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COMMUNICATION

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

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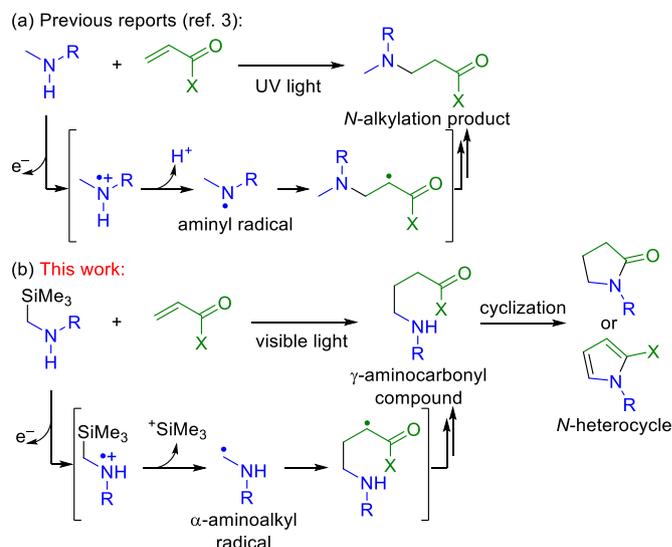
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We have succeeded in the visible light-mediated synthetic use of α -aminoalkyl radicals derived from α -silyl secondary-amines toward addition to α,β -unsaturated carbonyl compounds. The resulting γ -aminocarbonyl compounds are converted into γ -lactams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

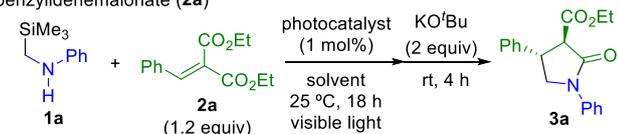
Hence, we have envisaged the use of α -silylamines as substrates because dissociation of the α -C-Si bond of the radical cations occurs readily, which is considered to be suitable for selective formation of α -aminoalkyl radicals over aminyl radicals (Scheme 1b).^{10,11} In fact, we have recently succeeded 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



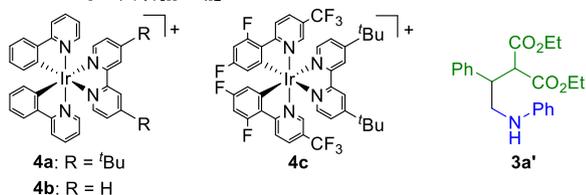
Scheme 1 Photoreactions of secondary amines via (a) aminyl radicals and (b) α -aminoalkyl radicals.

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 for one-pot synthesis of γ -lactams were conducted with *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 illumination with 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'**) is obtained in 58% yield along with **3a** in 34% yield (Table 1, entry 2). This result indicates addition of base

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

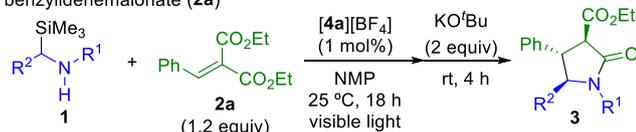
Entry	Photocatalyst	Solvent	Yield of 3a ^b	<i>trans/cis</i> ^c
1	[4a][BF ₄]	NMP	89%	>20/1 ^d
2 ^{e,f}	[4a][BF ₄]	NMP	34%	>20/1
3	[4a][BF ₄]	DMF	83%	>20/1
4	[4a][BF ₄]	DMSO	73%	12/1
5	[4a][BF ₄]	EtOH	31%	14/1
6	[4a][BF ₄]	THF	6%	>20/1
7	[4b][BF ₄]	NMP	74%	>20/1
8	[4c][BF ₄]	NMP	77%	>20/1
9	[Ru(bpy) ₃][BF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



^a All reactions of **1a** (0.25 mmol) with **2a** (0.30 mmol) were carried out in the presence of 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. ^e Without treatment with KO^tBu. ^f **3a**' is obtained in 58% yield.

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**][BF₄] and [**4c**][BF₄]) 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.

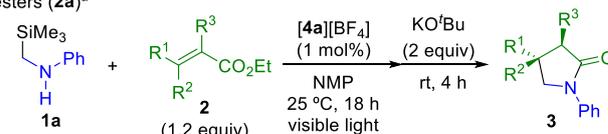
Next, we investigated reactions of various α -silylamines (**1**) with

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

Entry	α -Silylamine (1)	Yield of 3 ^b	<i>trans/cis</i> ^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**][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^tBu is 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.

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

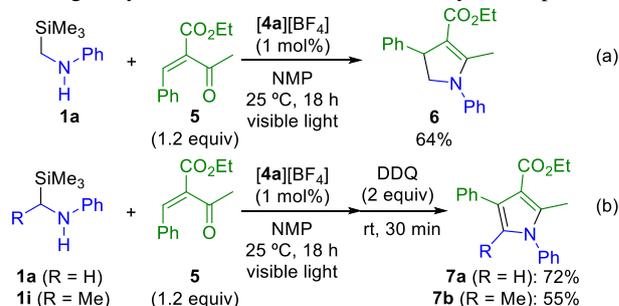
Entry	α,β -Unsaturated ester (2)	Yield of 3 ^b	<i>trans/cis</i> ^c
1	R ¹ = 4-ClC ₆ H ₄ , R ² = H, R ³ = CO ₂ Et (2b)	79% (3j)	>20/1
2	R ¹ = 4-MeC ₆ H ₄ , R ² = H, R ³ = CO ₂ Et (2c)	79% (3k)	20/1
3	R ¹ = 3-MeC ₆ H ₄ , R ² = H, R ³ = CO ₂ Et (2d)	62% (3l)	>20/1
4	R ¹ = 4-MeOC ₆ H ₄ , R ² = H, R ³ = CO 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)	-

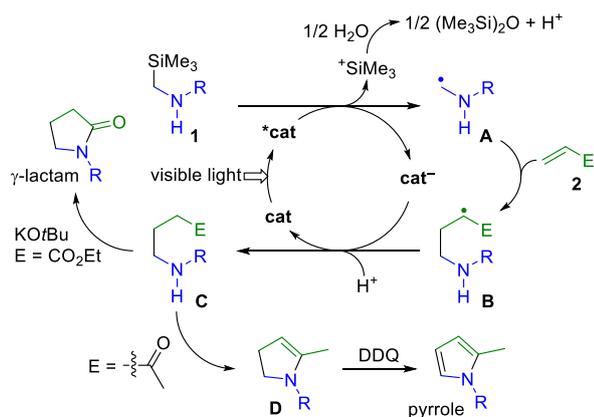
^a All reactions of **1a** (0.25 mmol) with **2** (0.30 mmol) were carried out in the presence of [**4a**][BF₄] (0.0025 mmol) in NMP (2.5 mL) under 14 W white LED illumination at 25 °C for 18 h. Then, the resulting mixture was treated with KO^tBu (0.50 mmol) at room temperature for 4 h. ^b Isolated yield. ^c The isomeric ratio was determined by ¹H NMR of the isolated products. ^d Treatment with KO^tBu is done at 100 °C for 17 h.

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 is successful to give **3g** in 75% yield (Table 2, entry 6). Dialkylamine derivative **1h** is also applicable to this reaction system to give the corresponding products in 44% yield (Table 2, entry 7). The use of 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 primary amine derivative (trimethylsilylmethyl)amine and amide derivative *N*-(trimethylsilylmethyl)acetamide were used as substrates, no formation of the corresponding products were 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 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 α,β -unsaturated ketone derivative (**5**) was examined in 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

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



Scheme 3 Plausible reaction pathways.

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 sequential redox process.⁸ Next, we monitored the photoreaction of **1a** with **2a** by GC-MS because isolation of the primary products without 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 the additional water did not affect the yield of γ -lactam.

Based on the experimental results, the reactions are considered to proceed by a similar reaction pathway 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 photo-excited catalysts (**cat*) occurs. Then, α -aminoalkyl radicals (**A**) are formed along with generation of trimethylsilyl cation.¹⁰ Trimethylsilyl cation is captured by adventitious water in the reaction system to give hexamethyldisiloxane and proton. Addition of **A** to α,β -unsaturated carbonyl compounds **2** affords the corresponding radical intermediates (**B**). The reduction of **B**¹³ by reduced catalyst (*cat*⁻)¹⁴ and subsequent protonation give γ -aminocarbonyl compounds (**C**) as primary products. Subsequently, base-mediated 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 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.

Notes and references

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- (a) M. B. Smith in *Science of Synthesis*, ed. S. M. Weinreb, Theme, Stuttgart, 2005, p. 647. (b) D. StC. Black in *Science of Synthesis*, ed. G. Maas, Theme, Stuttgart, 2001, p. 441.
- (a) B. Nay, N. Riache, L. Evanno, *Nat. Prod. Rep.*, 2009, **26**, 1044; (b) A. Lebedev, *Chem. Heterocycl. Compd.*, 2007, **43**, 673; (c) H. Hoffmann, T. Lindel, *Synthesis*, 2003, 1753; (d) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435.
- (a) S. Das, J. S. D. Kumar, K. Shivaramayya, M. V. George, *J. Photochem. Photobiol. A: Chem.*, 1996, **97**, 139; (b) S. Das, J. S. D. Kumar, K. Shivaramayya, M. V. George, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1797; (c) R. C. Cookson, S. M. deB. Costa, J. Hudec, *Chem. Commun.*, 1969, 753.
- (a) M. Schmittel, A. Burghart, *Angew. Chem. Int. Ed.*, 1997, **36**, 2550; (b) F. D. Lewis, P. E. Correa, *J. Am. Chem. Soc.*, 1984, **106**, 194; (c) F. D. Lewis, B. E. Zebrowski, P. E. Correa, *J. Am. Chem. Soc.*, 1984, **106**, 187; (d) R. W. Fessenden, P. Neta, *J. Phys. Chem.*, 1972, **76**, 2857.
- A. G. Fallis, I. M. Brinza, *Tetrahedron*, 1997, **53**, 17543.
- (a) J. Wang, P. Li, P. Y. Choy, A. S. C. Chan, F. Y. Kwong, *ChemCatChem*, 2012, **4**, 917; (b) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.*, 2009, **15**, 11058.
- (a) D. Harakat, J. Pesch, S. Marinković, N. Hoffmann, *Org. Biomol. Chem.*, 2006, **4**, 1202; (b) A. Bauer, F. Westkämper, S. Grimme, T. Bach, *Nature*, 2005, **436**, 1139; (c) E. S. de Alvarenga, C. J. Cardin, J. Mann, *Tetrahedron*, 1997, **53**, 1457.
- (a) Y. Miyake, Y. Ashida, K. Nakajima, Y. Nishibayashi, *Chem. Eur. J.*, 2014, **20**, 6120; (b) Y. Miyake, K. Nakajima, Y. Nishibayashi, *Chem. Eur. J.*, 2012, **18**, 16473; (c) Y. Miyake, Y. Ashida, K. Nakajima, Y. Nishibayashi, *Chem. Commun.*, 2012, **48**, 6966; (d) Y. Miyake, K. Nakajima, Y. Nishibayashi, *J. Am. Chem. Soc.*, 2012, **134**, 3338.
- (a) H. Zhou, P. Lu, X. Gu, P. Li, *Org. Lett.*, 2013, **15**, 5646; (b) L. R. Espelt, E. M. Wiensch, T. P. Yoon, *J. Org. Chem.* 2013, **78**, 4107; (c) S. Zhu, A. Das, L. Bui, H. Zhou, D. P. Curran, M. Rueping, *J. Am. Chem. Soc.*, 2013, **135**, 1823; (d) X. Ju, D. Li, W. Li, W. Yu, F. Bian, *Adv. Synth. Catal.*, 2012, **354**, 3561; (e) P. Kohls, D. Jadhav, G. Pandey, O. Reiser, *Org. Lett.*, 2012, **14**, 672; (f) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science*, 2011, **334**, 1114.
- (a) D. W. Cho, U. C. Yoon, P. S. Mariano, *Acc. Chem. Res.*, 2011, **44**, 204; (b) U. C. Yoon, P. S. Mariano, *Acc. Chem. Res.*, 1992, **25**, 233.
- (a) D. Lenhart, T. Bach, *Beilstein J. Org. Chem.*, 2014, **10**, 890; (b) E. Meggers, E. Steckhan, S. Blechert, *Angew. Chem. Int. Ed.*, 1995, **34**, 2137; (c) G. Pandey, G. D. Reddy, G. Kumaraswamy, *Tetrahedron*, 1994, **50**, 8185; (d) G. Pandey, G. Kumaraswamy, U. T. Bhalerao, *Tetrahedron Lett.*, 1989, **30**, 6059.
- (a) D. M. Schultz, T. P. Yoon, *Science*, 2014, **343**, 985; (b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (c) T. Koike, M. Akita, *Synlett*, 2013, **24**, 2492; (d) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.*, 2012, **51**, 6828; (e) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102.
- J. M. Kern, P. Federlin, *Tetrahedron Lett.*, 1977, **18**, 837.
- M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal Jr., G. G. Malliaras, S. Bernhard, *Chem. Mater.*, 2005, **17**, 5712.