> -butyl piperazine-1-carboxylate (2i)	70 (3i)
10	4-benzylpiperidine (2j)	74 (3j)
11	1-(4-fluorobenzyl)-1,4-diazepane (2k)	43 (3k)
12	1-(4-pyridyl)-piperazine (2l)	50 (3l)

^aAll reactions were performed with phenylglyoxal (1 mmol), secondary amine **2** (1.5 mmol), selenium dioxide (1 mmol) in the solvents of DCM/1,4-dioxane (3mL/1mL). All reactions were heated at 100°C for 20 min under microwave irradiation.

^bIsolated yield.

^cNot detected from [LC/MS] analysis.

Table 3

Preparation of α -ketoamides **3m** – **3v**.^a

Entry	Ar	2	Yield(%) ^b 3
1	6-methoxy-2-naphthyl (1b)	1-phenylpiperazine (2a)	49 (3m)
2	3-Br-Ph (1c)	4-benzylpiperidine (2j)	85 (3n)
3	3-NO ₂ -Ph (1d)	4-benzylpiperidine (2j)	66 (3o)
4	benzo[d][1,3]dioxol-5-yl (1e)	1- <i>p</i> -tolylpiperazine (2m)	56 (3p)
5	3,4- <i>di</i> -MeO-Ph (1f)	1- <i>p</i> -tolylpiperazine (2m)	62 (3q)
6	3,4,5- <i>tri</i> -MeO-Ph (1g)	1-(4-methoxyphenyl)piperazine (2n)	71 (3r)
7	4-F-Ph (1h)	1-(4-methoxyphenyl)piperazine (2n)	57 (3s)
8	4-NO ₂ -Ph (1i)	4-phenylpiperidine (2o)	56 (3t)
9	3,4- <i>di</i> -F-Ph (1j)	4-phenylpiperidine (2o)	72 (3u)
10	4-OMe-Ph (1k)	1-(2-fluorophenyl)piperazine (2p)	68 (3v)

^a All reactions were performed with arylglyoxal **1** (1 mmol), secondary amine **2** (1.5 mmol), selenium dioxide (1 mmol) in the solvents of DCM/1,4-dioxane (3mL/1mL). All reactions were heated at 100°C for 20 min under microwave irradiation.

^b Isolated yield.