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Synthesis of Lactams by Reductive Amination of Carbonyl Derivatives with ω -Amino Fatty Acids under Hydrosilylation Conditions

Satawat Tongdee,^{†[a]} Duo Wei,^{†[a]} Jiajun Wu,^{†[a]} Chakkrit Netkaew,^[a] and Christophe Darcel^{*[a]}

Dedication ((optional))

Abstract: An efficient method for the preparation of lactams from ω -amino fatty acids under hydrosilylation is described. A variety of lactams such as pyrrolidinones, piperidinones and 2-azepanones were selectively synthesised in moderate to excellent yields (29 examples, up to 95% isolated yields) with a good functional group tolerance. Noticeably, no metallic based catalyst was required to perform such transformation.

Amides, and more particularly lactams are crucial and versatile intermediates building blocks in pharmaceutical chemistry, polymer and synthetic organic chemistry.^[1] Particularly pyrrolidinones, piperidinones and 2-azepanones are present in a large class of natural products and biologically active molecules, among the most sold drugs.^[2] (Figure 1) Indeed, pyrrolidinones are usually base motifs in the drug racetams such as Levetiracetam, classically used for treatment of focal epilepsy in adults, or Lenatidomide for the treatment of multiple myeloma. Piperidinone motif is also widely met in pharmaceuticals like Apixaban used to prevent venous thromboembolism. Drugs based on caprolactam moiety are also popular as illustrated by Benzepiril used to treat high blood pressure and heart failure.

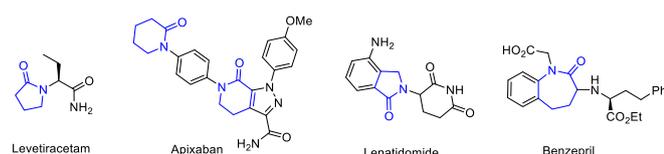
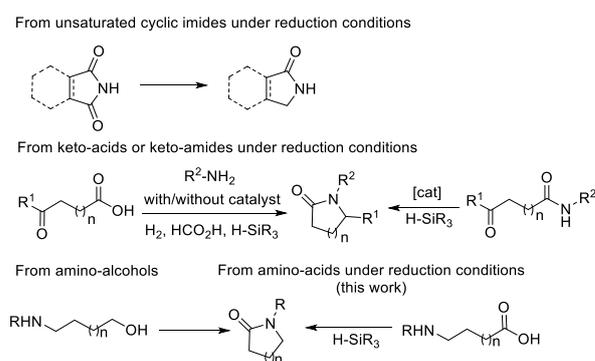


Figure 1. Selected examples for lactams used in pharmaceuticals.

Thus, this topical context still prompts to prepare cyclic amides in an efficient and simple way. Indeed, among the numerous methodologies,^[3] reductive ones were efficiently developed.^[4] Lactams can be obtained from the corresponding cyclic imides by selective reduction with red-Al (sodium bis(2-methoxyethoxy)aluminium hydride) or NaCNBH₃,^[5] hydrogenation using ruthenium based catalysts,^[6] TBAF or potassium hydroxide catalysed hydrosilylation^[7] or electrochemical reduction.^[8] Alternatively, *N*-substituted lactams

produced from keto-acids (e.g. levulinic acid) and primary amines under reductive conditions were reported in both catalytic and catalyst-free conditions such as hydrogenation,^[9] hydrogen transfer using formic acid^[10] or hydrosilylation.^[11] Similarly, Al(OTf)₃-catalysed hydrosilylation of keto-amides led to the corresponding pyrrolidinones and piperidinones.^[12] Noticeably, the preparation of lactams can be also conducted starting from amino alcohols.^[13]



Scheme 1. Representative pathways for lactam synthesis under reductive conditions.

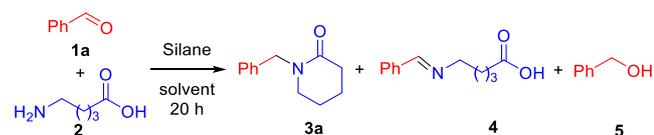
Recently, we have developed an iron-catalysed one-pot preparation of *N*-substituted cyclic amines *via* reductive amination of carbonyl derivatives with ω -amino fatty acids under hydrosilylation conditions.^[14] During this study, we identified that the first step of the synthesis leading to the lactams did not require iron catalyst. Thus, we report an efficient and selective one-pot preparation of *N*-substituted lactams (including pyrrolidinones, piperidinones and 2-azepanones) *via* reductive amination of carbonyl derivatives with ω -amino fatty acids by hydrosilylation (Scheme 1).

We began our initial optimization experiments based on the previous results in which we have identified that the formation of the piperidinone **3a** can be obtained selectively starting from 5-aminopentanoic acid **2** and benzaldehyde **1a** by reaction with 5 equiv. of phenylsilane at 100 °C for 3 h in toluene (Table 1, entry 1). When decreasing the quantity of silane from 5 to 1 equiv., and the temperature from 100 °C to RT, we observed a huge decrease of activity and selectivity (entries 2 and 3). We then studied the influence of the solvent. Performing the reaction at RT in the presence of 1 equiv. of phenylsilane, in dimethylcarbonate (DMC), ethyl acetate, or water led to low conversions and selectivities (entries 4-6).

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Table 1. Optimization of the reaction parameters.^[a]

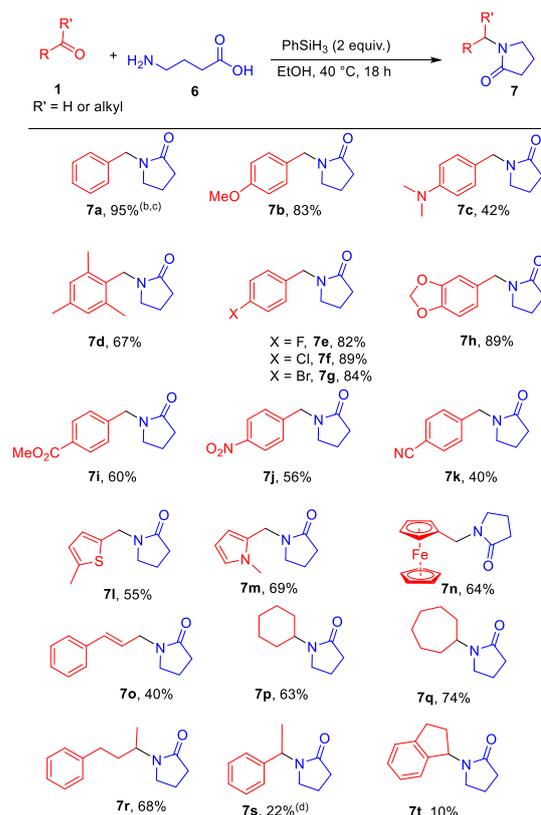
Entry	Silane [equiv.]	Solvent	T [°C]	Conv. [%]	Yield [%]		
					3a	4	5
1	PhSiH ₃ [5]	Toluene	100 ^(b)	95	95	0	0
2	PhSiH ₃ [2]	Toluene	50 ^(c)	78	73	0	5
3	PhSiH ₃ [1]	Toluene	RT	11	5	6	0
4	PhSiH ₃ [1]	DMC	RT	20	8	12	0
5	PhSiH ₃ [1]	EtOAc	RT	22	8	14	0
6	PhSiH ₃ [1]	water	RT	5	2	1	2
7	PhSiH ₃ [1]	EtOH	RT	88	68	20	0
8	PhSiH ₃ [1]	<i>t</i> -amylOH	RT	54	19	35	0
9	PhSiH ₃ [1]	Neat	RT	94	59	32	3
10	TMDS [1.5]	EtOH	RT	76	12	64	0
11	PMHS [3]	EtOH	RT	80	15	65	0
12	Et ₃ SiH [3]	EtOH	RT	85	7	78	0
13	Ph ₂ SiH ₂ [1.5]	EtOH	RT	88	27	61	0
14	(EtO) ₃ SiH [3]	EtOH	RT	93	48	44	0
15	none	EtOH	RT	78	3	75	0
16	PhSiH ₃ [1]	EtOH	50	85	64	21	0
17	PhSiH ₃ [1.5]	EtOH	50	79	74	5	0
18	PhSiH ₃ [1.5]	EtOH	30	73	69	4	0
19	PhSiH ₃ [2]	EtOH	30	99	95	4	0
20	PhSiH ₃ [1.5]	Neat	30	93	93	0	0

[a] General reaction conditions: **1a** (0.1 mmol), **2** (0.1 mmol), hydrosilane, solvent (0.5 mL) at RT-100 °C for 20 h under air atmosphere. The conversions and yields were determined by ¹H NMR spectroscopy; [b] 3 h; [c] 4 h.

Using protic solvents such as ethanol or *t*-amylalcohol or neat conditions permitted to increase the conversions, but with a modest selectivity (entries 7-9). Afterwards, different hydrosilanes were evaluated in order to study the selectivity of the reaction. Using TMDS (1,1,3,3-tetramethyldisiloxane, 1.5 equiv.) and PMHS (polymethylhydrosiloxane, 3 equiv.), good conversions were obtained (up to 80%) but the imine **4** was detected as the major product, with 12-15% of piperidinone **3a** (entries 10 and 11). When using triethylsilane, diphenylsilane, or triethoxysilane, similar results in terms of activity and selectivity were obtained (entries 12-14). Noticeably, in the absence of hydrosilanes, small amount of **3a** was obtained (3%), the main product being the imine **4** (75%, entry 15), highlighting the crucial importance of hydrosilane in this transformation. Having identified phenylsilane as the best hydrosilane, its ratio was then studied. The use of 2 equiv. of PhSiH₃ in ethanol at 30 °C permitted to obtain piperidinone **3a** in 95% yield, with trace amount of imine **4**. Similarly, under neat conditions, **3a** was obtained specifically in 93% yield (entries 16-20).

With our optimized conditions in hand, we then explored the substrate scope for the reductive amination of carbonyl derivatives with ω -amino fatty acids into *N*-substituted lactams (Tables 2 and 3). First, the reaction of 4-aminobutanoic acid **6** with several aldehydes was examined. Benzaldehyde was smoothly converted into the corresponding *N*-substituted pyrrolidinone **7a** in 95% isolated yield. Using substituted benzaldehyde by

donating groups such as *p*-anisaldehyde or *p*-(*N,N*-dimethylamino)benzaldehyde led to the corresponding pyrrolidinones **7b-7c** in 83 and 42% yields, respectively. Noticeably, starting from the hindered mesitaldehyde, the corresponding product **7d** was isolated in moderate yield (67%). The transformation also tolerated halides (F, Cl, Br) affording the derivatives **7e-7g** in 82-89% yields.

Table 2. Scope of the synthesis of pyrrolidinones by reductive amination of carbonyl derivatives with 4-aminobutanoic acid.^[a]

[a] General reaction conditions: **1** (0.6 mmol), **6** (0.5 mmol), PhSiH₃ (2 equiv.) and ethanol (0.5 mL), 40 °C, 18 h; Isolated yields of **7** are shown; [b] Reaction for 18 h in methanol, 69% NMR-yield, in ethanol, 60% NMR yield, in isopropanol, 56% NMR yield. [c] Reaction for 24 h. [d] Reaction at 80 °C.

Interestingly, benzodioxole, an important building block in pharmaceuticals can be easily linked to pyrrolidinone core leading to **7h** in 89% yield.

It should be also underlined that pyrrolidinones bearing reducible functional groups such as carboxylic ester (**7i**) nitro (**7j**) and cyano (**7k**) could be synthesized in moderate isolated yields (40-60%), exhibiting an interesting functional group tolerance of this transformation. In addition, hetero-aromatic aldehydes based on thiophene and pyrrole motifs were selectively converted to **7l-7m** in 55 and 69% yields, respectively. Pyrrolidinone **7n** bearing a ferrocenyl substituent was also produced in 64% yield. Interestingly, starting from cinnamaldehyde, the corresponding allylic pyrrolidinone **7o** was isolated in 40% yield, without observation of by-products resulting from the hydrosilylation of the

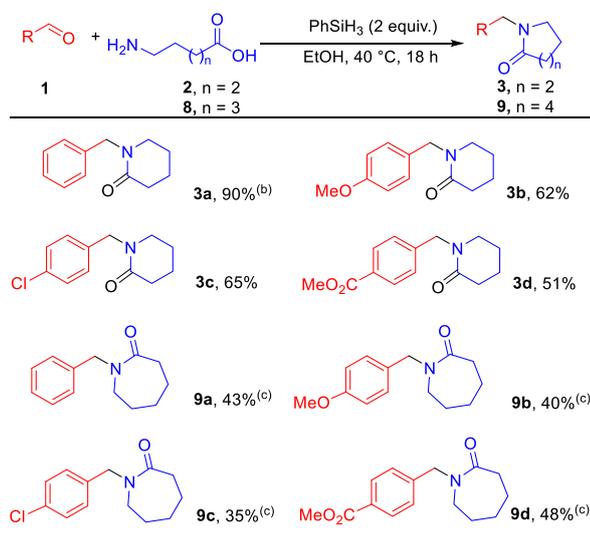
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conjugated C=C bond. Noticeably, when the reaction was performed with an alkanal such as 3-phenylpropanal under similar conditions, the corresponding 1-(3-phenylpropyl)pyrrolidin-2-one (**7u**) was obtained with only 10% isolated yield.

The reaction of 4-aminobutanoic acid was also evaluated with ketones. Noticeably, cyclohexanone and cycloheptanone reacted nicely leading to the corresponding *N*-cyclohexyl and *N*-cycloheptyl-pyrrolidinones **7p** and **7q** with 63 and 74% yields, respectively. Similarly, starting from 4-phenylbutan-2-one, **7r** was isolated in 68%. By contrast, when conducting the reaction with acetophenone and 1-indanone, the corresponding pyrrolidinones **7s** and **7t** were obtained in poor yields (22 and 10%, respectively).

Next, this reductive amination was extended to 5-aminopentanoic acid **2** in order to synthesise the corresponding piperidinones **3** (Table 3).

Table 3. Scope of the synthesis of piperidinones **3** and 2-azepanones **9** by reductive amination of carbonyl derivatives with 5-aminopentanoic acid and 6-aminohexanoic acid, respectively.^[a]



[a] General reaction conditions: **1** (0.6 mmol), **2** or **8** (0.5 mmol), PhSiH₃ (2 equiv.) and ethanol (0.5 mL), 40 °C, 18 h. Isolated yields of **3** or **9** are shown; [b] Reaction for 24 h; [c] Reaction for 48 h.

In the selected examples represented in Table 3, *p*-methoxy- and *p*-chloro- substituted benzaldehydes led to the corresponding piperidinones **3b** and **3c**, in 62 and 65% yields, respectively. Methyl ester reducible functional group was also tolerated affording **3d** in 51% yield. 6-Aminohexanoic acid **8** was then evaluated to prepare 2-azepanones **9** as shown in Table 3. Thus, benzaldehyde, *p*-anisaldehyde and *p*-chlorobenzaldehyde furnished **9a-9c** in moderate yields (35-43%). Methyl 4-formylbenzoate can be also transformed to the corresponding 2-azepanone **9d** in 48% without alteration of the ester moiety.

Interestingly, this transformation resulted from (i) the imine formation by condensation of amine with carbonyl derivatives, (ii) following by its reduction and finally an amidation of the acid moiety. Importantly, this transformation seems to be specific to ω -amino fatty acid derivatives. Indeed, the reaction of methyl 4-aminobutyric ester with benzaldehyde under similar conditions did

not lead to the expected pyrrolidinones, but only to the corresponding imine. In order to have experimental evidences of the pathway of this sequential transformation, we performed the reaction of benzaldehyde with *n*-butylamine in ethanol at 40 °C for 18 h (Table 4). In the absence of silane, only the condensation took place generating selectively the corresponding imine **10** (entry 1). In the presence of 2 equiv. of phenylsilane, **10** was still the main product with only trace amount of **11**, and **12**, resulting from the reductive amination and the double reductive amination of benzaldehyde, respectively (entry 2). By addition of 1 equiv. of carboxylic acid such as acetic acid, even if aldimine **10** was still obtained as the major compound, a significant amount of the derivatives resulting from reductive amination of benzaldehyde **11** and **12** were detected (70:21:9 ratio) (entry 3). Using a stronger acid such as TFA^[15] led to **11** and **12** in a 82:18 ratio (entry 4). These results clearly demonstrated that Brønsted acids such as carboxylic acids were helpful for the transformation of imines to lactams in the presence of hydrosilanes, *via* the reduction of the imines by hydrosilylation.^[16,17]

Table 4. Experimental evidences for the mechanism pathway.^[a]

Entry	PhSiH ₃ [equiv.]	additive [equiv.]	Conv. [%]	ratio [%]		
				10	11	12
1	PhSiH ₃ [0]	-	95	100	0	0
2	PhSiH ₃ [2]	-	> 99	93	3	3
3	PhSiH ₃ [2]	CH ₃ CO ₂ H [1]	94	70	21	9
4	PhSiH ₃ [2]	TFA [1]	> 99	0	82	18

[a] General reaction conditions: **1a** (0.5 mmol), *n*-butylamine (0.5 mmol), PhSiH₃ (0-2 equiv.) and ethanol (0.5 mL), 40 °C, 18 h. GC-yields.

In summary, this contribution described a simple reductive procedure for the easy preparation of *N*-substituted lactams (including pyrrolidinones, piperidinones and 2-azepanones) starting from ω -amino fatty acids and a variety of carbonyl derivatives, *via* reductive amination performed under hydrosilylation conditions. The reaction proceeds with a nice functional group tolerance as reducible groups such as carboxylic ester, nitro, cyano and C=C bond were well tolerated. Interestingly, this transformation involving a hydrosilylation step did not need an external catalyst, the acid moiety playing the role of internal activator during the reaction.

Experimental Section

Typical procedure for catalytic reductive amination of carbonyl derivatives with ω -amino fatty acids leading to lactams. In a 20 mL Schlenk tube under air, ω -amino fatty acids **2**, **6** or **8** (0.5 mmol), carbonyl derivatives **1** (0.6 mmol), PhSiH₃ (123.4 μ L, 2 equiv.) and ethanol (0.5 mL) were stirred at 40 °C for 18 h. After cooling to room temperature, the reaction mixture was dried under reduced pressure, and then the crude mixture was distilled using a bulb-to-bulb distillation apparatus. The distilled residue was then subjected to column chromatography (silica gel; ethyl acetate as the eluent) to afford the desired product.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: ω -Amino fatty acids • Hydrosilylation • Lactam • Reductive Amination • Metal catalyst Free

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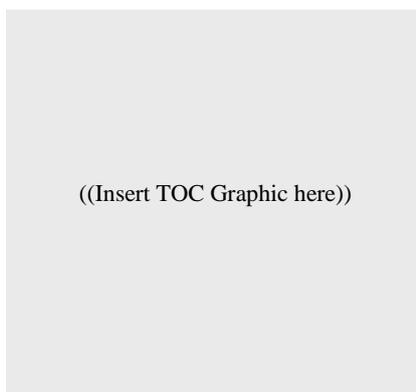
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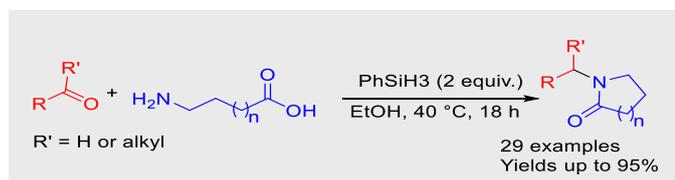
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Layout 2:

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An unprecedented efficient method for the reductive amination of carbonyl derivatives with ω -amino fatty acids under hydrosilylation conditions was developed leading to the corresponding lactams. A variety of pyrrolidinones, piperidinones, 2-azepanones were prepared in up to 95% isolated yields (29 examples).

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