Tetrahedron Letters, Vol.31, No.37, pp 5353-5356, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

NEW FACILE SYNTHESIS OF SUBSTITUTED 2-BENZYLIDENE-PYRROLIDINES BY THE ANIONIC CYCLIZATION OF δ-ALKYNYLAMINES

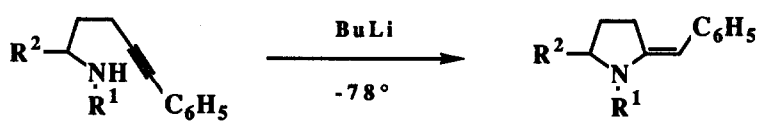
Masao Tokuda,* Hirotake Fujita, and Hiroshi Suginome*
Division of Organic Synthesis, Department of Chemical Process Engineering,
Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

Abstract: Treatment of δ-alkynylamines with butyllithium or lithium aluminum hydride brought about a facile anionic cyclization, giving high yields of the corresponding enamine pyrrolidines having an exo double bond.

We previously reported that the neutral aminyl radicals generated by anodic oxidation of the lithium amides of δ-alkenylamines undergo a regio- and stereoselective cyclization to give *cis*-1-methyl-2,5-disubstituted pyrrolidines.[1] In the course of our continuing studies on aminyl cyclizations, we have found a new facile anionic cyclization of δ-alkynylamines to give enamine pyrrolidines having an exo double bond. Although several methods have been reported for the synthesis of enamine pyrrolidines having an exo double bond,[2] the reported methods were limited to a synthesis of enamine pyrrolidines carrying an electron-withdrawing group at the terminal carbon of the exo double bond, probably because those studies were mainly carried out in order to prepare part of the corrin system.[2a]

In this communication we wish to report a new, facile one-step synthesis of enamine pyrrolidines having a benzylidene group at the C-2 position.

Treatment of δ-alkynylamines (**1a**~**1d**)[3] with butyllithium gave *N*-methyl- (**2a** and **2b**) and *N*-allyl-2-benzylidene-5-substituted pyrrolidines (**2c** and **2d**) in high yields, as outlined in Scheme 1. Typically, to a solution of *N*-methyl-1,5-diphenyl-4-



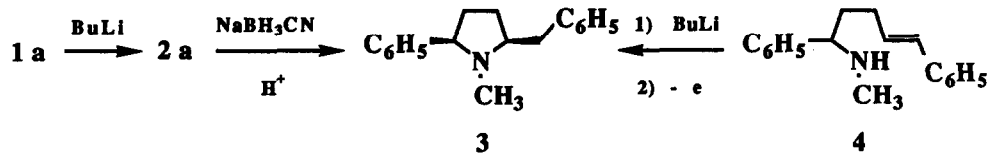
1a $R^1=CH_3$, $R^2=C_6H_5$
1b $R^1=CH_3$, $R^2=CH_3$
1c $R^1=CH_2CH=CH_2$, $R^2=C_6H_5$
1d $R^1=CH_2CH=CH_2$, $R^2=CH_3$
1e $R^1=CH_3$, $R^2=H$

2a $R^1=CH_3$, $R^2=C_6H_5$
2b $R^1=CH_3$, $R^2=CH_3$
2c $R^1=CH_2CH=CH_2$, $R^2=C_6H_5$
2d $R^1=CH_2CH=CH_2$, $R^2=CH_3$

Scheme 1

pentynylamine (**1a**) (100 mg, 0.4 mmol) in THF (6 ml) was added butyllithium (0.48 mmol) at -78°C under a nitrogen atmosphere and the solution was stirred for 30 min at -78°C and another 30 min at -10°C. After adding water at -10°C, the mixture was gradually warmed to room temperature. The usual work-up and product separation by TLC (Silica gel; $CHCl_3$/EtOAc/MeOH=20:1:0.1) gave 82 mg of (*E*)-2-benzylidene-1-methyl-5-phenylpyrrolidine (**2a**) (82% yield). The pyrrolidine **2a** was not stable and gradually decomposed upon heating or exposure to air.

The structure of **2a** was confirmed by both spectroscopic analysis and its transformation into a known pyrrolidine. The IR spectrum of **2a** exhibited strong absorption at 1632 cm^{-1}, ascribable to an enamine double bond. The ^1H NMR spectrum exhibited a singlet at δ 5.17 attributable to a vinylic proton, which is exchangable with deuterium upon the addition of D_2O.[2f] Moreover, an NOE enhancement (8.5%) was observed between the signal due to the vinylic proton and that due to the *N*-methyl protons in the ^1H NMR, indicating the (*E*)-configuration of the double bond of **2a**. A reduction of **2a** with sodium cyanoborohydride under acidic conditions gave *cis*-2-benzyl-1-methyl-5-phenylpyrrolidine (**3**) (72% yield), which was identical to the pyrrolidine **3** prepared by cyclization of neutral aminyl radical generated by anodic oxidation of lithium amide of *N*-methyl-1,5-diphenylpent-4-enylamine **4** (Scheme 2).[4]



Scheme 2

The yields of enamine pyrrolidines obtained by anionic cyclization with butyllithium are summarized in Table 1.

We subsequently found that treatment of γ,δ-alkynamide (*e.g.*, **5a**) with lithium aluminum hydride ($LiAlH_4$) also affords enamine pyrrolidine (*e.g.*, **2e**). Thus, 1-methyl-2-benzylidenepyrrolidine **2e** (57 mg, 82%) was obtained directly from *N*-methyl-5-phenyl-4-pentynamide **5a** (75 mg, 0.4 mmol)[5] by reduction with $LiAlH_4$

5a R=C_6H_5
5b R=H

2e R=C_6H_5

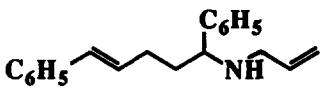
Scheme 3

Table 1. Anionic cyclization of δ-alkynylamines (1) and γ,δ-alkynamide (5)

Amine or amide	R^1	R^2	Product	Yield of 3 (%)[a]	
				BuLi	$LiAlH_4$
1a	CH_3	C_6H_5	2a	85	86
1b	CH_3	CH_3	2b	95	98
1c	$CH_2CH=CH_2$	C_6H_5	2c	82	0[b]
1d	$CH_2CH=CH_2$	CH_3	2d	80	82
5a	—	—	2e	—	82

a) Isolated yields. b) See text.

(0.8 mmol) in THF at room temperature for 12h, as outlined in Scheme 3. The role of the complex metal hydride in this case is apparently to reduce amide **5a** to *N*-methyl-5-phenyl-4-pentynylamine (**1e**; $R^1=CH_3$, $R^2=H$) and to generate a nitrogen anion which attacks the acetylenic carbon intramolecularly to give **2e**. The presence of a 5-aryl group in this cyclization is necessary since treatment of *N*-methyl-4-pentynamide **5b** with $LiAlH_4$ under the above-mentioned conditions gave simply *N*-methyl-4-pentynylamine in a quantitative yield and no pyrrolidine derivative. Treatment of δ-alkynylamines **1a~1d** with $LiAlH_4$ was then found to produce 2-benzyliden-pyrrolidines in high yields, as shown in Table 1, while treatment of *N*-allyl-1,5-diphenyl-4-pentynylamine (**1c**) with $LiAlH_4$ resulted in the formation of *N*-allyl-1,5-diphenylpent-4-enylamine **6** (82%) arising from reduction. The failure of the cyclization in pentynylamine **1c** may be attributable to a steric factor.



6

We examined the cyclization of **1a** using a number of bases and found that while potassium *t*-butoxide is effective to form pyrrolidine **2a** (62% yield), sodium ethoxide, sodium amide, and sodium borohydride are not, giving the recovered starting material.

Acknowledgement: Part of this work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 01607001) from the Ministry of Education, Science and Culture of Japan.

REFERENCES AND NOTES

1. M. Tokuda, Y. Yamada, T. Takagi, H. Suginome, and A. Furusaki, *Tetrahedron Lett.*, **26**, 6085 (1985); M. Tokuda, Y. Yamada, T. Takagi, H. Suginome, and A. Furusaki, *Tetrahedron*, **43**, 281 (1987).
2. *Inter alia*, synthesis by a reaction of lactim ether with activated methylene compounds: (a) H. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribe, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem. Int. Ed. Engl.*, **3**, 490 (1964), (b) Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.*, **17**, 2230 (1969), (c) J-P Celerier, E. Deloisy, G. Lhommet, and P.Maitte, *J. Org. Chem.*, **44**, 3089 (1979); by a Wittig reaction of 2-pyrrolidone derivatives: (d) M. Natsume, M. Takahashi, K. Kikuchi, and H. Sugaya, *Chem. Pharm. Bull.*, **19**, 2649 (1971); by a reaction of 2-thiopyrrolidone with α-bromoketone: (e) M. Roth, P. Dubs, E. Gotschi, and A. Eschenmoser, *Helv. Chim. Acta.*, **54**, 710 (1971); by a reaction of Δ^1-pyrroline *N*-oxide with phosphonates: (f) E. Breuer and S. Zbaida, *J. Org. Chem.*, **42**, 1904 (1977).
3. δ-Alkynylamines (**1**) were prepared by alkylation of ethyl benzoylacetate or ethyl acetoacetate with 3-bromo-1-phenyl-1-propyne (80-97%), decarbethoxylation (74-90%)[6] followed by reductive amination of the resulting ketones with methylamine or allylamine in the presence of sodium cyanoborohydride (70-95%).[7] Most of δ-alkynylamines were purified by distillation.
4. M. Tokuda, T. Miyamoto, and H. Suginome, unpublished results.
5. Amide **5a** was prepared by alkylation of ethyl malonate with 3-bromo-1-phenyl-1-propyne (75%), decarbethoxylation (69%),[6] hydrolysis of the ester followed by amidation with methylamine (64%).[8] Amide **5a** was purified by recrystallization from hexane.
6. A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973).
7. R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93**, 2987 (1971).
8. M. Miyano, *J. Amer. Chem. Soc.*, **87**, 3958 (1965).

(Received in Japan 5 June 1990)