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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) $\alpha\text{-aminoalkyl}$ 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**][BF₄], 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 1Reactions of N-(trimethylsilylmethyl)aniline (1a) with diethylbenzylidenemalonate $(2a)^a$



^{*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^tBu (0.50 mmol) at room temperature for 4 h. ^{*b*} Isolated yield. ^{*c*} The isomeric ratio was determined by ¹H NMR of the crude products. ^{*d*} The isomeric ratio of the isolated **3a** is 14/1. ^{*c*} Without treatment with KO^tBu. ^{*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^tBu 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][BF₄]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

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

SiMe	3	CO ₂ Et	[4a][BF ₄] (1 mol%)	KO ^t Bu (2 equiv)	Ph ₄₄	CO ₂ Et
R [∠] N ∣ H		CO ₂ Et	NMP	rt, 4 h	D2	-N_1
1		2a (1.2 equiv)	visible light	nt	R-	3 ^{R'}
Entry	α-Silyla	mine (1)		Yield of 3^b	(%)	Trans/cis ^c
1	$R^1 = 4$ -	CIC_6H_4 , $R^2 = H$ ((1b)	95 (3b)		>20/1
2	$R^1 = 4$ -	FC_6H_4 , $R^2 = H$ (1	lc)	85 (3c)		19/1
3	$R^1 = 4$ -	MeC_6H_4 , $R^2 = H$	(1d)	90 (3d)		20/1
4^d	$R^1 = 2$ -	MeC_6H_4 , $R^2 = H$	(1e)	66 (3e)		15/1
5^e	$R^1 = 4$ -	$MeOC_6H_4$, $R^2 = 1$	H (1f)	79 (3f)		6/1
6	$R^1 = 1$ -	Naphthyl, R ² = F	I (1g)	75 (3g)		9/1
$7^{d,f}$	$\mathbf{R}^1 = {}^t\mathbf{B}$	$u, R^2 = H(1h)$		44 (3h)		7/1
8	$R^1 = Pl$	n, $R^2 = Me(1i)$		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**][BF₄] (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^tBu (0.50 mmol) at room temperature for 4 h. b Isolated yield. c The isomeric ratio was determined by ¹H NMR of the isolated products. d Treatment with KO^fBu 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.

(trimethylsilylmethyl)amine and an amide derivative *N*-(trimethylsilylmethyl)acetamide were used as substrates, no formation of the corresponding products was observed.

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 $\alpha\beta$ -unsaturated esters (2a)^a

SiMe ₃ N ^{Ph} + H 1a	$R^{3} \xrightarrow{CO_{2}Et} CO_{2}Et = \frac{R^{2}}{2}$ (1.2 equiv)	[4a][BF ₄] (1 mol%) NMP 25 °C, 18 h visible light	KO ^t Bu (2 equiv) rt, 4 h	R ¹ , R ³ R ² N 3 Ph	D
Entry α,β-Unsat	urated ester (2)		Yiel of 3	d ^b (%) Trans	s/cis ^c
$ \begin{array}{ccc} 1 & R^{1} = 4\text{-CIC} \\ 2 & R^{1} = 4\text{-Me} \\ 3 & R^{1} = 3\text{-Me} \\ 4 & R^{1} = 4\text{-Me} \\ 5 & R^{1} = 4\text{-Ph} \\ 6 & R^{1} = 2\text{-Na} \\ 7 & R^{1} = {}^{n}\text{Pr}, 1 \\ 8^{d} & R^{1} = \text{Ph}, \text{F} \\ 9 & R^{1} = R^{2} = \\ 10 & R^{1} = R^{2} = \\ \end{array} $	$C_{6}H_{4}, R^{2} = H, R^{2}$ $C_{6}H_{4}, R^{2} = H, R^{3}$ $C_{6}H_{4}, R^{2} = H, R^{3}$ $C_{7}C_{6}H_{4}, R^{3} = CO$ $R^{2} = H, R^{3} = CO$ $R^{3} = H (2j)$ Me. R ³ = CO ₂ EI	$a^{3} = CO_{2}Et (2c^{3} = CO_{2}Et (2c^{3})))$ (2i) (2i)	2b) 79 ((2c) 79 ((2d) 62 ((12d) 62 ((12d) 61 ((2g) 61 (79 (81 (47 (77 ($\begin{array}{llllllllllllllllllllllllllllllllllll$	'1 '1 '1 '1 '1 '1 '1

^{*a*} All reactions of **1a** (0.25 mmol) with **2** (0.30 mmol) were carried out in the presence of [**4a**][BF₄] (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 ¹H 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 tetrasubstituted 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/H₂O = 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 (**cat**⁻)¹⁴ and subsequent protonation give γ -aminocarbonyl compounds (**C**) as primary products. Subsequently, base-mediated



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



Scheme 3 Plausible reaction pathways

cyclization of C (E = CO₂Et) affords γ -lactams, while oxidation of dihydropyrroles (**D**) formed by dehydration condensation of C (E = COCH₃) gives pyrroles.

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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