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Synthesis of nitrogen heterocycles *via* α-aminoalkyl radicals generated from α-silyl secondary amines under visible light irradiation†

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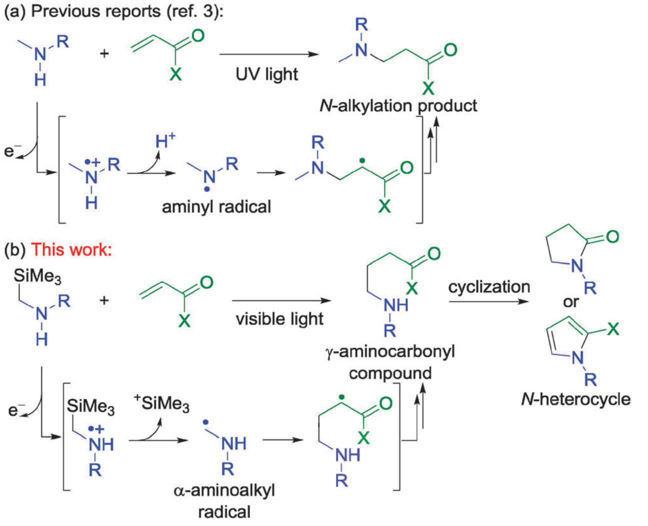
We have succeeded in the visible light-mediated synthetic use of α-aminoalkyl radicals derived from α-silyl secondary amines toward addition to α,β-unsaturated carbonyl compounds. The resulting γ-aminocarbonyl compounds are converted into γ-lactams and pyrroles in a one-pot process.

Five-membered nitrogen heterocycles such as γ-lactams and pyrroles are found in various natural products and pharmaceuticals.[1,2] Construction of these skeletons in a simple and efficient manner is one of the most important topics in synthetic organic chemistry. In this context, the development of a novel synthetic approach for γ-aminocarbonyl compounds composed of a secondary or primary amine moiety plays a pivotal role because a rapid 5-*exo*-cyclization between amine and carbonyl groups gives the corresponding nitrogen heterocycles.[1]

Construction of γ-aminocarbonyl skeletons by the addition of α-aminoalkyl radicals derived from secondary amines to α,β-unsaturated carbonyl compounds under the photoinduced electron transfer conditions is a potentially useful strategy to access the corresponding nitrogen heterocycles.[3] However, in these reaction systems, a large amount of *N*-alkylation products was usually observed due to the formation of aminyl radicals by oxidation of secondary amines (Scheme 1a)[4,5] or direct thermal aza-Michael addition,[6] where the desired γ-aminocarbonyl compounds were obtained only in low yields.[3] As a result, successful examples for synthetic utilization of α-aminoalkyl radicals under UV[3,7] or visible light[8,9] irradiation have been strictly limited to the use of tertiary amine derivatives. These results indicate that the generation and utilization of α-aminoalkyl radicals derived from secondary amines are quite difficult.



Scheme 1 Photoreactions of secondary amines *via* (a) aminyl radicals and (b) α-aminoalkyl radicals.

Hence, we have envisaged the use of α-silylamines as substrates because dissociation of the α-C–Si bond of the radical cations occurs readily, which is considered to be suitable for selective formation of α-aminoalkyl radicals over aminyl radicals (Scheme 1b).[10,11] In fact, we have recently succeeded in the synthetic utilization of α-aminoalkyl radicals generated from α-silyl tertiary amines in the presence of visible light-photoredox catalysts.[8,12] In the course of our study, we have disclosed visible light-mediated synthetic utilization of α-aminoalkyl radicals generated from α-silyl secondary amines toward the addition to α,β-unsaturated carbonyl compounds, where the produced γ-aminocarbonyl compounds are converted into the corresponding γ-lactams and pyrroles in simple one-pot procedures. The preliminary results are described here.

Initial investigations of one-pot synthesis of γ-lactams were conducted using *N*-(trimethylsilylmethyl)aniline (**1a**) and diethyl benzylidenemalonate (**2a**) as substrates (Table 1). In the presence of 1 mol% of [**4a**][BF_4], the reaction of **1a** with 1.2 equiv. of **2a** was carried out in *N*-methylpyrrolidone (NMP) under visible light

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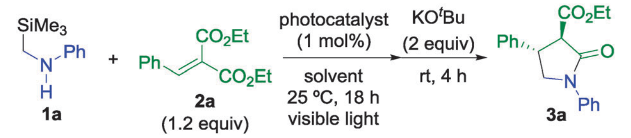
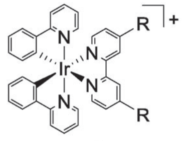
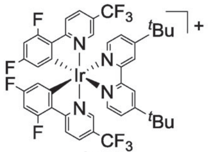
Table 1 Reactions of *N*-(trimethylsilylmethyl)aniline (**1a**) with diethyl benzylidenemalonate (**2a**)^a



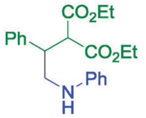
Entry	Photocatalyst	Solvent	Yield of **3a**^{b} (%)	*Trans*/*cis*^{c}
1	[**4a**][BF$_4$]	NMP	89	>20/1^d
2^{e,f}	[**4a**][BF$_4$]	NMP	34	>20/1
3	[**4a**][BF$_4$]	DMF	83	>20/1
4	[**4a**][BF$_4$]	DMSO	73	12/1
5	[**4a**][BF$_4$]	EtOH	31	14/1
6	[**4a**][BF$_4$]	THF	6	>20/1
7	[**4b**][BF$_4$]	NMP	74	>20/1
8	[**4c**][BF$_4$]	NMP	77	>20/1
9	[Ru(bpy)$_3$][BF$_4$]$_2$	NMP	86	>20/1



4a: R = ^{t}Bu
4b: R = H



4c



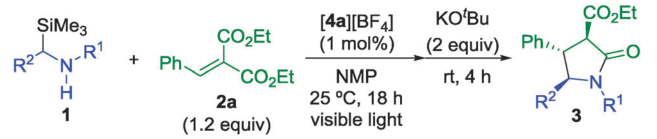
3a′

[a] All reactions of **1a** (0.25 mmol) with **2a** (0.30 mmol) were carried out in the presence of a photocatalyst (0.0025 mmol) in solvent (2.5 mL) under 14 W white LED illumination at 25 °C for 18 h. Then, the resulting mixture was treated with KO^{t}Bu (0.50 mmol) at room temperature for 4 h. [b] Isolated yield. [c] The isomeric ratio was determined by ^{1}H NMR of the crude products. [d] The isomeric ratio of the isolated **3a** is 14/1. [e] Without treatment with KO^{t}Bu. [f] **3a′** is obtained in 58% yield.

illumination using a 14 W white LED at 25 °C for 18 h. After the photoreaction, treatment of the resulting reaction mixture with 2 equiv. of KO^{t}Bu afforded *N*-phenyl-3-ethoxycarbonyl-4-phenyl-2-pyrrolidone (**3a**) in 89% yield (Table 1, entry 1). In the absence of base, uncyclized product (**3a′**) was obtained in 58% yield along with **3a** in 34% yield (Table 1, entry 2). These results indicate that addition of base is important to obtain the γ-lactam in a high yield. When reactions were carried out in other polar solvents such as *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO), **3a** was obtained in lower yields (Table 1, entries 3 and 4). Ethanol and tetrahydrofuran (THF) were not effective solvents in this reaction system (Table 1, entries 5 and 6). Use of other iridium complexes ([**4b**][BF$_4$] and [**4c**][BF$_4$]) and ruthenium(II) tris(2,2′-bipyridyl) complex ([Ru(bpy)$_3$][BF$_4$]$_2$) as photocatalysts gave **3a** in slightly lower yields (Table 1, entries 7–9). Separately, we confirmed that the photoreaction did not proceed at all in the absence of photocatalysts or visible light illumination.

Next, we investigated reactions of various α-silylamines (**1**) with **2a** (Table 2). Use of α-silylamines bearing an electron-withdrawing or donating group on the benzene ring afforded the corresponding products in excellent yields (Table 2, entries 1–5). Introduction of a naphthyl group instead of a phenyl ring was successful to give **3g** in 75% yield (Table 2, entry 6). Dialkylamine derivative **1h** was also applicable to this reaction system to give the corresponding products in 44% yields (Table 2, entry 7). The use of an α-aminoethyl radical generated from 1-(trimethylsilyl)ethyl amine (**1i**) gave the corresponding tri-substituted γ-lactam (**3i**) in 62% yield (Table 2, entry 8). Unfortunately, when a primary amine derivative (trimethylsilylmethyl)amine and an amide derivative *N*-(trimethylsilylmethyl)acetamide were used as substrates, no formation of the corresponding products was observed.

Table 2 Reactions of α-silyl secondary amines (**1**) with diethyl benzylidenemalonate (**2a**)^a

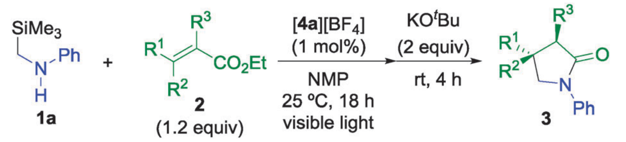


Entry	α-Silylamine (**1**)	Yield of **3**^{b} (%)	*Trans*/*cis*^{c}
1	R^1 = 4-ClC$_6$H$_4$, R^2 = H (**1b**)	95 (**3b**)	>20/1
2	R^1 = 4-FC$_6$H$_4$, R^2 = H (**1c**)	85 (**3c**)	19/1
3	R^1 = 4-MeC$_6$H$_4$, R^2 = H (**1d**)	90 (**3d**)	20/1
4^d	R^1 = 2-MeC$_6$H$_4$, R^2 = H (**1e**)	66 (**3e**)	15/1
5^e	R^1 = 4-MeOC$_6$H$_4$, R^2 = H (**1f**)	79 (**3f**)	6/1
6	R^1 = 1-Naphthyl, R^2 = H (**1g**)	75 (**3g**)	9/1
7^{d,f}	R^1 = ^{t}Bu, R^2 = H (**1h**)	44 (**3h**)	7/1
8	R^1 = Ph, R^2 = Me (**1i**)	62 (**3i**)	6/1^g

[a] All reactions of **1** (0.25 mmol) with **2a** (0.30 mmol) were carried out in the presence of [**4a**][BF$_4$] (0.0025 mmol) in NMP (2.5 mL) under 14 W white LED illumination at 25 °C for 18 h. Then, the resulting mixture was treated with KO^{t}Bu (0.50 mmol) at room temperature for 4 h. [b] Isolated yield. [c] The isomeric ratio was determined by ^{1}H NMR of the isolated products. [d] Treatment with KO^{t}Bu was done at 100 °C for 17 h. [e] For 48 h of photoreaction. [f] **1h** (0.30 mmol) and **2a** (0.25 mmol) were used. [g] The ratio of two major isomers.

Reactions of *N*-(trimethylsilylmethyl)aniline (**1a**) with a variety of α,β-unsaturated esters (**2**) were examined (Table 3). Use of α,β-unsaturated esters bearing various aromatic and alkyl groups gave the corresponding products in high yields (Table 3, entries 1–7). Introduction of a cyano group instead of an ester group was successful to give **3q** in 81% yield (Table 3, entry 8). When ethyl acrylate (**2j**) was used, **3r** was obtained in 47% yield (Table 3, entry 9). Tetra-substituted

Table 3 Reactions of *N*-(trimethylsilylmethyl)aniline (**1a**) with α,β-unsaturated esters (**2a**)^a



Entry	α,β-Unsaturated ester (**2**)	Yield of **3**^{b} (%)	*Trans*/*cis*^{c}
1	R^1 = 4-ClC$_6$H$_4$, R^2 = H, R^3 = CO$_2$Et (**2b**)	79 (**3j**)	>20/1
2	R^1 = 4-MeC$_6$H$_4$, R^2 = H, R^3 = CO$_2$Et (**2c**)	79 (**3k**)	20/1
3	R^1 = 3-MeC$_6$H$_4$, R^2 = H, R^3 = CO$_2$Et (**2d**)	62 (**3l**)	>20/1
4	R^1 = 4-MeOC$_6$H$_4$, R^2 = H, R^3 = CO$_2$Et (**2e**)	81 (**3m**)	20/1
5	R^1 = 4-PhC$_6$H$_4$, R^2 = H, R^3 = CO$_2$Et (**2f**)	61 (**3n**)	14/1
6	R^1 = 2-Naphthyl, R^2 = H, R^3 = CO$_2$Et (**2g**)	61 (**3o**)	19/1
7	R^1 = ^{n}Pr, R^2 = H, R^3 = CO$_2$Et (**2h**)	79 (**3p**)	11/1
8^d	R^1 = Ph, R^2 = H, R^3 = CN (**2i**)	81 (**3q**)	8/1
9	R^1 = R^2 = R^3 = H (**2j**)	47 (**3r**)	—
10	R^1 = R^2 = Me, R^3 = CO$_2$Et (**2k**)	77 (**3s**)	—

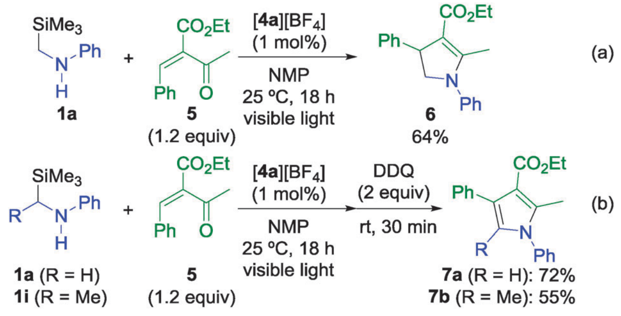
[a] All reactions of **1a** (0.25 mmol) with **2** (0.30 mmol) were carried out in the presence of [**4a**][BF$_4$] (0.0025 mmol) in NMP (2.5 mL) under 14 W white LED illumination at 25 °C for 18 h. Then, the resulting mixture was treated with KO^{t}Bu (0.50 mmol) at room temperature for 4 h. [b] Isolated yield. [c] The isomeric ratio was determined by ^{1}H NMR of the isolated products. [d] Treatment with KO^{t}Bu was done at 100 °C for 17 h.

alkene **2k** was also applicable to give the corresponding γ-lactam (**3s**) in 77% yield (Table 3, entry 10).

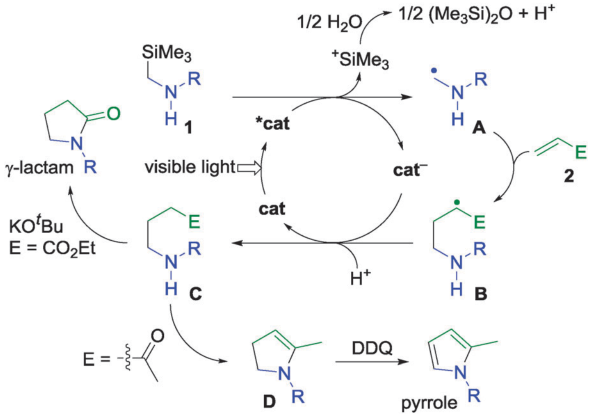
The success in synthesis of γ-lactams prompted us to investigate other nitrogen heterocycles such as pyrroles. We have designed α,β-unsaturated ketones as substrates for the construction of a pyrrole ring. When the reaction of **1a** with an α,β-unsaturated ketone derivative (**5**) was examined under similar reaction conditions to the γ-lactam synthesis, dihydropyrrole (**6**) was obtained in 64% yield (Scheme 2a). Encouraged by this result, we have successfully developed one-pot synthesis of pyrroles by oxidation of dihydropyrroles (Scheme 2b). After photoreactions of α-silyl secondary amines (**1a** and **1i**) with **5**, subsequent treatment of the resulting mixture with 2 equiv. of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for 30 min gave the corresponding tri- and tetra-substituted pyrroles (**7a** and **7b**) in high yields.

To obtain mechanistic insight, some additional experiments were carried out. At first, the quantum yield of the reaction of **1a** with **2a** was determined to be 0.13. The value is in the common range of the photoredox reactions which proceed by a sequential redox process.[8] Next, we monitored the photoreaction of **1a** with **2a** by GC-MS because isolation of the primary products without an aqueous work-up was not possible due to the high boiling point of NMP. GC-MS analyses indicate that the reaction mixture includes hexamethyldisiloxane and **3a′** (see Table 1 for the structure of **3a′**). This result shows that the trimethylsilyl group was captured by adventitious water[8,10] and **3a′** is the primary product in the reaction system. Separately, we carried out the reaction of **1a** with **2a** in the presence of a small amount of water (NMP/H_2O = 25/1), where **3a** was obtained in 86% yield. This result indicates that the additional water did not affect the yield of γ-lactam.

Based on the experimental results, the reactions are considered to proceed *via* a reaction pathway similar to the previously reported sequential redox pathway, as shown in Scheme 3.[8] At first, single electron oxidation of α-silyl secondary amines **1** by a photo-excited catalyst (***cat**) occurs. Then, α-aminoalkyl radicals (**A**) are formed along with generation of trimethylsilyl cations.[10] The trimethylsilyl cation is captured by adventitious water in the reaction system to give hexamethyldisiloxane and protons. Addition of **A** to α,β-unsaturated carbonyl compounds **2** affords the corresponding radical intermediates (**B**). The reduction of **B**[13] by a reduced catalyst ($\mathbf{cat}^-$)[14] and subsequent protonation give γ-aminocarbonyl compounds (**C**) as primary products. Subsequently, base-mediated cyclization of **C** (E = CO_2Et) affords γ-lactams, while oxidation of dihydropyrroles (**D**) formed by dehydration condensation of **C** (E = $COCH_3$) gives pyrroles.



Scheme 2 One-pot syntheses of dihydropyrrole (**6**) and pyrroles (**7a** and **7b**).



Scheme 3 Plausible reaction pathways.

In summary, we have developed a novel reaction system for generation and utilization of α-aminoalkyl radicals derived from secondary amines. The α-aminoalkyl radicals were successfully applied toward addition to α,β-unsaturated carbonyl compounds and subsequent cyclization into nitrogen heterocycles such as γ-lactams and pyrroles. We believe that the method described here provides a useful approach for syntheses of various nitrogen heterocycles, which are useful in pharmacological science. Further investigations on scope of substrates and mechanistic details are now under way.

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