Tetrahedron Letters, Vol. 33, No. 29, pp. 4103-4106, 1992
Printed in Great Britain

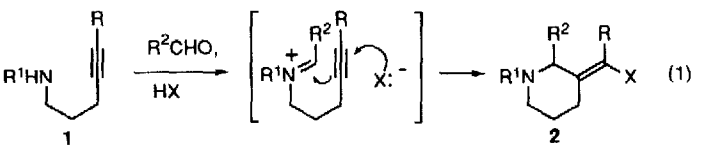
0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Iodide-Promoted Aldiminium Ion-Alkyne Cyclizations. A Convenient Synthesis of Substituted Tetrahydropyridines and 3-Alkylidenepiperidines.

Larry E. Overman* and Achintya K. Sarkar[1]
Department of Chemistry, University of California
Irvine, California 92717

Abstract: Iodide-promoted cyclizations of aldehydes with 4-alkynylamines and 3-alkynylamines provide direct synthetic access to alkylidenepiperidines **4** and tetrahydropyridines **8**, respectively.

Simple alkynes are less nucleophilic than alkenes and typically do not undergo intramolecular reactions with weak electrophiles such as iminium cations.[2,3] However, a promising Mannich chemistry of alkynes was recently revealed when formaldiminium ion-alkyne cyclizations were carried out in the presence of strong external nucleophiles such as iodide (eq 1, R^2 = H).[4-6] The iodide-promoted cyclization of formaldiminium ions derived from (L)-proline is the central step in the first practical synthetic entry to the



(1)

1 2

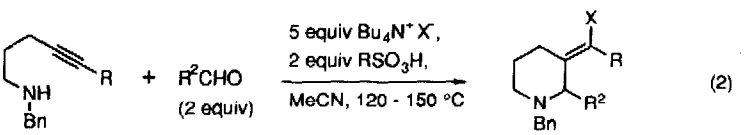
cardiotonic pumiliotoxin A alkaloids.[5] The scope of this convenient route to piperidines would be significantly expanded if related cyclizations of aldiminium ions could be occasioned under the aegis of external nucleophiles. In this communication we report that a variety of 2-substituted-3-alkylidenepiperidines (eq 1, R^2 = alkyl or CO_2R) and 2-substituted-1,2,5,6-tetrahydropyridines (eq 4) are formed in useful yields when iodide-promoted aldiminium ion-alkyne cyclizations are carried out in a polar aprotic solvent at elevated temperature.

After some preliminary optimization, we found that the cyclization of 4-alkynylamines **3** with an aldehyde was best accomplished in acetonitrile at 120-150 °C in the presence of 5 equiv of tetrabutylammonium iodide (eq 2).[7] The examples reported in Table 1 illustrate the scope of the reaction. Noteworthy features include the following: (1) Cyclization occurs exclusively in the exocyclic mode to afford the E alkylidene stereoisomer **4** selectively (>96%). (2) The cyclization of internal alkynes with aliphatic aldehydes takes place with good efficiency at 120-150 °C. (3) Less nucleophilic terminal alkynes cyclize more slowly as do conjugated iminium ions derived from aromatic aldehydes. (4) Tetrabutylammonium bromide is less effective as a cyclization-promoter. (5) 3-Alkylidenepipecolic esters

Table 1. Preparation of 2-Substituted-3-alkylidenepiperidines as Outlined in Equation 2.

		rxn conds			alkylidenepiperidine	
R	R^2	X	temp(°C)	time(h)	compd	yield(%)
Me	Me	I	150	2	**4a**	71
Me	Et	I	120	20	**4b**	68
H	Me	I	150	8	**4c**	47
Me	Ph	I	120	20	**4d**	18
Me	Me	Br	120	17	**4e**	25
Me	CO_2Et	I	120	3.5	**4f**	58
Me	CO_2Ph	I	120	2	**4g**	55
H	CO_2Et	I	150	1	**4h**	44

(**4f** - **4h**) can be prepared in modest yield from the iodide-promoted reaction of glyoxylate esters with both internal and terminal alkynes.[8,9] As expected, the cyclizations of these more electrophilic cations occurred more rapidly. (6) The major competing reaction is HI addition to alkyne **3** to afford acyclic vinyl iodides.

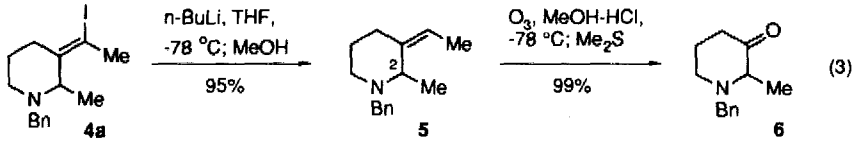


(2)

3 a R = Me,
b R = H

4

Stereochemical assignments for **4** are based on ^1H NMR coupling and NOE data. Structural assignments were further confirmed in the case of **4a** by the conversions shown in eq 3. The (*Z*)-alkylidenepiperidine **5** showed strong NOE enhancements between the vinylic methyl and the C(2) hydrogen, but not between the vinylic and C(2) hydrogens. Ozonolysis of **5** in acidic methanol gave the 3-piperidone **6**.[10]



(3)

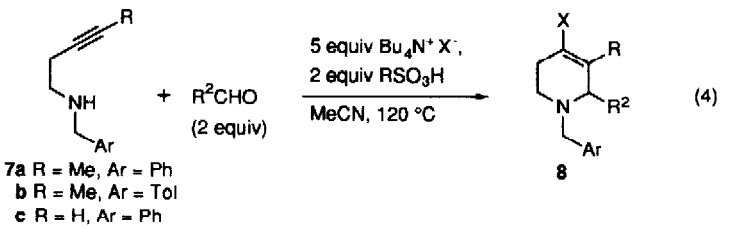
4a **5** **6**

Related cyclizations of aldehydes and 3-alkynylamines **7** took place at 120 °C exclusively in the endocyclic mode to yield substituted 1,2,5,6-tetrahydropyridines **8** (eq 4, Table 2).[7] Many of the characteristics of this reaction are similar to those of the alkylidenepiperidine synthesis. Specifically, iodide is a better cyclization promoter than bromide and iminium ions derived from glyoxylate esters cyclize more rapidly than those derived from aliphatic aldehydes. The structures of **8a** and **8d** were confirmed by deiodination (BuLi, ether, -78 °C; MeOH) to give known substituted tetrahydropyridines.[11] The major by-product isolated from the bromide-terminated cyclization of **7c** with acetaldehyde was the allenylamine **12** (R^2 = Me, Scheme I). The cyclization of **7c** with ethyl glyoxylate (Table 2, last entry) gave none of the expectedtetrahydropyridine **8**, but afforded 1-benzyl-4-iodo-1,2,5,6-tetrahydropyridine (**9**) in 25% yield.[4a]

Table 2. Preparation of 2-Substituted-1,2,5,6-tetrahydropyridines as Outlined in Equation 4.

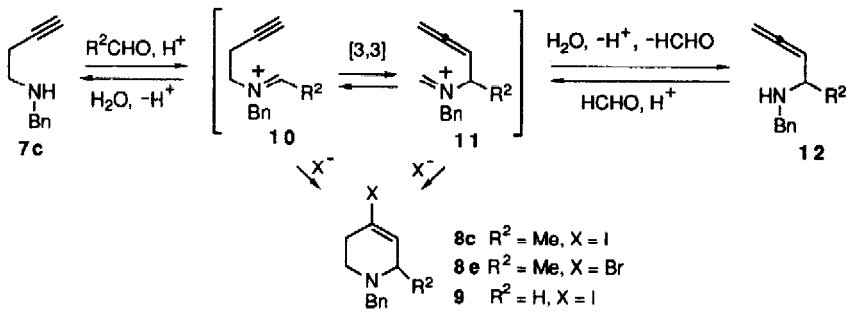
			rxn conds		tetrahydropyridine	
R	Ar	R^2	X	time(h)	compd	yield(%)
Me	Ph	Me	I	18	**8a**	71
Me	Ph	CO_2Et	I	3	**8b**	56
H	Ph	Me	I	17	**8c**	60
H	*p*-Tol	$PhCH_2CH_2$	I	17	**8d**	60
H	Ph	Me	Br	17	**8e**	33[a]
H	Ph	CO_2Et	I	17		[b]

[a] Allenylamine **12** (R^2 = Me) was isolated also (25% yield). [b] 1-Benzyl-4-iodo-1,2,5,6-tetrahydropyridine (**9**) was isolated in 25% yield.



The formation of allene **12** (R^2 = Me) and the 2-unsubstituted tetrahydropyridine **9** is consistent with a mechanistic scenario in which aza-Cope equilibration of iminium cations **10** and **11** occurs at least competitively with nucleophile-promoted cyclization of **10** or **11**.[12] The formation of **9** would arise from the reaction of **7c** with formaldehyde generated *in situ*.[13]

Scheme I



Two features of this synthesis of substituted tetrahydropyridines and alkylidenepiperidines commend its use: (a) a wide variety of alkylamines are available in two steps from commercially available alkynols[4b] and (b) the vinyl iodide functionality of the piperidine products allows for subsequent structural elaboration with a wide range of organometallic reagents.[4a] We anticipate that the simple route to unsaturated six-membered azacycles reported here will prove useful for the preparation of a variety of piperidines, pyridines and pipecolic acids.

Representative Experimental Procedure. (*E*)-1-Benzyl-2-ethyl-3-(1-iodoethylidene)piperidine (4b). A mixture of **3a** (100 mg, 0.53 mmol), propanal (62 mg, 1.1 mmol), camphorsulfonic acid (310 mg, 1.3 mmol), $(n\text{-Bu})_4$ NI (1g, 2.6 mmol) and dry MeCN (9 mL) was degassed and heated in a sealed glass ampule under an argon atmosphere at 120 °C for 20 h. After cooling to 23 °C, the reaction was partitioned between CH_2Cl_2 (20 mL) and aqueous 2 *N* NaOH (10 mL) and the organic phase was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography (SiO_2, 90:10:5 hexane-EtOAc-Et_3N) to give 129 mg (68%) of **4b** as a nearly colorless oil: IR (film) 2962, 2935, 2871, 1493, 1464, 1453, 1225, 1175, 1124, 1058, 1048, 1027, 866 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.35-7.27 (m, 5H, Ph), 3.71 (s, 2H, PhCH_2), 3.60 (t, J = 7.5 Hz, NCH), 3.09 (dt, J = 2.5, 10 Hz, 1H), 2.76-2.62 (m, 2H), 2.43 (app d, J = 2 Hz, =CH_3), 2.33-2.30 (m, 1H), 1.90-1.62 (m, 3H), 1.51-1.46 (m, 1H), 0.82 (t, J = 7.5 Hz, Me); ^{13}C NMR (75.5 MHz, $CDCl_3$) 140.8, 139.7, 128.6, 128.1, 126.8, 95.3, 59.6, 57.7, 45.6, 36.0, 29.8, 23.3, 22.6, 10.8; HRMS (CI) m/z 356.0874 (356.0875 calcd for $C_{16}H_{23}IN$). Maleate salt: mp 122-123 °C (EtOAc); Anal. Calcd. for $C_{20}H_{26}INO_4$: C, 50.96; H, 5.56; N, 2.97. Found: C, 51.07; H, 5.59; N, 2.93.

Acknowledgment. This investigation was supported by P.H.S. Grant HL-25854. NMR and mass spectra were determined on instruments purchased with the assistance of N.S.F. Shared Instrumentation Grants. We wish to thank Dr. Richard Heys, SmithKline Beecham, for sharing with us his results in this area.

References and Notes

1. Current address: Department of Chemistry, Bose Institute, 93/1, A.P.C. Road, Calcutta-700009, India.
2. For a recent brief review, see: Overman, L. E.; Ricca, D. J. *Comp. Org. Synthesis* **1991**, *2*, 1007.
3. Alkynes do undergo intramolecular reactions with the much more reactive *N*-acyliminium cations, see: Heimstra, H.; Speckamp, W. N. *Comp. Org. Synthesis* **1991**, *2*, 1047.
4. (a) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612, 5934. (b) Arnold, H. J.; Overman, L. E.; Sharp, M. J.; Witschel, M. C. *Org. Synth.* **1991**, *70*, 111.
5. (a) Overman, L. E.; Robinson, L. E.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368. (b) Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901.
6. For an early example with water as the external nucleophile, see: Ahmad, V. U.; Feuerherd, K. -H.; Winterfeldt, E. *Chem. Ber.* **1977**, *110*, 3624.
7. All new pyrrolidines were characterized by ^1H and ^{13}C NMR, IR, and mass spectral data as well as by combustion analyses on the oxalate or maleate salts. Yields refer to pure products isolated after silica gel chromatography.
8. For recent syntheses of pipecolic acids from iminium ion-alkene cyclizations, see, *inter. alia.*: (a) Tietze, L.; Bratz, M. *Synthesis* **1989**, 439. (b) Tietze, L.; Bratz, M. *Liebigs Ann. Chem.* **1989**, 559. (c) Agami, C.; Couty, F. *Synlett* **1990**, 731.
9. For recent syntheses of pipecolic acids from *N*-acyliminium ion-initiated cyclizations, see, *inter. alia.*: (a) Mooiweer, H. H.; Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 3285. (b) Esch, P. M.; Boska, I. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 4039.
10. Iorio, M. A.; Gatta, F.; Michalek, H. *Eur. J. Med. Chem.-Chim. Ther.* **1980**, *15*, 165. *Chem. Abstr.* **1980**, *93*, 125408*r*.
11. Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097.
12. Low temperature ^{13}C NMR studies in CD_3CN establish that the [3,3]-sigmatropic rearrangement of 3-alkynyl formaldiminium ions occurs at -30 °C. Unpublished studies of A. Weier and L. E. Overman.
13. If full equilibration of all sigmatropically-related iminium cations with their corresponding amine salts and carbonyl components occurred, the formation of two propargylamines, two allenylamines and four tetrahydropyridines would be possible. Such equilibration apparently does not occur prior to cyclization for the reactions reported in the first four entries of Table 2, since only a single tetrahydropyridine product was observed.[14] These details will be discussed in detail in a subsequent full account of nucleophile-promoted Mannich cyclization reactions of alkynes.
14. Under different conditions ($MeSO_3H$, NaI, MeCN, 90 °C) that likely involve lower concentrations of iodide, full equilibration can occur and all eight possible products can be detected. Personal communication from Dr. Richard Heys, Synthetic Chemistry Department, SmithKline Beecham.

(Received in USA 3 April 1992)