Cyclizations

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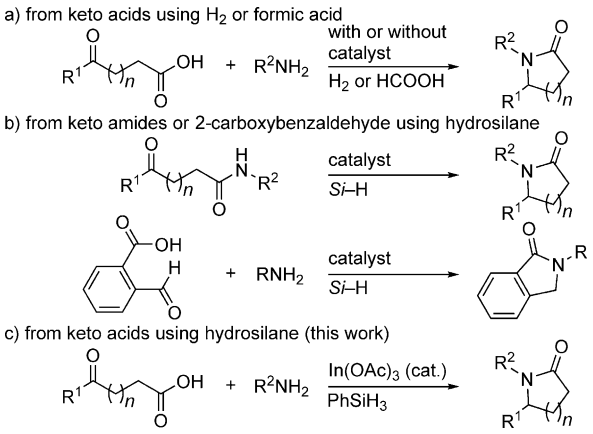
Reductive Amination/Cyclization of Keto Acids Using a Hydrosilane for Selective Production of Lactams versus Cyclic Amines by Switching of the Indium Catalyst

*Yohei Ogiwara, Takuya Uchiyama, and Norio Sakai**

Abstract: *Described herein is that the catalytic construction of N-substituted five- and six-membered lactams from keto acids with primary amines by reductive amination, using an indium/silane combination. This relatively benign and safe catalyst/reductant system tolerates the use of a variety of functional groups, especially ones that are reduction-sensitive. A direct switch from synthesizing lactams to synthesizing cyclic amines is achieved by changing the catalyst from $In(OAc)_3$ to InI_3. This conversion occurs by further reduction of the lactam using the indium/silane pair.*

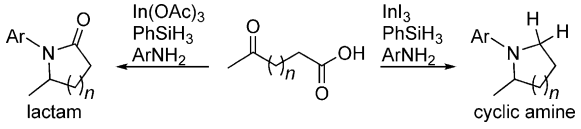
Since *N*-substituted lactams are important core structural units in many research fields such as organic and pharmaceutical chemistry, an efficient and versatile method for the construction of valuable lactam skeletons from simple and inexpensive substrates would be desirable. The combination of a reductive amination of keto acids and a subsequent cyclization is one of the most attractive approaches to these ring structures, because the starting keto acids are easily acquired compounds. Levulinic acid (**1**; 4-oxopentanoic acid) is accessible from lignocellulosic biomass, and the other starting compounds are primary amines which readily introduce a variety of *N*-substituents to the ring skeleton. In this context, several catalytic or catalyst-free preparations of *N*-substituted lactams using keto acids and primary amines through reductive amination have been reported, but the reducing reagents are limited to relatively active ones, such as H_2 or formic acid (Scheme 1 a).[1] In terms of functional-group tolerance and chemoselectivity for the production of fine chemicals, hydrosilanes are mild and highly selective reducing agents which are considered alternative reductants for achieving this concept, even though siloxane waste is an unavoidable byproduct.[2,3] Although several synthetic procedures, such as hydrosilane reductive amination of keto-amides[4] and 2-carboxybenzaldehyde[5] for the synthesis of *N*-substituted lactams have been reported (Scheme 1 b), to the best of our knowledge, the use of keto acids as a substrate in this type of conversion remains unexplored.

We report herein a one-pot $In(OAc)_3$-catalyzed preparation of *N*-substituted lactams from keto acids and primary amines by a reductive amination strategy using $PhSiH_3$ as a mild reductant (Scheme 1 c). A large variety of aromatic and aliphatic amines are readily available for this reaction, which gives *N*-substituted lactams and transforms 2-carboxybenzaldehyde into *N*-arylisoindolinone derivatives.



Scheme 1. Reductive amination strategies for the synthesis of lactams.

Also, we disclose a divergent synthesis for cyclic amines, such as pyrrolidine and piperidine, from the reaction of keto acids with amines in the presence of the InI_3 (Scheme 2). InI_3 has a stronger Lewis acidity than $In(OAc)_3$, and thus results in an over-reduction of the lactam to give *N*-substituted pyrrolidines and piperidines.[6]



Scheme 2. Selective production of lactams and cyclic amines (this work).

Initially, we conducted the reaction of levulinic acid (**1**) with 1 equivalent of 4-methylaniline (**2a**) in the presence of an indium catalyst and a hydrosilane. After several screenings of the reaction conditions,[7] 1 mol % of $In(OAc)_3$ with 1 equivalent of $PhSiH_3$ in toluene at 120 °C was found to be the best catalytic system, thus giving the desired γ-lactam **3a** in a 98 % yield upon isolation [Eq. (1)].

The use of other primary amines (**2**) as a nitrogen source for the lactam skeleton was explored with the $In(OAc)_3$/$PhSiH_3$ system (Scheme 3). A variety of aromatic amines, **2b**–**u**, were applicable in this reaction and formed the corre-

[*] Dr. Y. Ogiwara, T. Uchiyama, Prof. Dr. N. Sakai
Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science
2641 Yamazaki, Noda, Chiba 278-8510 (Japan)
E-mail: sakachem@rs.noda.tus.ac.jp

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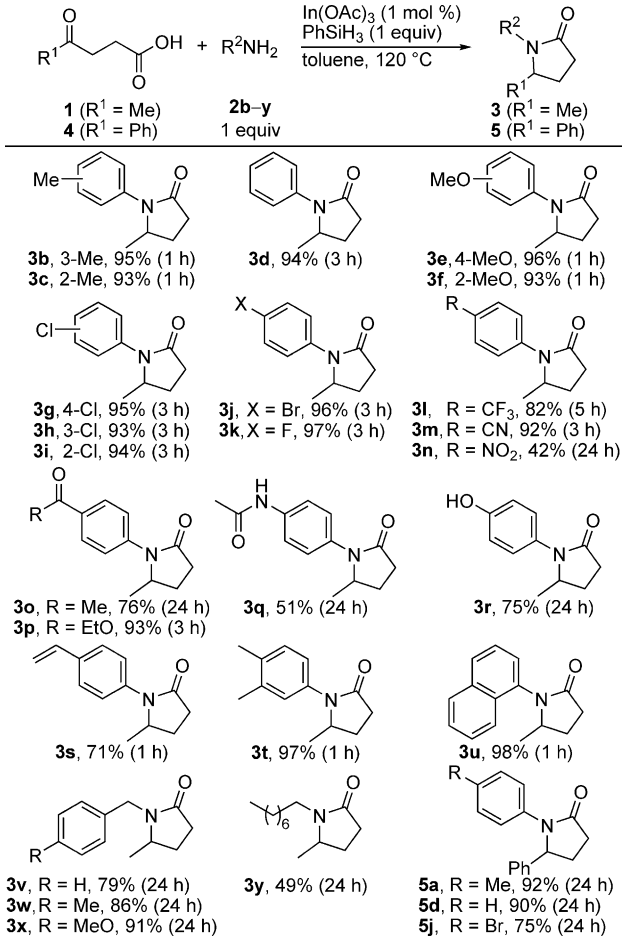
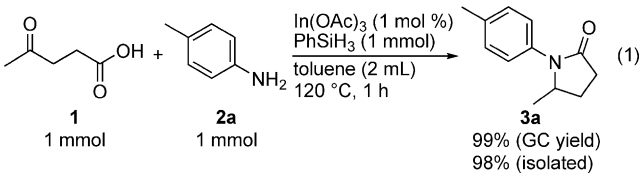


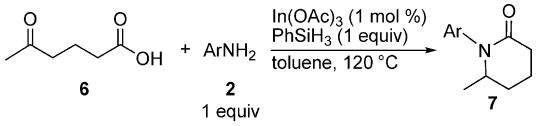
Scheme 3. Substrate scope for γ-lactams. Reaction conditions: **1** or **4** (1 mmol), **2** (1 mmol), $In(OAc)_3$ (0.01 mmol), and $PhSiH_3$ (1 mmol) in toluene (2 mL) at 120 °C. Yields of isolated **3** and **5** are shown.



sponding *N*-aryl γ-lactams **3b**–**u** in excellent yields. The benzylic amines **2v**–**x** and alkyl amine **2y** were also converted into the corresponding *N*-benzyl (**3v**–**3x**) and alkyl (**3y**) γ-lactams, respectively, in good yields, although the process required a 24 hour reaction time. When 3-benzoylpropionic acid (**4**) was used as a substrate, the reactivity was slightly decreased compared with that of **1**, but the corresponding 5-phenyl-substituted *N*-aryl γ-lactams **5a**, **5d**, and **5j** were obtained in good yields. A noteworthy feature of these examples is that functional groups such as a cyano, nitro, acyl, ethoxycarbonyl, amide, hydroxy, and vinyl group, which are sensitive to the conventional reductive amination conditions, were well-tolerated under our reaction conditions. These results proved that an $In(OAc)_3/PhSiH_3$ system functions as a relatively mild reducing system.

To construct the δ-lactam skeleton, an annulation of 4-acetylbutyric acid (**6**) with various aniline derivatives (**2**) was next conducted (Table 1). The reactions of the methyl-substituted anilines **2a**–**c** and aniline (**2d**), as well as 4- and 2-methoxy anilines (**2e** and **2f**) afforded the *N*-aryl δ-lactams

Table 1: Substrate scope for δ-lactams.[a]



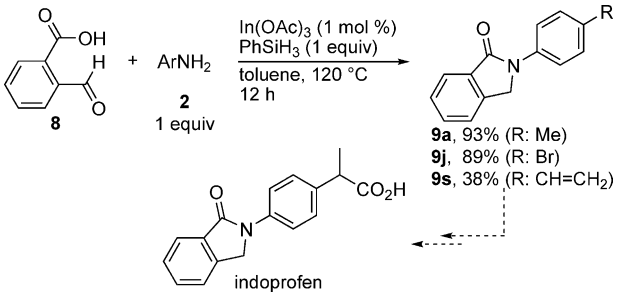
Entry	Ar	*t* [h]	Product	Yield [%][b]
1	4-MeC_6H_4 (**2a**)	1	**7a**	91
2	3-MeC_6H_4 (**2b**)	1	**7b**	94
3	2-MeC_6H_4 (**2c**)	1	**7c**	92
4	Ph (**2d**)	3	**7d**	88
5	4-$MeOC_6H_4$ (**2e**)	1	**7e**	91
6	2-$MeOC_6H_4$ (**2f**)	1	**7f**	90
7	4-ClC_6H_4 (**2g**)	3	**7g**	94
8	3-ClC_6H_4 (**2h**)	3	**7h**	90
9	2-ClC_6H_4 (**2i**)	3	**7i**	92
10	4-BrC_6H_4 (**2j**)	5	**7j**	91
11	4-FC_6H_4 (**2k**)	2	**7k**	96
12	4-NCC_6H_4 (**2m**)	5	**7m**	89
13	4-$EtOC(O)C_6H_4$ (**2p**)	5	**7p**	91
14	3,4-$Me_2C_6H_3$ (**2t**)	1	**7t**	94
15	3,4-$Cl_2C_6H_3$ (**2z**)	3	**7z**	87

[a] Reaction conditions: **6** (1 mmol), **2** (1 mmol), $In(OAc)_3$ (0.01 mmol), and $PhSiH_3$ (1 mmol) in toluene (2 mL) at 120 °C. [b] Yield of isolated product.

7a–**f** in excellent yields (entries 1–6). Anilines bearing a halogen atom (**2g**–**k**), a cyano group (**2m**), and an ethoxycarbonyl group (**2p**) also provided the corresponding products **7g**–**p** without the loss of those functional groups. In the cases with disubstituted anilines, the six-membered lactams **7t** and **7z** were isolated in 94 and 87% yields, respectively (entries 14 and 15).

One of the most advantageous features of the present reaction is that complete conversion into the lactam can be achieved by using a small quantity of the catalyst with only 1 equivalent of each of the substrates, a keto acid, an amine, and a silane. Hence, the siloxane which is generated during the reaction is the sole organic byproduct and enables facile isolation of the *N*-substituted lactam in its pure form by a simple workup. Indeed, after a gram-scale reaction of **1** (10 mmol), **2a** (10 mmol), and $PhSiH_3$ (10 mmol) with 0.05 mol% $In(OAc)_3$ in toluene for 48 hours, the desired lactam **3a** was isolated in a 94% yield (1.78 g) by the addition of methanol, filtration of the precipitate derived from the siloxane, and silica gel column chromatography. The turnover number (TON) was 1880 and **3a** was isolated in analytically pure form (as determined by ^1H NMR spectroscopy).[7]

The use of a substrate other than a keto acid for this transformation was next investigated (Scheme 4). Conversion of 2-carboxybenzaldehyde (**8**) using the anilines **2a**, **2j**, and **2s** proceeded to provide the corresponding *N*-arylisoindolinone derivatives **9a**, **9j**, and **9s** in 38–93% yields. Isoindolinone



Scheme 4. Applications for isoindolinone derivatives.

skeletons have been found in many important biologically active compounds such as indoprofen, which is used as a nonsteroidal anti-inflammatory drug.[8] The carbon–bromine bond in **9j** and a vinyl functional group in **9s** makes both of them good reaction sites for further transformations, and these products are considered precursor compounds for indoprofen.[9]

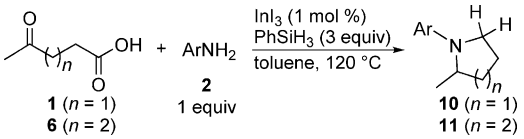
During the screening of a series of indium catalysts for reductive amination/cyclization [Eq. (1)], the *N*-aryl pyrrolidine derivative **10a** was generated when InI_3, which is known as a stronger Lewis acid than $In(OAc)_3$, was used as a catalyst.[7] The pyrrolidine **10a** was also obtained by reduction of **3a** using an $InI_3/PhSiH_3$ system. In contrast, the reduction was not observed in case of $In(OAc)_3$ (Scheme 5).

Scheme 5. Formation of the cyclic amine **10a** by reduction of the lactam **3a**.

Since **10** would be formed by the further reduction of **3** after the reductive amination/cyclization, an InI_3-catalyzed formation of **10** was examined with an excess of $PhSiH_3$ (3 equiv; Table 2). The reaction of **1** with **2a** provided **10a** as the sole product in a 91% yield (entry 1), and annulation of **6** with **2a** successfully produced the *N*-aryl piperidine **11a** in a 85% yield (entry 2). The anilines **2d** and **2k** also provided the corresponding five- and six-membered cyclic amines (**10** and **11**) selectively without any lactams as byproducts (entries 3–6).

To gain some insight into the mechanism of this reaction, several spectroscopic investigations were conducted by using ^1H NMR analysis.[7] The reaction of the keto acid **1** and **2d** with $In(OAc)_3/PhSiH_3$ in $[D_8]$toluene at 120 °C for 3 hours afforded a new singlet, ascribed to H_2 ($\delta = 4.51$ ppm), with the signals for the lactam product **3d**. It was implied that there was formation of a silyl ester from **1** and $PhSiH_3$ with the generation of H_2. However, no other new signals, including those of the silyl ester, were observed during this reaction

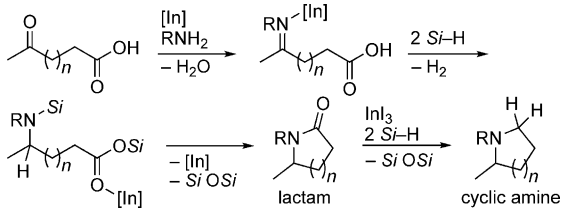
Table 2: InI_3-catalyzed reductive transformation for cyclic amines.[a]



Entry	*n*	Substrate	Ar	Product	Yield [%][b]
1	1	**1**	4-MeC_6H_4 (**2a**)	**10a**	91
2	2	**6**	4-MeC_6H_4	**11a**	85
3	1	**1**	Ph (**2d**)	**10d**	92
4	2	**6**	Ph	**11d**	89
5	1	**1**	4-FC_6H_4 (**2k**)	**10k**	86
6	2	**6**	4-FC_6H_4	**11k**	84

[a] Reaction conditions: **1** or **6** (1 mmol), **2** (1 mmol), InI_3 (0.01 mmol), and $PhSiH_3$ (3 mmol) in toluene (2 mL) at 120 °C for 24 h. [b] Yield of isolated product.

series (see Figure S2 in the Supporting Information). It can be considered that the rate-determining step would exist in the initial stage of all processes in this reaction. When using a mixture of **1**, $In(OAc)_3$, and $PhSiH_3$ (the conditions without **2d**), no reaction proceeded after 4 hours (see Figure S3). In contrast, when the reaction of **1**, **2d**, and $In(OAc)_3$ (conditions without $PhSiH_3$) was carried out for 24 hours, several weak signals, which presumably correspond to the imine and/or ketoamide derivatives, appeared. Therefore, when $PhSiH_3$ was added into the mixture, both the formation of the desired lactam **3d** and the disappearance of the imine and/or ketoamide derivative signals were observed, thus confirming the stepwise reaction (see Figure S4). Although additional detailed information about the intermediates have not been obtained at this stage, we propose a possible mechanism through a reductive amination at the carbonyl group of a keto acid (Scheme 6). First, the condensation of a ketone with



Scheme 6. A plausible mechanism.

a primary amine occurs to form a ketimine. This step is estimated to be the rate-determining step. Then, a silyl ester forms through dehydrogenative silylation of a carboxylic acid with concomitant generation of H_2[10] and hydrosilylation of the imine. Subsequently, the cyclization affords the *N*-substituted lactams with the release of the indium catalyst and the siloxane. In contrast, another pathway through the cyclization/hydrogenation from a ketoamide is also possible.[4] In the case of InI_3, an over-reduction of the carbonyl group of the lactam occurs to produce the corresponding pyrrolidine or piperidine skeleton.[11]

In summary, we demonstrated an efficient and straightforward annulation to *N*-substituted γ- and δ-lactams through

an $In(OAc)_3$-catalyzed reductive amination of keto acids using $PhSiH_3$ as a reducing agent. As a nitrogen source, various primary amines are available for this reaction, and a variety of reduction-sensitive groups are tolerated under the reaction conditions. The major byproduct, a siloxane, derived from $PhSiH_3$ can be removed as a precipitate by the simple addition of methanol, and therefore, the desired lactams were obtained easily in a pure form and could even be synthesized on gram-scale. When the reaction was conducted in the presence of InI_3, instead of $In(OAc)_3$, and 3 equivalents of $PhSiH_3$ an over-reduction of the lactam occurred to generate five- and six-membered cyclic amines as the sole products.

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Keywords: amines · cyclizations · indium · lactams · silanes

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[9] Syntheses of indoprofen from either **9j** or **9s** are now in progress.

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[12] The indium salts, $In(OAc)_3$ (Aldrich 99.99%) and InI_3 (Aldrich 99.998%), were purchased and used without purification, these purities were also checked by inductively coupled plasma (ICP) analysis. We regard trace transition-metal impurities of indium salts as unimportant for the observed reactivity. See the Supporting Information for the details (Figure S1).

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