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SeO_2 mediated efficient synthesis of amides and α-ketoamides of secondary amines with wide substrate scope

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ABSTRACT

SeO_2 mediated oxidative amidation of acetophenones, Phenylacetylenes, phenylacetaldehydes to α-ketoamides and aldehydes to amides is reported. Amidation selectively proceeds with secondary amines. *α*-Ketoamide derivatives of natural products 16-dehydropregnenolone acetate (**8**), pregnenolone acetate (**10**) and progesterone (**11**) were synthesized.

α-Ketoamide is an important functionality of various bioactive molecules (anti-HIV, anti-tumor, anti-IBD and anti-bacterial).[1] pharmaceuticals (rapamycin, enzyme inhibitors) and agrochemicals (FK506).[2-4]

α-Ketoamides are synthesized from diverse substrates such as methyl-ketones,[5-10] aldehydes/arylglyox-als,[11-16] α-ketoacids,[17-20] terminal alkynes,[21-24] cyanamides,[25] carbamoyl stannane/ silane with acid chlorides,[26-28] addition of aroyl to aryl-acetamides,[29] 2,2-dibromo-1-aryl ethanones[30] and double carbonylation of aryl iodides.[31-33] Usually in these oxidative amidation, a co-oxidant is required. Recent advances in catalytic synthesis of α-ketoamides has been reviewed recently.[1]

Shaw et *al*, synthesized a series of various α-ketoamides from arylglyoxals and secondary amines by using SeO_2.[13] Selenium dioxide is common oxidant and reported for synthesis of arylglyoxals from acetophenones[34] and phenylacetylenes.[35] Keeping in view the above findings, it was reasoned to explore SeO_2 for synthesis of α-ketoamides from acetophenones and amides from arylaldehydes.

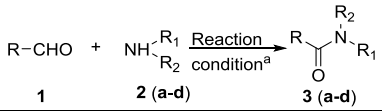
In order to investigate SeO_2 mediated amidation, a model reaction of benzaldehyde with diethylamine was selected. Use of one equivalent of SeO_2 and diethylamine (**2a**) in dioxane at 80 ^oC gave the desired product **3a** in 90% yield (Table 1, entry 1). Among the different amines screened, secondary amines provided encouraging results with high yields 88-92% (Table 1, **3b-d**) and no product formation was observed with primary amines probably due to their week nucleophilicity (Table 1, **3e** and **3f**). Next we explored SeO_2 mediated amidation for α-ketoamide from acetophenone (**4a**) [36] and piperidine (**2d**) to obtain **6a** (Table 2, entry 1). Different substituted acetophenones were explored to obtain α-ketoamide in good yield (Table 2, entry 2-8 and 11). Again product formation was not observed with primary amines (Table 2, entry 14 and 15).

Further this method was explored for the synthesis of natural product derivatives of 16-dehydropregnenolone acetate, progesterone and pregnenolone acetate. 16-dehydropregnenolone acetate was treated with piperidine and morpholine under optimized reaction condition[36] to obtain α-ketoamide derivatives **8** (65%) and **9** (70%) respectively. 2-Me-piperidine **10** (70%) derivative of pregnenolone acetate was obtained as mixture of two diastereoisomers of equal ratio (Epimers), as the 2-Me-piperidine was a racemic mixture. Method was extended to synthesize α-ketoamide derivative **11** of progesterone with piperidine (Figure 1).

Oxidation of phenylacetylene with SeO_2 under acidic condition produces phenylglyoxal,[35] therefore we selected phenylacetylenes as another substrate for synthesis of α-ketoamides. Reaction of Phenylacetylene (**5a**) and piperidine (**2d**) under mild acidic condition (conc. H_2SO_4, 10 mol %) was carried out to produce α-ketoamide **6a** in good yield (Table 2, entry 1). Catalytic amount of acid (10 mol %) improved the yield however low yield (<20%) was observed in absence of acid even after 30h. The substitution of alkynes with both electron withdrawing and electron donating groups were well tolerated (Table 2, entry 9, 10, 12 and 13). Further the methodology was extended on phenylacetaldehyde (**7**) with secondary amines to obtain α-ketoamide products in good yield (Table 3, entry 1, and 2) whereas no product formation was observed with primary amines. We concluded that these reaction conditions are not suitable for weak nucleophiles such as aromatic amines and primary amines, though in recent investigations by Ahmed and co-worker synthesized α-carbonylamide of various weak nucleophiles amine using SeO_2-pyridine as a versatile reagent for

the oxidation of α-carbonylimines, of weak nucleophilic amines.[38]

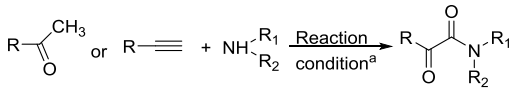
Table 1. SeO_2 mediated amidation of arylaldehydes with secondary amines



Entry	**R**	**2** (Amine)	**3**	Yield[b]
1	Ph (**1a**)	Diethylamine (**2a**)	**3a**	90
2	Ph (**1a**)	Pyrrolidine (**2b**)	**3b**	85
3	Ph (**1a**)	4-Phenylpiperidine (**2c**)	**3c**	88
4	2,6-$Cl_2C_6H_3$ (**1b**)	4-Phenylpiperidine (**2c**)	**3d**	92
5	Ph (**1a**)	Aniline	**3e**	00
6	Ph (**1a**)	Tryptamine	**3f**	00

[a]Equivalent amount of aldehyde (**1,** 1.0 mmol) with amine (**2**, 1.0 mmol) and SeO_2 (1.0 mmol), heated at 80 ℃/12 hr in dioxane. [b] isolated yield

Table 2. SeO_2 mediated α-ketoamides of acetophenones and phenylacetylene with secondary amines



Entry	**R**	**2** (Amine)	**6**	Yield[b]
1	Ph (**4a**, **5a**)	Piperidine (**2d**)	**6a**	85,86
2	Ph (**4a**, **5a**)	Morpholine (**2e**)	**6b**	80,82
3	Ph (**4a**, **5a**)	4-Phenylpiperidine (**2c**)	**6c**	82,86
4	Ph (**4a**, **5a**)	4-Ethylpiperidine (**2f**)	**6d**	86,88
5	Ph (**4a**, **5a**)	4-Benzylpiperidine (**2g**)	**6e**	78,81
6	2-ClC_6H_4 (**4b**, **5b**)	*N*-Methylpiperazine (**2h**)	**6f**	85,89
7	2-ClC_6H_4 (**4b**, **5b**)	Morpholine (**2e**)	**6g**	88,90
8	2,6-$Cl_2C_6H_3$ (**4c**)	Morpholine (**2e**)	**6h**	85
9	4-FC_6H_4 (**5c**)	4-Ethylpiperidine (**2f**)	**6i**	80
10	4-*ter*BuC_6H_4 (**5d**)	Piperidine (**2d**)	**6j**	76
11	2-OH,5-F C_6H_3 (**4d**)	4-Phenylpiperidine (**2c**)	**6k**	72
12	4-CNC_6H_4 (**5e**)	Piperidine (**2d**)	**6l**	78
13	4-$NO_2C_6H_4$ (**5f**)	Piperidine (**2d**)	**6m**	75
14	Ph (**4a**, **5a**)	Aniline	**6n**	00
15	Ph (**4a**, **5a**)	Tryptamine	**6o**	00

[a]Equivalent amount of acetophenones (**4**, 1.0 mmol) or alkyne (**5**, 1.0 mmol) with amine (**2**, 1.0 mmol) and SeO_2 (1.0 mmol) same as mentioned for table 1, in case of substrate **5**, 10 mole % of H_2SO_4 was added. [b]isolated yield

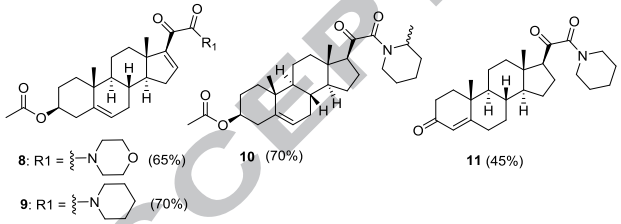
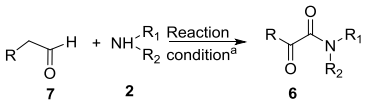


Figure 1. New α-ketoamide derivatives of 16-dehydropregnenolone acetate, pregnenolone acetate and progesterone

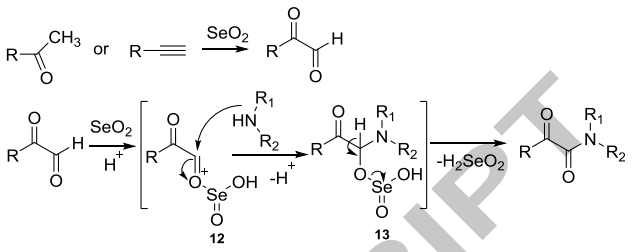
Table 3. SeO_2 mediated α-ketoamides of phenylacetaldehydes with secondary amines



Entry	**R**	**2** (Amine)	**6**	Yield[b]
1	Ph (**7a**)	Piperidine (**2d**)	**6a**	65
2	2,6-$Cl_2C_6H_3$ (**7b**)	Morpholine (**2e**)	**6f**	70

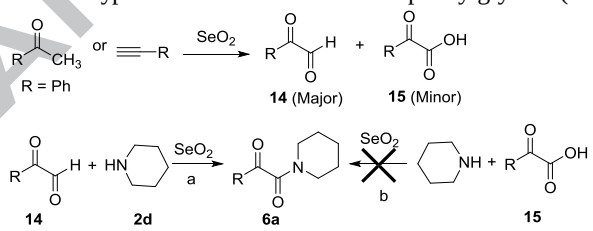
[a]Same as mentioned for table 1. [b]isolated yield

In order to get insight into reaction mechanism, we considered the aryl aldehydes may be oxidized to acids, hence reaction of benzoic acid with **2a** was investigated under optimized condition but no product formation was observed. This result indicates that acid is not an intermediate of this SeO_2 mediated oxidative amidation. SeO_2 oxidizes acetophenones and phenylacetylenes to corresponding phenylglyoxals. Further phenylglyoxals were converted to α-ketoamide *via* O–Se bond formation with carbonyl oxygen atom to give the unstable intermediate **12**. O–Se bond formation generates strong electrophilic centre at carbon, followed by nucleophilic attack of amine to give the selenite intermediate **13**. Further oxidative decomposition of **13** led to the final α-ketoamide product (Scheme 1).



Scheme 1. Plausible mechanism of amidation

To support mechanism, acetophenone (**4a)** and phenylacetylene (**5a)** were treated with SeO_2 to give phenylglyoxal (**14**) and phenylglyoxylic acid (**15**) as products. In a separate set of experiments phenylglyoxal (**14**) and phenylglyoxylic acid (**15**) were treated with piperidine (**2d**) in presence of SeO_2 under optimized reaction condition. Reaction proceeded as expected, product **6a** was obtained only from phenylglyoxal (**14**) (Scheme 2). These experiments confirmed amidation proceeds through aryl glyoxal intermediate and the phenylglyoxylic acid (**15**) was obtained as byproduct on over oxidation of phenylglyoxal (**14**).



Scheme 2. Synthesis of α-ketoamides through phenyl-glyoxal intermediate.

In summary, a concise SeO_2 mediated methodology for the synthesis of amides from aryl aldehydes and α-ketoamides from acetophenones and phenylacetylene was developed. Application of method has been demonstrated on some natural product derivative synthesis.

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Supplementary data

Experimental procedures and NMR of compounds are available in supplementary data. Supplementary data can be found in the online version at http://sciencedirect.com.

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36. Standard reaction procedure: SeO2 is very toxic material. All the experiments were performed using impervious clothing, gloves, protective mask, and safety goggles. All the reactions were performed under exhaust ventilation. SeO2 (1.0 mmol) was added to a solution of arylaldeydes or phenylacetones or terminal alkyne (1.0 mmol) in dioxan (1 ml) followed by the addition of catalytic amount of H2SO4 (in case of alkyne only) and amine (1.0 mmol). The reaction mixture was then heated at 80 oC for 10-12 h and the product formation was monitored by TLC. After completion, reaction mixture was partioned with water-ethylacetate and extracted with ethyl acetate (3 x 50ml). The combined organic layers were washed with brine solution, concentrated on rotary evaporator and purified by column chromatography using ethyl acetate and hexane to afford corresponding pure products
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Graphical Abstract

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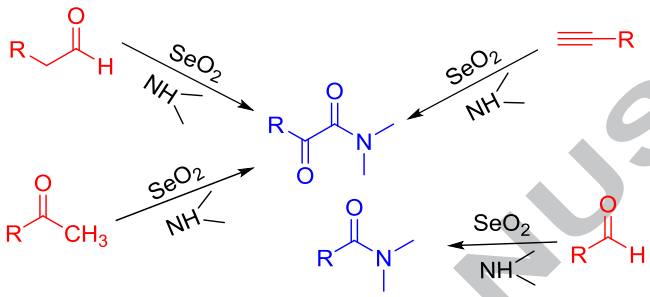

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Highlights

- Amidation and α-ketoamidation of aromatic aldehydes, aryl alkynes and acetophenones
- Practical, single pot and good yielding method
- Applicable for synthesis of derivative of natural product