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Intramolecular Cyclization of β-Alkynylpropanamides to γ-Alkylidene-γ-butyrolactams

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Abstract. A general method for the base-catalized intramolecular cyclization of β-alkynylpropanamides **1** to γ-alkylidene-γ-butyrolactames **2** (and **3**) was established. Reactions of β-alkynylamides **1c-h,** possessing alkyl groups at the terminal acetylenes, in the presence of a catalytic amount of $LiN(TMS)_2$ / AgOTf (= 2:1) in toluene gave exclusively (*Z*)-alkylidenelactames **2c-h** in good yields.
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The intramolecular addition of nitrogen nucleophiles to acetylenic triple bonds, giving rise to a variety of *N*-heterocycles, is of importance in organic synthesis[1]. In many cases, the synthesis of cyclic amines from alkynylamines (or amides) has been conducted using bases[2] or transition metals[3]. Many indoles have also been obtained in this manner[4]. Little study has been directed to the synthesis of lactams by the intramolecular cyclization of alkynylamides: e.g., Bu_4NF- or $LiAl(NHBn)_4$-catalyzed cyclization of alkynylamides[5], cyclization of ω-phenylseleno-substituted alkynylamides by Bu^tOK-18-crown-6[6], or the synthesis of 1,3-oxazolidine-2-ones by base-catalyzed cyclization of alkynylcarbamates in the presence of Ag-, Cu-salt or Pd[7]. In the case of β-alkynylamides (e.g.**1c-h**) possessing alkyl groups at terminal acetylenes, no such cyclization has been reported. The intramolecular cyclization of *o*-alkynylbenzamide by Et_3N in the presence of Ag_2CO_3 was previously shown to afford a mixture of lactam and iminolactone (ratio 1:1) but when conducted with $LiN(TMS)_2$ in THF the lactam compound was obtained predominantly[8]. The authors thus sought to establish a general method for the base-catalyzed intramolecular cyclization of β-alkynylamides (R = H, Ar, alkyl)[9] and the results summarized in Table 1 are discussed in the following.

By the above method (i.e., $LiN(TMS)_2$ in THF at 66°C for 18 h)[8], the cyclization of aryl-substituted alkynylamide **1a** was conducted to provide moderate yield of **2a** and **3a** (Run 1). When done in DMF, the yield increased but product isolation from DMF was tedius (Run 4). $KN(TMS)_2$ / 18-crown-6 in THF at room temperature gave the best results (Run 3). With **1b** having a bulky *N*-substituted group, $LiN(TMS)_2$ treatment alone in DMF at 60°C afforded **3b** predominantly as the thermodynamically stable product (Run 6). Under these conditions or using bases in the presence of phase-transfer-catalyst or absence, alkyl-substituted alkynylamide **1c** could make no progress (Run 7). With the catalytic $LiN(TMS)_2$ / AgOTf (= 2:1) system in toluene[10, 11], the cyclization of **1c** proceeded more efficiently (Run 8). THF or DME instead of toluene as the solvent had no significant effect (Run 10). This catalytic system used with various alkyl-substituted alkynylamides (R^1= chloropropyl, dodecyl, H: **1g**, **1h**, **1i**, respectively) or alkynylamides having bulky *N*-substituted alkyl groups (**1d**, **1e**, **1f**) led to satisfactory yields and stereoselectivity (Runs 9, 11-15)[10, 12].

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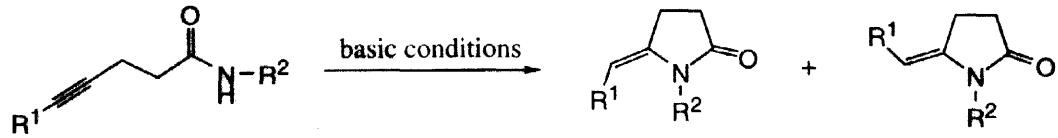
Table 1. Intramolecular Cyclization of β-Alkynylpropanamides to γ-Alkylidene-γ-butyrolactams Under Basic Conditions.



1a-i **2a-i** **3a-i**

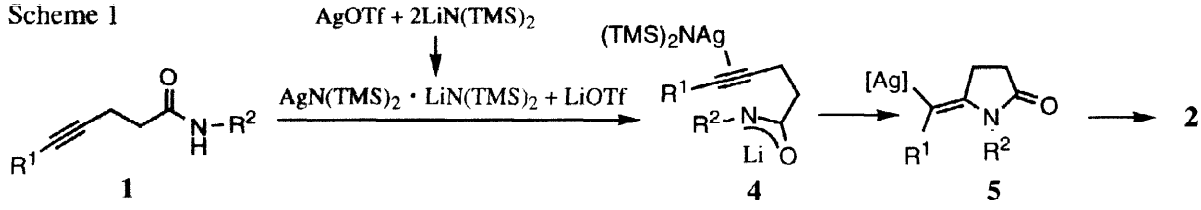
Run	Alkynylamide **1a-i** R^1, R^2	Base (eq)	Additive (eq)	Solvent	Temp. (°C)	Time (h)	Yield (%)[a] and Isomer Ratio (**2** : **3**)[b]	
1	**1a**: R^1=*p*-methoxyphenyl R^2=*m*-methoxybenzyl	LHMDS (1.0)	---	THF	66	18	42	(85 : 15)
2	**1a**:	n-BuLi (1.0)	---	THF	0-66	10	8	---
3	**1a**:	KHMDS (0.5)	18-crown-6 (0.4)	THF	r.t.	3	71	(64 : 36)
4	**1a**:	LHMDS (1.0)	---	DMF	60-65	3	64	(55 : 45)
5	**1a**:	LHMDS (0.3)	AgOTf (0.15)	THF	65-70	3	85	(96 : 4)
6	**1b**: R^1=*p*-methoxyphenyl R^2=CH(Ph)CH_2OTBS (*R*)	LHMDS (1.0)	---	DMF	60-65	3	67	(12 : 88)
7	**1c**: R^1=CH_3 R^2=*m*-methoxybenzyl	KHMDS (0.3)	18-crown-6 (0.3)	THF	r.t.-60	18	0	---
8	**1c**:	LHMDS (0.3)	AgOTf (0.15)	toluene	65-70	3	89	(100 : 0)
9	**1d**: R^1=CH_3 R^2=CH(Ph)CH_3 (*S*)	LHMDS (0.3)	AgOTf (0.15)	toluene	65-70	3	89	(100 : 0)
10	**1d**:	LHMDS (0.3)	AgOTf (0.15)	THF	66	18	46	(100 : 0)
11	**1e**: R^1=CH_3 R^2=CH(Ph)CH_2OCH_3 (*R*)	LHMDS (0.3)	AgOTf (0.15)	toluene	65-70	3	88	(100 : 0)
12	**1f**: R^1=CH_3 R^2=CH(Ph)CH_2O-  (*R*)	LHMDS (0.3)	AgOTf (0.15)	toluene	65-70	4	85	(100 : 0)
13	**1g**: R^1=n-C_3H_6Cl R^2=*m*-methoxybenzyl	LHMDS (0.3)	AgOTf (0.15)	toluene	65-70	3	84	(100 : 0)
14	**1h**: R^1=n-$C_{12}H_{25}$ R^2=*m*-methoxybenzyl	LHMDS (0.3)	AgOTf (0.15)	toluene	65-70	4	89	(100 : 0)
15	**1i**: R^1=H R^2=*m*-methoxybenzyl	LHMDS (0.3)	AgOTf (0.15)	toluene	65-70	3	86	---

[a] Isolated yield after purification by NH-silicagel column. [b] Determined based on ^{1}H NMR spectra of the crude products.

Further, when **1a** was applied to this system, **2a** was obtained in 82% yield along with **3a** in 3% yield (Run 5). However, this method with 5-hexynamide failed to bring about 6-membered ring formation. Compound **2** was found to have the Z-form structure by NOE[13], as was also supported by examination of the isomerization of **2** to thermodynamically stable product **3** (*E*-form) in $CDCl_3$ for several hours[14] or on standing at room temperature for 2~3 days.

The reaction mechanism for the present cyclization remains to be clarified. The $LiN(TMS)_2$ / AgOTf (= 1:1) system in toluene gave no product, thus suggesting the mechanism in scheme 1. Reaction of **1** with silver- and lithium-amides, prepared from a mixture of 1 eq AgOTf and 2 eq $LiN(TMS)_2$, produced bis-metallated complex **4**, which underwent *trans*-aminometallation to vinylmetal-species **5**, followed by the protonolysis of **5** to **2**. However, the cyclization of 5-hexynamide to δ-valerolactam under the same conditions failed to occur, the reasons for which, at present, are not understood.

Scheme 1



1 **4** **5**

The authors have thus established a new method for the efficient intramolecular cyclization of β-alkynylamides to γ-alkylidenelactams. It is particularly significant that alkyl-substituted alkynylamides by the catalytic $LiN(TMS)_2$ / AgOTf system could efficiently undergo intramolecular cyclization to produce alkylidenelactams. The alkylidenelactam obtained in the present study should prove useful for the synthesis of α-substituted pyrrolidine derivatives.

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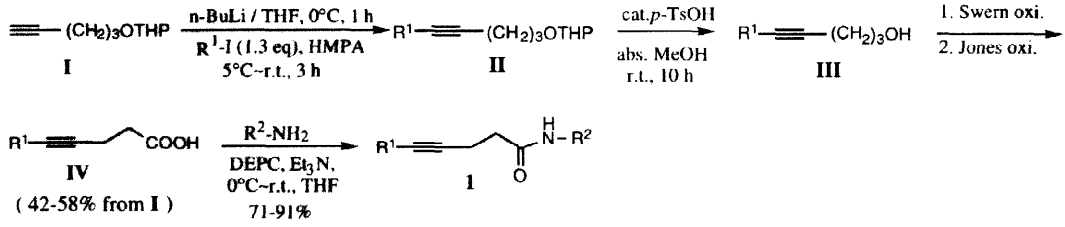
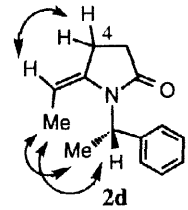
9. **1a, b, i** were prepared in the present study in the same manner as described in the previous paper[8]. **1d-h** were prepared as outlined below.



Synthesis of **IV** (R^1= Me) from **I** by a little different conditions was reported in a total yield of 35% ; Carling, R.W.; Clark, J.S.; Holmes, A.B.; Sartor, D. *J. Chem. Soc., Perkin Trans 1* **1992**, 95-101.

10. Synthesis of **2e** (general procedure for **1c-h**). To a solution of alkynylamide **1e** (400 mg, 1.630mmol) and AgOTf (64 mg, 0.24 mmol) in abs. toluene (6 ml) stirred under argon atmosphere was added slowly at r.t. a solution of $LiN(TMS)_2$ in hexane (1.0 M, 0.49 ml, 0.49 mmol). After 0.5 h, the mixture consisting of a clear solution and black-brown paste, was stirred at 65-70°C for 3 h, whereupon, the system became a black suspension. The reaction mixture was quenched with ice-water and filtered through celite by suction. The filtrate was extracted with AcOEt according to a conventional work-up. The crude product was purified by chromatography on NH-silica gel (eluent : hexane / AcOEt = 20 :1) to give the **2e** (353 mg) in 88 % yield as a colorless solid. mp 73-74°C (from iPr_2O-hexane). IR (KBr, cm^{-1}) 2900, 1670, 1320. ^{1}H-NMR (300 MHz, CDCl3) δ; 1.53 (d, *J* = 7.4 Hz, 3H), 2.48 (m, 2H), 2.66 (m, 2H), 3.42 (s, 3H), 4.00 (dd, *J* = 5.9, 9.7 Hz, 1H), 4.35 (dd, *J* = 8.2, 9.7 Hz, 1H) 4.52 (q, *J* = 7.4 Hz, 1H), 5.38 (dd, *J* = 5.9, 8.2 Hz, 1H) 7.32 (m, 5H). ^{13}C-NMR (75 MHz, $CDCl_3$) 12.3, 27.9, 30.3, 58.5, 58.7, 72.8, 96.8, 126.6, 127.2, 128.4, 138.4, 139.6, 178.0; MS m/z 235 (M^+); $[\alpha]^{24}_D$ +70.1 ° (c 1.02, toluene). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.42; H, 7.81; N, 5.68.
11. Based on the catalysis of Cu^+ and Ag^+ with appropriate bases, the intramolecular addition of 2-propynyl carbamates to their own acetylenic triple bonds has been reported [7d, 7f].
12. Synthesis of **2i**. A mixture of $LiN(TMS)_2$ / AgOTf (2:1) in toluene was added *via* syringe at r.t. to a solution of **1i** in toluene to form a black-brown precipitate gradually, followed by the same work-up described for general procedure to afford **2i** in 86% yield.
13. NOESY (500 MHz NMR, pyridine-d_5) demonstrated **2d** to have the *Z*-form as evident by the NOE interaction between 4-H and vinyl-H, vinyl-$C\underline{H}_3$ and benzyl-H, and vinyl-$C\underline{H}_3$ and $NCH(C\underline{H}_3)$.
14. Isomer **3d** was determined to have the *E*-form by NOESY subsequent to the isomerization of **2d** in $CDCl_3$ at r.t. for several hours.



2d