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FULL PAPER

Intramolecular Keto-lactam Condensation: A Convenient and Straightforward Approach to Bicyclic Vinylogous Lactams

Pei-Qiang Huang,* [a,b] and Ting Fan[a]

Abstract: While aldol condensation is a well-known reaction, the aza-type aldol condensation, namely, intramolecular condensation of common keto-lactams leading to bicyclic vinylogous lactams is a highly demanding yet challenging transformation in both organic synthesis and medicinal chemistry. The known methods for this type of cyclization require several steps. We disclose in this paper a straightforward approach that consists of the in situ formation of silyl enol ether with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), lactam activation with triflic anhydride (Tf_2O), and tandem cyclocondensation reaction. The reaction can run in a one-pot manner or in a two-step fashion both under mild conditions. The yields for the one-pot version are 52-80%. In some cases, the two-step version afforded higher overall yields (44-85%) as compared with those of the one-pot version.

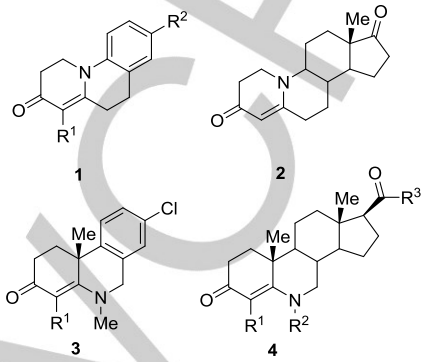

Figure 1. Structures of bicyclic vinylogous lactams and structurally related medicinal agents

Introduction

Bicyclic vinylogous lactams of types **A** and **B** (Fig. 1) are found as key structural features in medicinal agents,[1-3] and serve as versatile intermediates for the synthesis of alkaloids.[4,5] For example, benzo[*c*]quinolizin-3-ones of generic structure **1**,[2a-c] 19-nor-10-azasteroids such as **2**,[2d] phenanthridin-3-one derivatives **3**,[3a] and 6-azasteroids **4**[3b] represent four classes of potent and selective non-steroidal inhibitors of the type 1 human isozyme of 5α-reductase (5αR-1).

Retrosynthetically, a straightforward approach for the construction of the structural motifs **A** and **B** would be the intramolecular keto-amide condensation reaction of keto-lactams **C** and **D**, respectively (Fig. 2). However, this attractive route is hampered by the low electrophilicity of amide carbonyl. For example, to bring about the cyclization of keto-lactam **5** to vinylogous lactam **8** (Scheme 1), about two dozen different methods have been investigated, but all were unsuccessful.[6]

To tackle this problem, two stepwise alternatives have been developed. The first one was developed by Heathcock and co-workers during the first total synthesis of a *Daphniphyllum* alkaloid, methyl homodaphniphyllate.[4] This method involves the pre-conversion of lactam **5** to thiolactam **7** with Lawesson's reagent **6**, followed by *in situ* *S*-ethylation with Meerwein's reagent, and NEt_3-promoted cyclization to give vinylogous

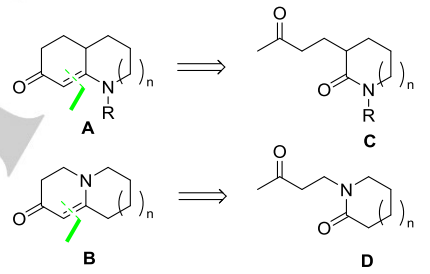

Figure 2. One-step retrosynthetic analysis of bicyclic vinylogous lactam.

lactam **8** (Scheme 1, eq. 1). The second approach, developed by Danishefsky and co-workers, is based on the diazo-thioamide coupling reaction.[5] This method consists of thionation of lactams **9**, aza-conjugate addition of thiolactams **10** with diazomethylvinylketone **11**, rhodium acetate promoted cyclocondensation, and desulfurization with Raney-Nickel to generate bicyclic vinylogous lactams **13** (Scheme 1, eq. 2). A longer but more general version of the Danishefsky's method[5] involves the stepwise incorporation of the diazoketone moiety by aza-conjugate addition with methy acrylate, followed by saponification, mixed anhydride formation, and conversion to the diazoketone **12**. Danishefsky's method has been applied to the synthesis of iso-A58365A[5a] and indolizomycin.[5b,c] By replacing Meerwein's reagent with dimethyl sulfate, Heathcock's method has been applied to the synthesis of phenanthridin-3-one derivatives,[3a] and extended by Guarna and co-workers[2b] to allow the syntheses of a series of benzo[*c*]quinolizin-3-ones.[2b,c]

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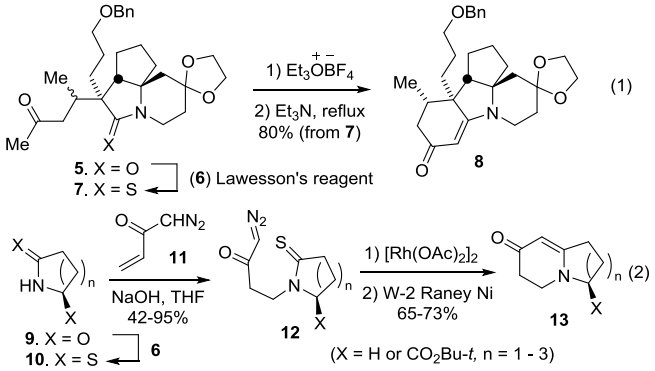


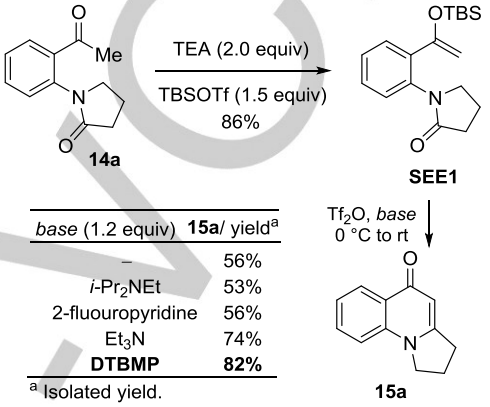
Scheme 1. Heathcock's and Danishefsky's methods.

Both Heathcock's and Danishefsky's methods as well as the extended version, although robust, require the pre- transformation of lactams to thiolactams. Moreover, all of those methods use hazardous reagents such as Lawesson's reagent, dimethyl sulfate, diazo compounds, and Raney-Nickel. Thus, it is highly desirable to develop convenient methods for the direct transformation of keto-lactams to bicyclic vinylogous lactams.

In recent years, the direct transformation of amides/ lactams has emerged as an active research area.[7] Among the many methods developed so far,[8-10] the strategy based on the activation of amides/ lactams with triflic anhydride (Tf_2O) is quite attractive for its versatility and chemoselectivity.[9,10] In this context, Bélanger and co-workers reported the Tf_2O-mediated two-step aldehyde-amides/ lactams cyclization to afford β-formylenamines (vinylogous formamides).[9u,v] In one case, a phenyl keto-amide was employed as the substrate affording a monocyclic vinylogous amide.[9u] Our group[10] also developed, on one hand, a Tf_2O/ halogen-source-mediated cyclization of keto-lactams to generate halo-tropinone derivatives,[10a] and on the other hand, the amide/ lactam-based aza-Knovenagel-type condensation reaction of both *tert*- and *sec*-amides/ lactams.[10b,h] The reported results included three examples of intermolecular condensation of methyl ketones with *N*-benzyl-γ-lactam.[10h] In spite of these progresses, the intramolecular keto-lactam condensation reaction remains elusive. In this article, we report the Tf_2O-mediated one-pot intramolecular keto-lactam condensation reaction for the synthesis of bicyclic vinylogous lactams.

Results and Discussion

We opted for the known keto-lactam **14a**[11] as the first substrate for our initial investigation. For the cyclocondensation of keto-lactam **14a**, a two-step cyclization method was first investigated (Scheme 2). For this purpose, keto-lactam **14a** was converted to the corresponding silyl enol ether **SEE1** by reacting with TBDMSOTf/ trimethylamine (TEA), which afforded silyl enol ether **SEE1** in 86% yield. Pleasantly, simple exposure of **SEE1** to Tf_2O in CH_2Cl_2 at 0 °C ~ r.t. produced the desired cyclization product **15a** in 56% yield. Next, effects of base additives were examined. While yield was not improved by the introduction of Hünig base (*i*-Pr_2NEt) or 2-fluoropyridine as a base additive, running the reaction in the presence of 1.2 equiv of triethylamine or 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)[12,9u] furnished the tricyclic vinylogous lactam **15a** in 74% and 82% isolated yield, respectively. Thus, DTBMP was employed as the base additive for the subsequent investigations.



base (1.2 equiv)	**15a**/ yield[a]
–	56%
i-Pr_2NEt	53%
2-fluouropyridine	56%
Et_3N	74%
DTBMP	**82%**

[a] Isolated yield.

Scheme 2. Two-step cyclization reaction of **14a.**

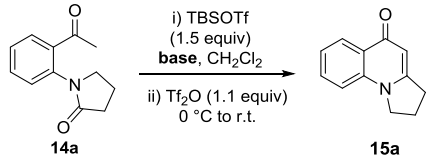
Encouraged by these results, a one-pot reaction was envisaged. Thus **14a** was successively treated with TBDMSOTf (1.5 equiv)/ trimethylamine (3.0 equiv) and Tf_2O (1.1 equiv) at 0 °C to r.t. In this one-pot manner, **15a** was obtained in 72% yield (80% based on the recovered starting material) (Table 1, entry 1). Screening six bases other than TEA showed that the use of TEA as a base gave the highest yield (Table 1, entry 1 versus entries 2-7). A quick examination of effects of equivalents of both TEA and TBDMSOTf on the reaction (Table 1, entries 8-11) allowed identifying the optimal conditions, consisting of using 2.0 equiv of TEA and 1.5 equiv of TBDMSOTf. Under the optimized conditions **15a** was obtained in 76% yield (Table 1, entry 9). It is worth noting that when DTBMP or 4-*t*-Bu-pyridine was used as a base in combination with TBDMSOTf, the formation of silyl enol ether was not observed. The observation implicated that silyl enol ether is the reactive intermediate for the subsequent cyclization reaction.

The intramolecular condensation reaction was extended to the higher homologue **14b**. Thus, under the optimal conditions, **14b** was converted to the desired vinylogous lactam **15b** in 72% yield (78% based on the recovered starting material, BRSM) (Table 2, entry 2). By the two-step version **SEE2** and lactam **15b** were obtained in yields of 86% and 83%, respectively.

Next, we focused on the cyclization of common keto-lactams **14c** – **14f**. Under the one-pot cyclization conditions [TEA (2.0 equiv), TBDMSOTf (1.5 equiv), CH_2Cl_2; Tf_2O (1.1 equiv), 0 °C, to r.t.], the reaction of **14c** afforded the desired vinylogous lactam **15c** in 48% yield (55% BRSM) (Table 2, entry 3).

Alternatively, the two-step procedure was also examined, which afforded silyl enol ether **SEE3a**,**b** and the cyclization

Table 1. Optimization of conditions for the one-pot cyclization reaction of **14a**.



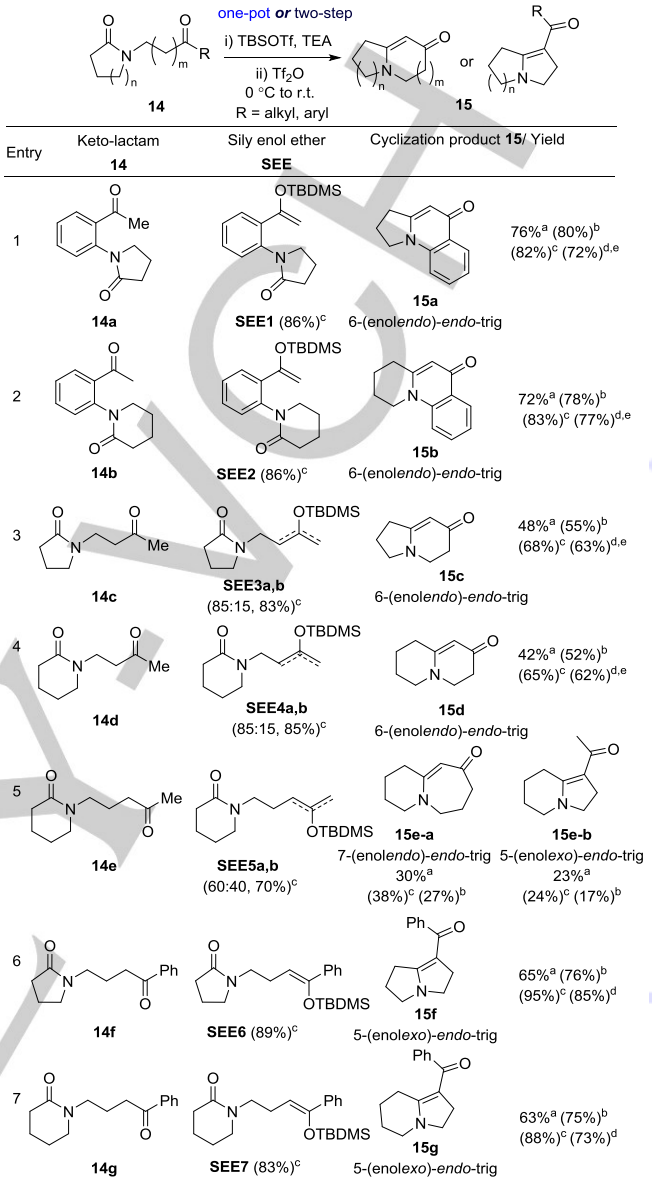
14a **15a**

Entry	Base (equiv)	TBDMSOTf (equiv)	Yield[a]
1	TEA (3.0)	2.0	72%
2	DABCO (3.0)	2.0	48%
3	DTBMP (3.0)	2.0	0[b]
4	4-t-Bu-pyridine (3.0)	3.0	0[b]
5	2,4,6-Collidine (3.0)	2.0	68%
6	2,6-lutidine (3.0)	2.0	70%
7	DBU (3.0)	2.0	65%
8	TEA (3.0)	2.5	73%
9	**TEA (2.0)**	**1.5**	**76%**
10	TEA (2.0)	1.5	63%
11	TEA (2.0)	1.0	53%

[a] Isolated yield. [b] Silyl enol ether was not formed.

product **15c** in 83%, and 68% yield, respectively. Similarly, following the one-pot procedure, the cyclization of keto-lactam **14d** gave vinylogous lactam **15d** in 42% yield (52% BRSM) (Table 2, entry 4). The yields of the two-step method were 85% (for silyl enol ether **SEE4a**,**b**) and 65% (for **15d**), respectively. Comparing with the reactions described in entry 4 (Table 2), where the products could be coined as aza-Robinson annulation products,[13] the cyclization of keto-lactam **14e** is interesting. Indeed, when subjecting **14e** to the one-pot cyclization conditions, two regioisomeric non-aza-Robinson annulation products **15e-a** (30%) and **15e-b** (23%), resulted from terminal **SEE5a** and internal silyl enol ethers **SEE5b**, respectively, were obtained in a combined yield of 53% (Table 2, entry 5). In this case, the two-step protocol resulted in a lower overall yield. Finally, the cyclization reactions of phenyl keto-lactams **14f** and **14g** were examined. By the one-pot procedure, the reaction of **14f** afforded **15f** in 65% yield (Table 2, entry 6). In this case, the two-step method afforded a higher overall yield (85%). Similarly, the direct cyclization of **14g** provided **15g** in 63%yield (Table 2, entry 7), while the two-step method afforded **15g** in an overall yield of 73%.

Table 2. Intramolecular keto-lactam condensation leading to bicyclic vinylogous lactams.

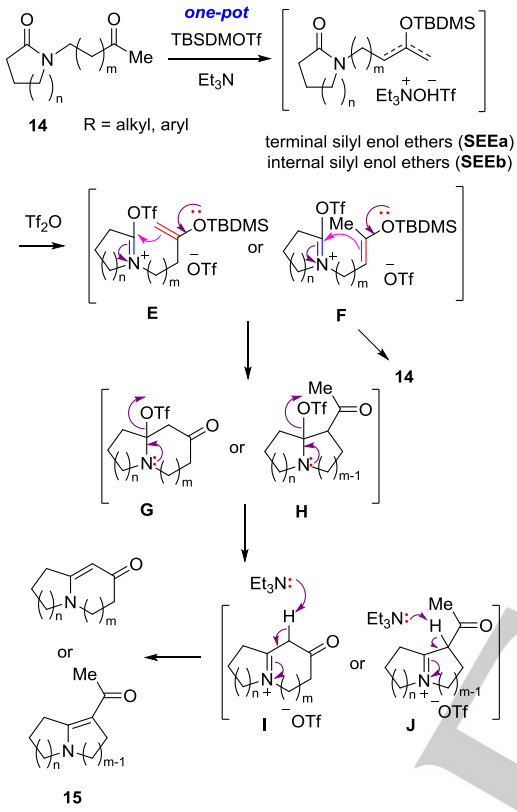


[a] Isolated yield of the one-pot method: i) TBDMSOTf, Et_3N, r.t., CH_2Cl_2; ii) Tf_2O 0 °C to r.t. [b] Yield based on the recovered starting materials. [c] Isolated yield of the two-step method: (1) TBDMSOTf, Et_3N, CH_2Cl_2, r.t.; (2) DTBMP, Tf_2O, 0 °C to r.t. [d] Combined isolated yield of **SEEa** (terminal) and **SEEb** (internal), regioisomeric ratio determined by 1H NMR. [e] Yield based on the recovered starting materials of the two-step method.

Mechanistic considerations

A plausible mechanism of the keto-lactam condensation is depicted in Scheme 3. The first step of the reaction involves the formation of silyl enol ether. In the case where the starting ketone contains two kind of acidic α–hydrogen, two regioisomeric silyl enol ethers, terminal (**SEEa**) and internal (**SEEb**) are formed. Then the lactam carbonyl reacts with Tf_2O to generate highly electrophilic *O*-triflyl imidate salts **E** and **F**, which undergo a rapid intramolecular addition with nucleophilic silyl enol ether partners to generate *N,O*-acetals **G** and **H**. Then, the nitrogen lone pair-assisted elimination of $^{-}$OTf occurs spontaneously generating iminium triflate intermediates **I** and **J**. Finally, base-promoted tautomerization affords the corresponding vinylogous lactams **15**.

Comparing the yield of **15c** (48%) with that of **15g** (63%) obtained by the one-pot method allows concluding that the difference of 15% corresponds to the minor regioisomer **SEE3b** (**SEE3a**: **SEE3b** = 85:15) that is unable to undergo a 4-(enol*exo*)-*endo*-trig cyclization,[14] and yields back, after workup, the starting keto-lactam **14c**. It is also worthy of mention that silyl enol ethers **SEE** are mixtures of geometric isomers.[15]



Scheme 3. Plausible mechanisms for the intramolecular keto-lactam condensation leading to vinylogous lactams.

Conclusions

In summary, one-pot *O*-silylation - amide activation - cyclization method has been developed for the direct cyclization to yield bicyclic vinylogous lactams. In addition, a complementary two-step version of the one-pot method has also been developed. The method provides a ready access to diverse tricyclic and bicyclic vinylogous lactams, which are as key structural features found in medicinal agents, and versatile blocks for the synthesis of alkaloids. We believe that this convenient solution to the longstanding problem of the direct intramolecular condensation reactions of common keto-lactams would find applications in organic synthesis and medicinal chemistry.

Experimental Section

General method: Melting points were determined on a Büchi M560 Automatic Melting Point apparatus and are uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film/KBr pellet techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD on an instrument at 500/125 MHz or 400/100 MHz, respectively. Chemical shifts (δ) are reported in ppm and respectively referenced to internal standard Me_3Si. Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus LC-MS apparatus (ESI direct injection). HRMS spectra were recorded on a 7.0T FT-MS apparatus. Tf_2O was distilled over phosphorus pentoxide and used within a week. THF was distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

General procedure for intramolecular condensation of keto-lactams 14 (the one-pot method: General procedure A).

To a dried 10-mL round-bottom flask were added successively a tertiary keto-lactams (0.25 mmol), dichloromethane (5 mL) and triethylamine (0.5 mmol) under an argon atmosphere. After being cooled to 0 °C, *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (0.375 mmol) was added and the mixture was stirred at r.t. until the complete consumption of starting material as indicated by TLC monitoring (*ca.* 15 h; for **14g**,**h**, overnight). To the resulting mixture, trifluoromethanesulfonic anhydride (Tf_2O) (0.275 mmol) were added at 0 °C. The mixture was allowed warming-up and stirred at r.t. for 15 min. The reaction was quenched with sat. $NaHCO_3$, and the mixture was extracted with dichloromethane (3× 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired vinylogous lactam **15**.

General procedure for intramolecular condensation of keto-lactams 14 (the two-step method: General procedure B).

To a dried 10-mL round-bottom flask were added successively a tertiary keto-lactams (0.5 mmol), dichloromethane (10 mL) and triethylamine (1.0 mmol) under an argon atmosphere. After being cooled to 0 °C, *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (0.75 mmol) was added and the mixture was stirred at r.t. until the complete consumption of starting material as indicated by TLC monitoring. The reaction was quenched with sat. $NaHCO_3$, and the mixture was extracted with dichloromethane (3× 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired silyl enol ether. To a dried 10-mL round-bottom flask containing silyl enol ether (0.25 mmol) were added 4-methyl-2,6-di-*tert*-butylpyridine (DTBMP) (0.3 mmol) and trifluoromethanesulfonic anhydride (Tf_2O) (0.275 mmol) at 0 °C. The mixture was allowed warming-up and stirred at r.t. for 15 min. The reaction was quenched with sat. $NaHCO_3$, and the mixture was extracted with dichloromethane (3× 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired vinylogous lactam **15**.

2,3-Dihydropyrrolo[1,2-*a*]quinolin-5(1*H*)-one (15a). Following general procedure A, the one-pot reaction of tertiary amide **14a** (101 mg, 0.5 mmol) afforded **15a** (70 mg, yield: 76%) and the recovered starting material **14a** (*ca.* 5%). Following general procedure B, the two-step reaction afforded silyl enol ether **SEE1** and **15a** in 86% and 82% yield, respectively. In addition, about 2% of starting material was observed. **15a**: beige solid, R_f = 0.4 (10% MeOH/ethyl acetate). Mp: 173-174 °C (lit.[11] 167-173 °C). IR (film) ν_{max}: 3468, 3378, 2958, 2842, 1626, 1599, 1555, 1497, 1469, 1427, 1306, 1262, 1152, 1066, 959, 835, 757, 620 cm^{-1}; ^{1}H NMR (500 MHz,

CD_3OD) δ 8.12 (d, J = 8.2 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.34 – 7.22 (m, 2H), 6.03 (s, 1H), 4.09 (t, J = 7.3 Hz, 2H), 3.04 (t, J = 7.7 Hz, 2H), 2.28 – 2.18 (m, 2H) ppm; ^{13}C NMR (1 25 MHz, CD_3OD) δ 179.4, 158.9, 139.6, 133.2, 126.3, 125.9, 124.8, 117.5, 105.0, 51.8, 32.6, 21.5 ppm; HRMS (ESI) *m/z* calcd for $[C_{12}H_{11}NONa]^+$ (M + Na)$^+$: 208.0733; found: 208.0731.

1,2,3,4-Tetrahydro-6*H*-pyrido[1,2-*a*]quinolin-6-one (15b). Following general procedure A, the one-pot reaction of tertiary amide **14b** (109 mg, 0.5 mmol) afforded **15b** (72 mg, yield: 72%) and the recovered starting material **14b** (*ca.* 8%). Following general procedure B, the two-step reaction afforded silyl enol ether **SEE2** and **15b** in 86% and 83% yield, respectively. In addition, about 2% of starting material was observed. **15b**: beige solid, R_f = 0.4 (10% MeOH/ethyl acetate). Mp: 189-190 °C. IR (film) ν_{max}: 3410, 3098, 3068, 2939, 1619, 1596, 1567, 1494, 1470, 1313, 1173, 1075, 1036, 845, 763 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 8.19 (d, J = 8.1 Hz, 2H), 7.63 – 7.57 (m, 2H), 7.37 – 7.31 (m, 1H), 6.00 (s, 1H), 4.01 (t, J = 6.4 Hz, 2H), 2.86 (t, J = 6.5 Hz, 2H), 2.00 – 2.00 (m, 2H), 1.82 – 1.75 (m, 2H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 178.1, 155.5, 142.4, 133.3, 127.0, 126.3, 125.1, 116.9, 110.0, 47.3, 31.1, 23.7, 19.4 ppm; HRMS (ESI) *m/z* calcd for $[C_{13}H_{13}NONa]^+$ (M + Na)$^+$: 222.0889; found: 222.0883.

2,3,5,6-Tetrahydroindolizin-7(1*H*)-one (15c). Following general procedure A, the one-pot reaction of tertiary amide **14c** (39 mg, 0.25 mmol) afforded **15c** (16 mg, yield: 48%) and the recovered starting material **14c** (*ca.* 13%). Following general procedure B, the two-step reaction afforded silyl enol ether **SEE3** and **15c** in 83% and 68% yield, respectively. In addition, about 11% of starting material was observed. **15c**: R_f = 0.3 (10% MeOH/ethyl acetate). IR (film) ν_{max}: 2933, 2843, 1668, 1575, 1418, 1264, 1171, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (s, 1H), 3.46 (t, J = 7.9 Hz, 2H), 3.38 (t, J = 6.9 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H), 2.51 (t, J = 7.9 Hz, 2H), 2.01 – 2.04 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 169.2, 93.3, 53.3, 45.4, 35.1, 31.8, 21.3 ppm; HRMS (ESI) *m/z* calcd for $[C_8H_{11}NONa]^+$ (M + Na)$^+$: 160.0733; found: 160.0733.

3,4,6,7,8,9-Hexahydro-2*H*-quinolizin-2-one (15d). Following general procedure A, the one-pot reaction of tertiary amide **14d** (43 mg, 0.25 mmol) afforded **15c** (16 mg, yield: 42%) and the recovered starting material **14d** (*ca.* 19%). Following general procedure B, the two-step reaction afforded silyl enol ether **SEE4** and **15d** in 85% and 65% yield, respectively. In addition, about 12% of starting material was observed. **15d**: R_f = 0.3 (10% MeOH/ethyl acetate). IR (film) ν_{max}: 2939, 2846, 1617, 1552, 1501, 1312, 1245, 1168, 1114, 803, 630 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (s, 1H), 3.40 (t, J = 7.7 Hz, 2H), 3.21 (t, J = 6.1 Hz, 2H), 2.47 – 2.42 (m, 4H), 1.90 – 1.84 (m, 2H), 1.70 – 1.63 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 163.7, 98.5, 50.5, 50.3, 35.2, 29.8, 23.2, 19.7 ppm; HRMS (ESI) *m/z* calcd for $[C_9H_{13}NONa]^+$ (M + Na)$^+$: 174.0889; found: 174.0883.

1,2,3,4,7,8-Hexahydropyrido[1,2-*a*]azepin-9(6*H*)-one (15e-a) and 1-(2,3,5,6,7,8-Hexahydroindolizin-1-yl)ethan-1-one (15e-b). Following general procedure A, the one-pot reaction of tertiary amide **14e** (46 mg, 0.25 mmol) afforded **15e-a** (13 mg, yield: 30%) and **15e-b** (10 mg, yield: 23%) in a combined yield of 53%. Following general procedure B, the two-step reaction afforded silyl enol ether **SEE5**, **15e-a** and **15e-b** in 70%, 38% and 24% yield, respectively.

15e-a: pale yellow oil, R_f = 0.27 (10% MeOH/ethyl acetate). IR (film) ν_{max}: 2920, 2850, 1543, 1444, 1349, 1285, 1235, 1139 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (s, 1H), 3.45 – 3.41 (m, 2H), 3.30 (t, J = 6.2 Hz, 2H), 2.57 (t, J = 6.7 Hz, 2H), 2.42 (t, J = 6.5 Hz, 2H), 2.02 –1.96 (m, 2H), 1.83 – 1.78 (m, 2H), 1.68 – 1.63 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 158.1, 101.8, 56.7, 52.0, 41.4, 32.5, 23.6, 23.2, 19.8 ppm; HRMS (ESI) *m/z* calcd for $[C_{10}H_{15}NONa]^+$ (M + Na)$^+$: 188.1046; found: 188.1045.

15e-b: pale yellow oil, R_f = 0.3 (10% MeOH/ethyl acetate). IR (film) ν_{max}: 2932, 2858, 1635, 1545, 1268, 1170, 925, 678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.43 (t, J = 9.9 Hz, 2H), 3.07 (t, J = 6.0 Hz, 2H), 2.89 (t, J = 6.4 Hz, 2H), 2.78 (t, J = 9.9 Hz, 2H), 2.06 (s, 3H), 1.83 – 1.77 (m, 2H), 1.68 – 1.62 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 162.3, 106.3, 52.9, 46.6, 28.6, 27.1, 25.5, 22.6, 19.6 ppm; HRMS (ESI) *m/z* calcd for $[C_{10}H_{15}NONa]^+$ (M + Na)$^+$: 188.1046; found: 188.1040.

(2,3,5,6-Tetrahydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone (15f). Following general procedure A, the one-pot reaction of tertiary amide **14f** (58 mg, 0.25 mmol) afforded **15c** (35 mg, yield: 65%) and the recovered starting material **14f** (*ca.* 15%). Following general procedure B, the two-step reaction afforded silyl enol ether **SEE6** and **15f** in 89% and 95% yield, respectively. **15f**: R_f = 0.3 (10% MeOH/ethyl acetate). IR (film) ν_{max}: 3053, 2925, 2854, 1680, 1445, 1260, 1049, 876, 704, 658 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.41 – 7.36 (m, 5H), 3.58 (t, J = 9.2 Hz, 2H), 3.35 – 3.32 (m, 2H), 3.22 (t, J = 9.2 Hz, 2H), 2.22 – 2.15 (m, 2H), 2.09 – 1.98 (m, 2H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 189.0, 178.0, 143.7, 130.2, 129.2 (2C), 128.2 (2C), 104.9, 32.8, 28.6 (2C), 26.7 (2C) ppm; HRMS (ESI) *m/z* calcd for $[C_{14}H_{15}NONa]^+$ (M + Na)$^+$: 236.1046; found: 236.1049.

(2,3,5,6,7,8-Hexahydroindolizin-1-yl)(phenyl)methanone (15g). Following general procedure A, the one-pot reaction of tertiary amide **14g** (58 mg, 0.25 mmol) afforded **15c** (35 mg, yield: 65%) and the recovered starting material **14g** (*ca.* 15%). Following general procedure B, the two-step reaction afforded silyl enol ether **SEE7** and **15g** in 83% and 88% yield, respectively. **15g**: R_f = 0.3 (10% MeOH/ethyl acetate). IR (film) ν_{max}: 3056, 2920, 2843, 1503, 1501, 1444, 1269, 1175, 1088, 707 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.40 – 7.31 (m, 5H), 3.58 (t, J = 9.6 Hz, 2H), 3.23 (t, J = 6.1 Hz, 2H), 2.85 (t, J = 9.6 Hz, 2H), 2.28 – 2.19 (m, 2H), 1.80 – 1.75 (m, 2H), 1.52 – 1.47 (m, 2H) ppm; ^{13}C NMR (126 MHz, CD_3OD) δ 188.7, 169.1, 144.9, 130.0, 129.3 (2C), 128.0 (2C), 108.8, 54.1, 47.2, 27.4, 27.3, 23.0, 20.0 ppm; HRMS (ESI) *m/z* calcd for $[C_{15}H_{17}NONa]^+$ (M + Na)$^+$: 250.1202; found: 250.1198.

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Keywords: Cyclization Reaction • Keto-lactams • Condensation Reaction • Heterocycles • Amides

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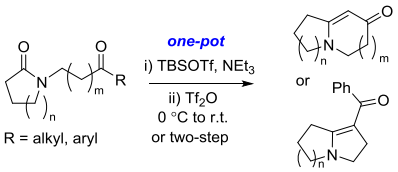
By pass thioamides: Intramolecular keto-lactam condensation leading to bicyclic vinylogous lactams has been achieved in either one-pot or in a two-step manner. The method consists of silyl enol ether formation and *in situ* amide activation with triflic anhydride.



- Heterocycles, synthetic method

Synthetic Method

Pei-Qiang Huang, and Ting Fan*

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Intramolecular Keto-lactam Condensation: A Convenient and Straightforward Approach to Bicyclic Vinylogous Lactams