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PAPER

Radical carbonylation of ω-alkynylamines leading to α-methylene lactams. Synthetic scope and the mechanistic insights†‡

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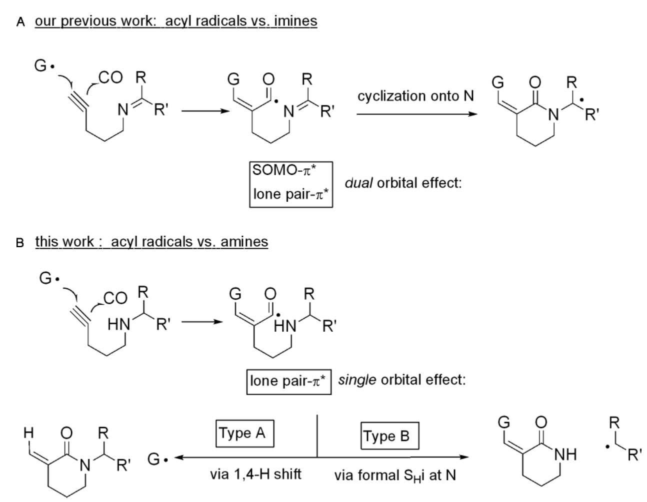
Tin hydride mediated radical carbonylation and cyclization reaction was investigated using a variety of ω-alkynyl amines as substrates. In this reaction α-methylene and α-stannylmethylene lactams having five to eight membered rings were obtained as principal products. In cases where the nitrogen has a substituent capable of giving stable radicals, such as an α-phenethyl group, the lactam ring formation again took place with extrusion of an α-phenethyl radical. Coupled with the subsequent protodestannylation procedure (TMSCl plus MeOH), these reactions provide a useful entry to α-methylene lactams with incorporation of CO as a lactam carbonyl group. In cases where the amines do not have a substituent acting as a radical leaving group, a reaction course involving a 1,4-H shift is chosen so as to liberate tin radicals ultimately. Thus the proposed mechanism involves (i) nucleophilic attack of amine nitrogen onto a carbonyl group of α,β-unsaturated acyl radicals/α-ketenyl radicals *via* lone pair–π* interaction, which leads to zwitterionic radical species, (ii) the subsequent proton shift from N to O to give hydroxyallyl radicals, (iii) 1,4-hydrogen shift from O to C, and (iv) β-scission to give lactams with liberation of tin radicals. DFT calculations reveal that the 1,4-hydrogen shifts, the key step of the reaction mechanism, can proceed under usual reaction conditions. On the other hand, an S_Hi type reaction to give lactams may be the result of the β-scission of the similar zwitterionic radical intermediates. DFT calculations also predict that an S_Hi type reaction would result when the intermediate has a good (radical) leaving group such as a phenethyl group.

Introduction

In pursuit of new carbonylation/cyclization processes based on radical reactions,[1] we recently reported that polarity-matched acyl radical cyclization onto imine N–C double bonds is a powerful tool for the synthesis of lactams (Scheme 1A).[2,3] Theoretical study suggests that the observed highly efficient cyclization of acyl radicals onto imine nitrogen can be rationalized by *dual orbital effects* composed of (i) π* of imine N–C bond, SOMO of acyl radicals, lone pair of nitrogen and π* of acyl radicals.[4] We thought that even in the case of amines, lone pair–π* interaction between an amine nitrogen and acyl radicals would still cause cyclization reactions, providing a useful carbonylative approach to give lactams.[5] The cyclization reaction of acyl radicals at an amine nitrogen indeed proceeds to lead to the formation of a series of lactams, in which carbonyl addition by nitrogen followed by either of two types of elimination reaction (Scheme 1B).[6] In this article, we discuss both synthetic and theoretical aspects of these intriguing acyl radical/amine cyclization reactions.



Scheme 1 Possible [*n*+1] annulation strategies based on radical carbonylation and acyl radical/nitrogen interaction.

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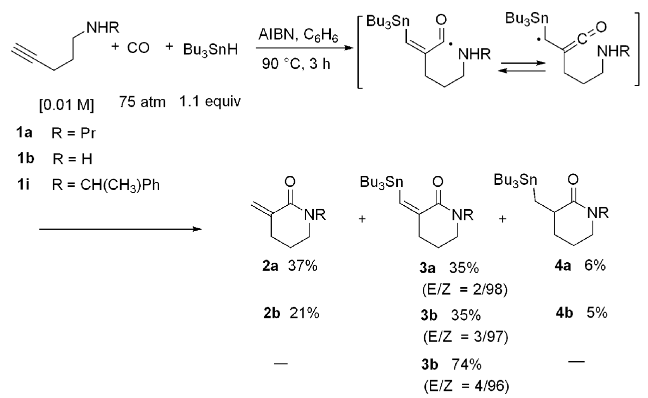
† Electronic supplementary information (ESI) available: spectroscopic data for **2a–2h**, **2j–2o**, **3a–3b**, **4a–b** and optimized geometries and energies for all model compounds. See DOI: 10.1039/c1ob05145h

‡ Dedicated to the memory of Professor Athel Beckwith

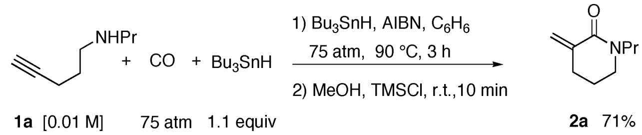
Results and Discussion

We found that *in situ* generated α,β-unsaturated acyl radicals can be trapped by internal amino groups to give lactams as the products. Treatment of 4-pentynylpropylamine (**1a**) with tributyltin hydride as radical mediator (1.1 equiv) under CO pressure (75 atm) in the presence of AIBN (2,2′-azobisisobutyronitrile) as a radical initiator at 90 °C for 3 h gave, after chromatographic separation, unsaturated α-methylene lactam **2a** (37%) and β-stannyl-attached -methylene lactam **3a** (35%) as major products (Scheme 2). While α-stannylmethyl lactam **4a** (6%) was formed as a byproduct, a separate experiment suggested that byproduct **4a** would be formed by further hydrostannylation of initially formed α-methylene lactam **2a**. Treatment of 4-pentynylamine (**1b**) with tributyltin hydride under CO pressure (75 atm) in the presence of AIBN at 90 °C for 3 h gave a similar set of six-membered ring lactams, **2b**, **3b** and **4b**, having no substituent at nitrogen. Interestingly, when 4-pentynylbenzylamine was used, six-membered ring lactam **3b**, which does not have a substituent on nitrogen, was involved in the product mixture. Consequently, we found that the substrate **1i** having an α-phenylethyl group on nitrogen rather than benzyl group resulted in the formation of **3b** in good yield (Scheme 2). In this reaction ethylbenzene was detected, which explained that the reaction process involves the elimination of α-phenylethyl radicals.



Scheme 2 Intramolecular trapping experiment of α,β-unsaturated acyl radicals by amines.

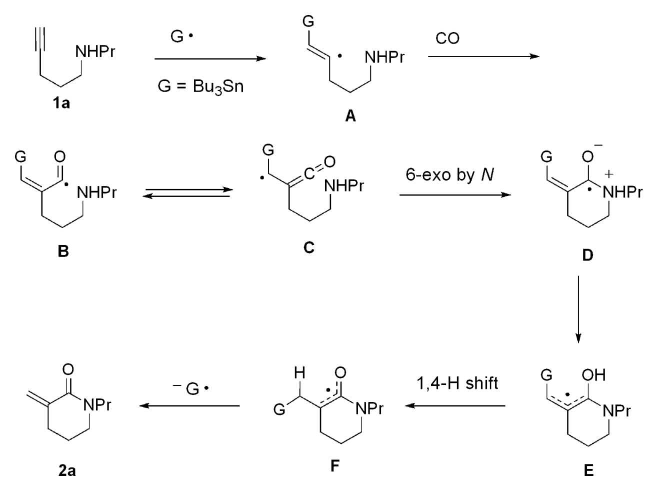
Since α-stannylmethylene lactams were prone to hydrolysis during chromatographic separation using silica gel, they were treated with HCl, generated *in situ* from TMSCl and MeOH, which resulted in the quantitative conversion to α-methylene lactams. For example, stannylcarbonylation of **1a** and the subsequent protodestannylation (TMSCl (10 equiv) plus MeOH, r.t., 10 min) gave α-methylene lactam **2a** in 71% yield after isolation by silica gel chromatography (Scheme 3).



Scheme 3 Consecutive stannylcarbonylation/protodestannylation procedure for the synthesis of α-methylene lactam **2a**.

Having a convenient protodestannylation procedure, a variety of α-methylene lactams were synthesized from ω-aminoalkynes and CO *via* *n* + 1 type annulation reaction (Table 1). The Type A reaction permitted efficient formation of five-, six-, seven-, and eight-membered ring lactams, which include bicyclic and chiral α-methylene lactams (entries 1–7). The lactam ring forming reaction by carbonylation/substitution sequence (Type B) using *N*-α-phenethyl substituted alkynylamines proved to suit the synthesis of five- and six-membered ring lactams (entries 8–14). The substitution reactions onto amine-nitrogen can be extended to include tertiary amines, which gave *N*-susbtituted lactams with elimination of α-phenethyl group in preference to other alkyl groups (entries 9–12). Chiral α-phenethylamines are commercially available. Thus we applied the present procedure for the synthesis of chiral lactams which would be useful as chiral building blocks. Thus, using chiral α-phenethylamine having (*R*)-configuration, a diastereomeric mixture of the alkynylamine **1n** and **1o** were prepared in an 81% yield, which was separated by crystallization to give a set of enantiomers **1n** and **1o**. Thus prepared chiral alkynylamines gave the corresponding chiral γ-substituted α-methylene-γ-butyrolactams **2n** and **2o** in good yields (entries 13 and 14).

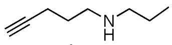
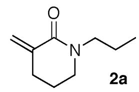
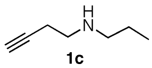
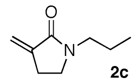
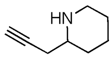
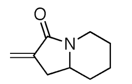
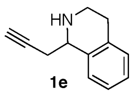
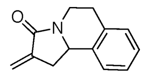
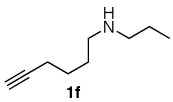
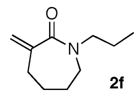
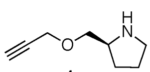
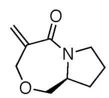
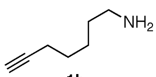
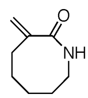
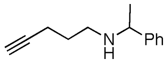
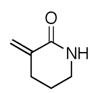
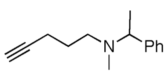
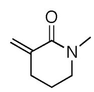
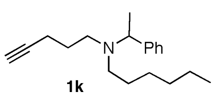
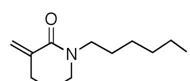
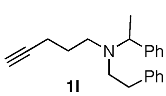
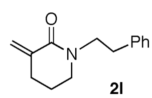
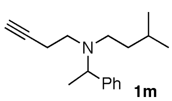
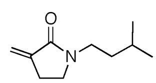
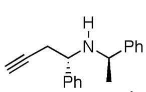
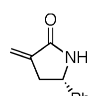
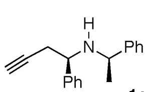
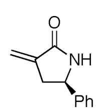
The formation of α-methylene lactams as major products in Type A reaction brings about intriguing mechanistic issues. Scheme 4 illustrates a proposed mechanism using **1a** as the substrate. We propose that 1-hydroxyallyl radicals **E** would be the first key intermediate, which can be formed by nucleophilic addition of an amine NH bond to the ketene carbonyl of **C** followed by proton transfer *via* **D**. The subsequent 1,4-H shift from the hydroxyallyl radical **E** would lead to oxoallyl radical **F**, which then would undergo liberation of tributyltin radical to give α-methylene lactam **2a**. On the other hand, the formation of α-stannylmethylene lactam **3a** requires a formal "oxidation" step from **E** and/or **F**, which serves as a chain termination step.[7]



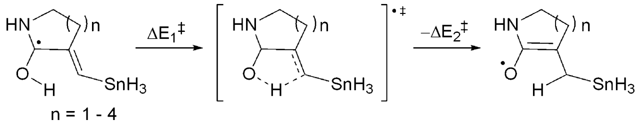
Scheme 4 Proposed mechanism leading α-methylene lactams (Type A).

Since 1,4-hydrogen shift[8] is not common compared with 1,5-hydrogen shift, we carried out DFT calculations at the BHandHLYP/DZP[9] level. Energy barriers for the forward process of 1,4-hydrogen shifts of 5–8 membered model lactams (Scheme 5) were calculated to be 71.2–105.7 kJ mol^{-1} (Fig. 1), indicating that the 1,4-hydrogen shifts were calculated to be highly exothermic and can proceed under usual reaction conditions.

Table 1 Synthesis of α-methylene lactams by radical carbonylation and protodestannylation[a]

Entry	Alkynylamines **1**	Type	Methylene lactams **2**	Yield[b]
1	 **1a**	A	 **2a**	71%
2	 **1c**	A	 **2c**	64%
3	 **1d**	A	 **2d**	61%
4	 **1e**	A	 **2e**	48%
5	 **1f**	A	 **2f**	69%
6	 **1g**	A	 **2g**	52%
7	 **1h**	A	 **2h**	59%
8	 **1i**	B	 **2b**	74%
9	 **1j**	B	 **2j**	86%
10	 **1k**	B	 **2k**	84%
11	 **1l**	B	 **2l**	79%
12	 **1m**	B	 **2m**	62%
13	 **1n**	B	 **2n**	69%
14	 **1o**	B	 **2o**	73%

[a] Conditions for Type A reaction: **1** (0.5 mmol), AIBN (20–30 mol%), Bu_3SnH (1.1–1.5 equiv), CO (70–80 atm), C_6H_6 (50 mL), 90 °C, 3–8 h. For entry 4, V-40 (1,1′-azobis(cyclohexane-1-carbonitrile)) was used as a radical initiator and the reaction was carried out at 110 °C. Conditions for Type B reaction: **1** (0.5 mmol), AIBN (20 mol%), Bu_3SnH (1.3–1.5 equiv), C_6H_6 (50 mL), 90 °C, 4 h. After stannylcarbonylation reactions, the subsequent treatment with TMSCl (10 equiv) in MeOH at room temperature for 10 min gave α-methylene lactams **2**. [b] Isolated yields by flash chromatography on silica gel.



Scheme 5 Model lactams having 5 to 8 membered rings for DFT calculation of 1,4-hydrogen shift.

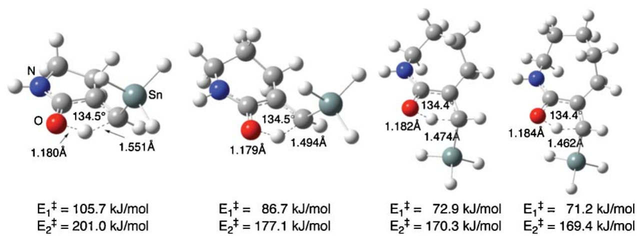
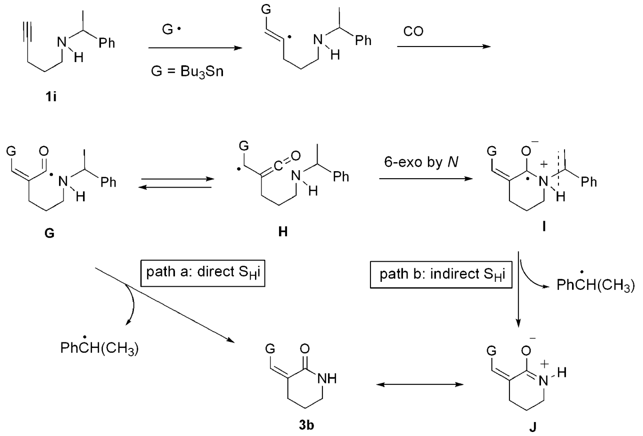


Fig. 1 BHandHLYP/DZP optimized geometries of most stable transition states for the 1,4-hydrogen shift in model lactams.

It is conceivable that acyl radical **G** would undergo an S_Hi reaction onto nitrogen to give **3b** (Scheme 6). To our knowledge, elements available for S_Hi-type reactions are limited mainly to group 14 and 16 elements, such as Si, Ge, Sn, S, Se, and Te,[10,11] and in contrast, such S_Hi-type ring formations at nitrogen, the first low atom of Group 15, has been scarcely reported.[12] Since the trap of α,β-unsaturated acyl radical/ketenyl radical by amino groups is plausible as discussed above (Scheme 4), we are inclined to postulate a two step mechanism for the present S_Hi-type reaction at nitrogen atom rather than direct substitution mechanism. Thus, nucleophilic trap of α,β-unsaturated acyl radical/α-ketenyl radical by nitrogen would result **I**, which then undergoes β-fission to leave α-phenethyl radical out to give **J**, which is a canonical form of the product **3b**. In order to provide further insights into the reaction mechanism, DFT calculations were carried out, and results are summarized in Fig. 2.



Scheme 6 Two possible reaction mechanisms for substitution onto nitrogen.

Searching the $C_{14}H_{18}NO$ potential energy surface located structure **M** as the intermediate for the radical substitution reaction of *N*-phenethyl-5-amino-2-methylenepentanoyl radical (**K**). Transition states **L** involved in the ring-closure reaction of the acyl radical to amine moiety in **K**, and transition state **N** involved

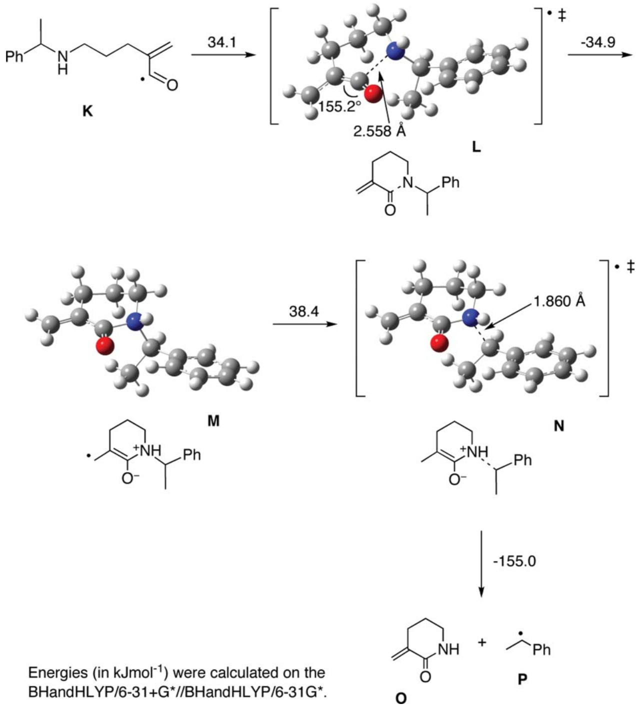


Fig. 2 Profile of radical substitution reaction on the nitrogen atom of *N*-phenethyl-5-amino-2-methylenepentanoyl radical.

in the expulsion process of phenethyl radical (**P**), were also found on the potential energy surface.

Using the BHandHLYP/6-31+G*//BHandHLYP/6-31G* level, activation energies for the "forward processes" of ring-closure and expulsion of a phenethyl radical were calculated to be 34.1 and 38.4 kJ mol^{-1}, respectively, while the "reverse processes" of those reactions were predicted to be 34.9 and 155.0 kJ mol^{-1}. The ring-closure step is predicted to be reversible. However, once generated, the intermediate would irreversibly release a phenethyl radical to give α-methylene lactam **O**. Importantly, existence of the intermediate **M** on the DFT calculation strongly supports an indirect S_Hi mechanism for this substitution reaction. Thus, the suggested stepwise reaction involving the intermediate **M** is ensured by strong polar interaction between lone pair of amine nitrogen and π* of unsaturated acyl radicals. It is a key to the success of the seemingly unusual S_Hi reaction onto nitrogen.

Conclusions

In summary, five- to eight-membered ring lactams were prepared by free-radical mediated stannylcarbonylations of alkynylamines (Type A). The nucleophilic trapping of the α-ketenyl radical by an amino group to give a hydroxyallyl radical and the subsequent 1,4-hydrogen shift and β-elimination of tin radicals would account for the formation of α-methylene lactams. Using α-phenethyl amines, we have also demonstrated that unusual homolytic substitution at nitrogen atom took place to give lactams accompanied with extrusion of a phenethyl substituent (Type B). Theoretical studies predict that the 1,4-hydrogen shift could proceed in a Type A reaction and that the indirect S_Hi reactions with a reversible ring-closing reaction followed by an irreversible extrusion of a phenethyl radical would occur in a Type B reaction.

According to the present protocol combined with the subsequent protodestannylation protocol, α-methylene lactams were prepared in good yields. Thus, polar interaction between acyl radicals and amine nitrogen can provide a reliable tool for lactam ring formation with incorporation of CO as a carbonyl group.

Experimental

General information

^{1}H NMR spectra were recorded with a JEOL JMN ECP-500 (500 MHz) or JEOL JMN AL-400 (400 MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (δ) downfield from internal TMS at 0.00. ^{13}C NMR spectra were recorded with a JEOL JMN ECP-500 (125 MHz) or JEOL JMN AL-400 (100 MHz) spectrometer and referenced to the solvent peak at 77.00 ppm. For ^{1}H–Sn and ^{13}C–Sn coupling constants, the central signals are normally associated with two close pairs of satellites corresponding to both ^{117}Sn and ^{119}Sn isotopes, and average values of the two different coupling constants are reported. Infrared spectra were obtained on a JASCO FT/IR-5300 spectrometer; absorptions are reported in reciprocal centimetres. Both conventional and high resolution mass spectra were recorded with a JEOL MS700 spectrometer. Products were purified by flash chromatography on silica gel (nacalai tesque int. Silica Gel 60, 230–400 mesh). Optical rotations were obtained on JASCO DIP-370 Digital Polarimeter at a wavelength of 589 nm (sodium D line). Alkynylamines **1a–1j**, **1n**, and **1o** were prepared as previously described.[6] Alkynylamines **1k**, **1l**, and **1m** were prepared from the corresponding *N*-ω-alkynyl-*N*-(1-phenylethyl) amines and alkyl bromides.

Typical procedure for consecutive stannylcarbonylation/protodestannylation of alkynylamine 1

A magnetic stirring bar, AIBN (2,2′-azobisisobutyronitrile, 16.2 mg, 0.1 mmol), benzene (50 mL), Bu_3SnH (170.2 mg, 0.58 mmol), and 4-pentynylpropylamine **1a** (65 mg, 0.52 mmol) were placed in a 100-mL stainless steel autoclave. The autoclave was closed, purged three times with carbon monoxide, pressurized with 75 atm of CO and then heated 90 °C for 3 h. Excess CO was discharged at room temperature. The solvent was removed under reduced pressure. The residue was dissolved into MeOH and TMSCl (5.2 mmol) was added. The reaction mixture was stirred at room temperature for 10 min. After evaporation, the resulting mixture was purified by flash chromatography on SiO_2 to give **2a** (R_f 0.2, EtOAc/MeOH = 5 : 1, 71%, 56.5 mg).

1-Propyl-3-methylene-2-piperidinone (2a)

Colorless oil, (R_f 0.2, hexane/EtOAc = 5 : 1), ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.87 (sext, J = 7.3 Hz, 2H), 1.83 (quint, J = 6.0 Hz, 2H), 2.52 (t, J = 6.2 Hz, 2H), 3.30–3.38 (m, 4H), 5.21 (s, 1H), 6.15 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) d 11.29, 20.25, 23.19, 30.06, 48.36, 49.26, 121.16, 137.79, 163.91; IR (neat) ν_{max} 1659, 1615 cm^{-1}; MS (EI) m/z (rel intensity) 153 (M^+, 22), 139 (36), 124 (61), 110 (100); HRMS (EI) m/z calcd for $C_9H_{15}NO$ (M^+) 153.1153, found 153.1159.

1-Propyl-3-tributylstannylmethylene-2-piperidinone (3a)

Z isomer: Colorless oil, (R_f 0.3, hexane/EtOAc = 20 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78–0.92 (m, 18H), 1.23–1.30 (sext, J = 7.3 Hz, 6H), 1.37–1.60 (m, 6H), 1.82–1.87 (m, 2H), 2.61–2.63 (m, 2H), 3.32–3.36 (m, 4H), 6.33 (s, J ^{1}H–Sn = 71.0 Hz 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 11.9, 13.9, 20.42, 23.83, 27.57, 29.45, 33.85, 48.68, 49.27, 143.87, 144.22, 165.09; IR (neat) ν_{max} 1636, 1584; MS (EI), *m/z calculated from major ^{120}Sn isotope* (rel intensity); 386 (M^+-C_4H_9, 100), 272 (48); HRMS (EI) m/z calcd for $C_{17}H_{32}NO^{120}Sn$ (M^+-C_4H_9) 386.1506, found 386.1513.

1-Propyl-3-tributylstannylmethyl-2-piperidinone (4a)

Colorless oil, (R_f 0.3, hexane/EtOAc = 5 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76–1.11 (m, 19H), 1.24–1.32 (m, 7H), 1.35–1.56 (m, 9H), 1.68–1.78 (m, 1H), 1.82–1.98 (m, 2H), 2.38–2.57 (m, 1H), 3.18–3.30 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.85, 11.38, 13.67, 13.78, 20.38, 21.85, 27.53, 29.32, 31.36, 40.00, 48.21, 49.00, 173.85; IR (neat) ν_{max} 1634 cm^{-1}; MS (EI), *m/z calculated from major ^{120}Sn isotope* (rel intensity); 388 (M^+-C_4H_9, 67), 350 (100); HRMS (EI) m/z calcd for $C_{17}H_{34}NO^{120}Sn$ (M^+-C_4H_9) 388.1662, found 388.1664.

3-Methylene-2-piperidione (2b)

Colorless oil, (R_f 0.18, EtOAc/MeOH = 19 : 1), ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87 (quint, J = 6.0 Hz, 2H), 2.57–2.60 (m, 2H), 3.39–3.41 (m, 2H), 5.32 (d, J = 1.4 Hz, 1H), 6.21 (d, J = 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.08, 29.75, 42.63, 122.07, 137.51, 166.04; IR (neat) ν_{max} 1668, 1618 cm^{-1}; This product is a known compound and was identified by NMR with comparison of literature data.[13]

3-Tributylstannylmethylene-2-piperidinone (3b)

Z isomer: Colorless oil, (R_f 0.20, hexane/EtOAc = 4 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77–0.92 (m, 15H), 1.28 (sext, J = 7.3 Hz), 1.40–1.49 (m, 6H), 1.66–1.95 (m, 2H), 2.63 (m, 2H), 3.35–3.38 (m, 2H), 6.45 (s, J ^{1}H–Sn = 69.2 Hz, 1H), 6.85 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.83, 13.78, 23.63, 27.46, 29.33, 33.29, 42.80, 142.85, 146.17, 166.81; IR (neat) ν_{max} 1663, 1586 cm^{-1}; MS (EI) *m/z calculated from major ^{120}Sn isotope* (rel intensity) 344 (M^+-C_4H_9, 100), 230 (45); HRMS (EI) m/z calcd for $C_{14}H_{26}NO^{120}Sn$ (M^+-C_4H_9) 344.1037, found 344.1039.

3-Tributylstannylmethyl-2-piperidinone (4b)

Colorless oil, (R_f 0.13, hexane/EtOAc = 4 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0,78–0.89 (m, 15H), 1.14–1.32 (m, 8H), 1.35–1.50 (m, 7H), 1.63–1.73 (m, 1H), 1.81–1.85 (m, 1H), 1.91–1.97 (m, 1H), 2.42 (quint, J = 7.8 Hz, 1H), 3.24–3.26 (m, 2H), 6.70 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.83, 12.93, 13.65, 21.67, 27.40, 29.23, 31.27, 39.49, 42.50, 176.71; IR (neat) ν_{max} 1659 cm^{-1}; MS (EI) *m/z calculated from major ^{120}Sn isotope* (rel intensity) 346 (M^+- C_4H_9, 27), 324 (100), 230 (33), 198 (22), 151 (52); HRMS (EI) m/z calcd for $C_{14}H_{28}NO^{120}Sn$ (M^+-C_4H_9) 346.1193, found 346.1195.

1-Propyl-3-methylene-2-pyrrolidinone (2c)

Colorless oil, (R_f 0.10, hexane/EtOAc = 2 : 1), ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.57 (sext, J = 7.5 Hz, 2H), 2.73 (m, 2H), 3.32 (t, J = 7.6 Hz, 2H), 3.37 (t, J = 6.6 Hz, 2H), 5.28 (s, 1H), 5.94 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.28, 20.43, 24.01, 43.94, 44.77, 114.94, 139.89, 167.92; IR (neat) ν_{max} 1686, 1659 cm^{-1}; MS (EI), m/z (rel intensity) 139 (M^+, 36), 124 (61), 110 (100); HRMS (EI) m/z calcd for $C_9H_{15}NO$ (M^+) 139.0997, found 139.0982.

1-Oxo-2-methyleneoctahydroindolizine (2d)

Colorless oil, (R_f 0.18, Hexane/EtOAc = 1:1), ^1H NMR (500 MHz, $CDCl_3$) δ 1.08–1.20 (m, 1H), 1.30–1.47 (m, 2H), 1.66–1.69 (m, 1H), 1.84–1.90 (m, 2H), 2.27–2.30 (m, 1H), 2.68–2.73 (m, 1H), 2.86–2.90 (m, 1H), 3,41–4.44 (m, 1H), 4.18–4.20 (m, 1H), 5.21–5.28 (m, 1H), 5.88–5.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.90, 24.67, 31.84, 33.74, 40.69, 54.50, 115.05, 139.60, 166.84; IR (neat) ν_{max} 1685, 1658 cm^{-1}; MS (EI) m/z (rel intensity) 151 (M^+, 100), 122 (34), 110 (19), 95 (21); HRMS (EI) m/z calcd for $C_9H_{13}NO$ (M^+) 151.0997, found 151.0985.

Pyrrolo[2,1-a]isoquinolin-3(2H)-one (2e)

Colorless oil, (R_f 0.18, Hexane/EtOAc = 1:1), ^1H NMR (400 MHz, $CDCl_3$) δ 2.68–2.83 (m, 2H), 2.98–3.06 (m, 1H), 3.16–3.23 (m, 1H), 3.40 (ddd, J = 16.6, 7.8, 2.0 Hz, 1H), 4.39 (ddd, J = 12.9, 6.1, 2.2 Hz, 1H), 5.36–5.37 (m, 1H), 5.98–6.02 (m, 1H), 7.11–7.26 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.35, 33.43, 37.69, 54.05, 115.17, 124.92, 126.80, 126.98, 129.07, 133.64, 137.22, 139.61, 166.33; IR (neat) ν_{max} 1686 cm^{-1}; MS (EI) m/z (rel intensity) 199 (M^+, 77), 198 (100), 149 (26), 130 (20); HRMS (EI) m/z calcd for $C_{13}H_{13}NO$ (M^+) 199.0997, found 199.0996.

1-Propyl-3-methylene-2-azacycloheptanone (2f)

Colorless oil, (R_f 0.18, hexane/EtOAc = 1 : 1), ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.3 Hz, 3H), 1.50 (sext, J = 7.5 Hz, 2H), 1.56–1.72 (m, 4H), 2.23–2.29 (m, 2H), 3.19–3.24 (m, 2H), 3.26–3.32 (m, 2H), 5.12 (s, 1H), 5.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.35, 21.28, 27.82, 28.87, 32.36, 48.97, 49.48, 117.99, 147.78, 172.95; IR (neat) ν_{max} 1644 cm^{-1}; MS (EI) m/z (relative intensity), 167 (M^+, 52), 138 (100); HRMS (EI) m/z calcd for $C_9H_{15}NO$ (M^+) 167.1311, found 167.1305.

Hexahydro-4-methylene-(9a-S)-1*H*,5*H*-pyrrolo[2,1-c][1,4]-oxazepine-5-one (2g)

Colorless oil, (R_f 0.16, hexane/EtOAc = 1 : 1), ^1H NMR (500 MHz, $CDCl_3$) δ 1.44–1.58 (m, 1H), 1.70–1.81 (m, 1H), 1.82–1.92 (m, 1H), 2.25–2.42 (m, 1H), 3.34 (dd, J = 11.9, 9.2 Hz, 1H), 3.40 (ddd, J = 15.6, 8.7, 6.8, 1H), 3.81 (ddd, J = 11.9, 7.8, 3.7, 1H), 3.82–3.89 (m, 1H), 3.90 (dd, J = 12.4, 1.8 Hz, 1H), 4.01 (d, J = 12.8 Hz, 1H), 4.30 (d, J = 12.8 Hz, 1H), 5.50 (s, 1H), 5.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.81, 29.67, 47.29, 60.01, 70.54, 73.80, 125.51, 144.22, 169.27; IR (neat) ν_{max} 1647 cm^{-1}; MS (EI) m/z (rel intensity) 167 (M^+, 12), 149 (11), 137 (21), 109 (28), 83 (100); HRMS (EI) m/z calcd for $C_9H_{13}NO$ (M^+) 167.0946, found 167.0946.

3-Methylene-2-azacyclooctanone (2h)

Colorless oil, (R_f 0.2, EtOAc/MeOH = 19 : 1), ^1H NMR (500 MHz, $CDCl_3$) δ 1.52–1.61 (m, 6H), 2.37–2.40 (m, 2H), 3.26–3.30 (m, 2H), 4.98–5.13 (m, 1H), 5.14–5.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.53, 26.22, 31.59, 37.36, 41.54, 114.34, 145.75, 176.31; IR (neat) ν_{max} 1738, 1640 cm^{-1}; MS (EI) m/z (rel intensity) 139 (M^+, 14), 111 (100), 67 (62); HRMS (EI) m/z calcd for $C_{15}H_{30}N$ (M^+) 415.1901, found 415.1910.

1-Methyl-3-methylene-2-piperidinone (2j)

Colorless oil, (R_f 0.2, Hexane/EtOAc = 1 : 1), ^1H NMR ($CDCl_3$, 500 MHz) δ 1.88 (quint, J = 6.0 Hz, 2H), 2.55 (t, J = 6.4 Hz, 2H), 3.01 (s, 3H), 3.37 (t, J = 6.0 Hz, 2H), 5.24 (s, 1H), 6.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.07, 30.11, 35.09, 50.30, 120.90, 137.82, 164.35; IR (neat) ν_{max} 1657, 1613 cm^{-1}; EIMS, m/z (rel intensity) 125 (M^+, 100), 96 (17), 82 (18), 69 (24), 54 (100); HRMS (EI) m/z calcd for $C_7H_{11}NO$ (M^+) 125.0841, found 125.0848.

1-Hexyl-3-methylene-2-piperidinone (2k)

Colorless oil, (R_f 0.24, Hexane/EtOAc = 1 : 1), ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86–0.88 (m, 3H), 1.25–1.34 (m, 6H), 1.54–1.57 (m, 2H), 1.87 (quint, J = 6.0 Hz, 2H), 2.53–2.58 (m, 2H), 3.35–3.44 (m, 4H), 5.25 (s, 1H), 6.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.98, 22.47, 23.23, 26.58, 27.00, 30.08, 31.56, 47.79, 48.36, 121.21, 137.81, 163.85; IR (neat) ν_{max} 1659, 1633 cm^{-1}; EIMS, m/z (rel intensity) 195 (M^+, 33), 138 (26), 124 (100), 69 (24), 54 (100); HRMS (EI) m/z calcd for $C_{12}H_{21}NO$ (M^+) 195.1623, found 195.1630.

1-(2-Phenylethyl)-3-methylene-2-piperidinone (2l)

Colorless oil, (R_f 0.24, Hexane/EtOAc = 1 : 1), ^1H NMR ($CDCl_3$, 400 MHz) δ 1.74–1.80 (m, 2H), 2.50–2.55 (m, 2H), 2.91 (t, J = 7.5 Hz, 2H), 3.20 (t, J = 5.9 Hz, 2H), 3.62 (t, J = 7.5 Hz, 2H), 5.26 (s, 1H), 6.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.10, 29.94, 33.50, 49.33, 50.14, 121.28, 126.24, 128.41, 128.80, 164.02; IR (neat) ν_{max} 1631 cm^{-1}; EIMS, m/z (rel intensity) 215 (M^+, 39), 124 (100), 91 (20); HRMS (EI) m/z calcd for $C_{14}H_{17}NO$ (M^+) 215.1310, found 215.1319.

1-(3-Methylbutyl)-3-methylene-2-pyrrolidinone (2m)

Colorless oil. (R_f 0.24, Hexane/EtOAc = 1 : 1), ^1H NMR ($CDCl_3$, 500 MHz) δ 0.94 (d, J = 6.4 Hz, 6H), 1.42–1.48 (m, 2H), 1.52–1.65 (m, 1H), 2.74–2.76 (m, 2H), 3.35–3.40 (m, 4H), 5.29 (s, 1H), 5.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.44, 24.08, 25.87, 35.88, 41.47, 43.82, 114.79, 139.90, 167.71; IR (neat) ν_{max} 1691, 1659 cm^{-1}; EIMS, m/z (rel intensity) 167 (M^+, 15), 111 (81), 110 (100), 55 (17); HRMS calcd for $C_{10}H_{17}NO$ (M^+) 167.1310, found 167.1311.

3-Methylene-5-phenyl-2-pyrrolidinone (2n and 2o)

2n: white solid, mp = 169–170 °C, (R_f 0.15, hexane/EtOAc = 1 : 1), ^1H NMR ($CDCl_3$, 500 MHz) δ 2.60–2.69 (m, 1H), 3.22–3.34 (m, 1H), 4.74 (m, 1H), 5.34 (s, 1H), 6.00 (s, 1H), 7.22–7.38 (m, 5H), 7.49 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.89, 54.96, 116.48, 125.76, 128.00, 129.01, 139.05, 142.85, 171.19; IR (KBr) ν_{max} 1656, 1591 cm^{-1}; EIMS, m/z (rel intensity) 173 (M^+, 100), 144 (27), 104 (37); HRMS calcd for $C_{11}H_{11}NO$ (M^+) 173.0840, found 173.0843.

2o: white solid, mp = 169–170 °C, ^{1}H-NMR, ^{13}C-NMR, IR and EIMS were identical with those of **2n**. HRMS calcd for $C_{11}H_{11}NO$ (M^+) 173.0840, found 173.0845.

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