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Triarylaminium Salt Induced Oxidative Cyclizations of Tertiary Amines. Convenient Access to 2-Substituted Pyrrolidinium Salts

Ullrich Jahn* and Susanne Aussieker

Institut für Organische Chemie, Technische Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany

u.jahn@tu-bs.de

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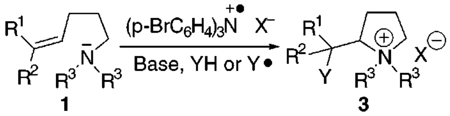
ABSTRACT



Although they are common intermediates, the application of aliphatic tertiary aminium radical cations to organic synthesis has so far been restricted to α-deprotonation and related reactions. We report the very convenient oxidative generation and facile 5-exo cyclization of tertiary amimium radical cations to distonic 2-substituted pyrrolidinium radical cations. These can be further oxidized to 1,3-dications and trapped by nucleophiles as water, alcohols, or chloride ion. Preliminary mechanistic issues and implications will be presented.

Pyrrolidines and their salts play a pivotal role in many aspects of organic chemistry.[1] For their synthesis, the development of strategies that exploit *reactive nitrogen-centered intermediates* is an active and attractive area of research. The most widely applied methods are intramolecular N-alkylations,[1] [3 + 2] cycloadditions,[1,2] or intramolecular additions to multiple bonds. Most notable for the last strategy are Li-,[3] Pd-[4] or lanthanoid-catalyzed[4c,5] cyclizations, intramolecular halo- or selenoaminations,[1,6] or cyclizations of aminyl radicals,[7] generated from *N*-haloamines,[8] *N*-sulfenylamines,[9] or PTOC-carbamates.[10]

However, almost all of these methods are applicable only to primary and secondary amine derivatives[11] and require usually the preparation of N-functionalized precursors.

In a research program, directed to the development of oxidative electron transfer induced reactions,[12] we became interested in the activation of amines via single electron transfer (SET) oxidation. Unsaturated tertiary amines are especially suitable for the initial exploration of the intramolecular reaction behavior of oxidatively generated aliphatic

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[1] Recent reviews: (a) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493−3513 and earlier reviews in this series. (b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927−964.

[2] Reviews: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475−2486.

[3] Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* **1992**, *33*, 6359−6362.

[4] Reviews: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199−207. (c) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703. (d) Tamaru, Y.; Kimura, M. *Synlett* **1997**, 749−757.

[5] Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633−3639 and references therein.

[6] (a) Leading references: Jones, A. D.; Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1999**, *40*, 3267−3270. (b) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120−2126.

[7] Reviews: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594. (b) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem.* **1993**, *58*, 1−45.

[8] Boate, D.; Fontaine, C.; Guittet, E.; Stella, L. *Tetrahedron* **1993**, *49*, 8397−8406 and references therein.

[9] Bowman, W. R.; Broadhurst, M. J.; Coghlan, D. R.; Lewis, K. A. *Tetrahedron Lett.* **1997**, *38*, 6301−6304 and references therein.

[10] Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738−7748 and references therein.

[11] A few *stoichiometric* Pd-mediated direct cyclizations of tertiary amines have been reported: van der Schaaf, P. A.; Sutter, J.-P.; Grellier, M.; van Mier, G. P. M.; Spek, A. L.; van Koten, G.; Pfeffer, M. *J. Am. Chem. Soc.* **1994**, *116*, 5134−5144 and references therein.

[12] (a) Jahn, U.; Hartmann, P. *Chem. Commun.* **1998**, 209−210. (b) Jahn, U. *J. Org. Chem.* **1998**, *63*, 7130−7131.

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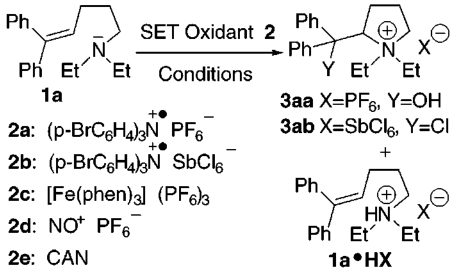
aminium radical cations.[13] So far, only the facile α-deprotonation or desilylation of tertiary aminium radical cations to α-amino radicals has been exploited in synthetic applications.[14]

Here, we demonstrate that tertiary 4-pentenylaminium radical cations can be efficiently generated from amines **1** by tris(*p*-bromophenyl)aminium salts **2a,b** and cyclize directly to functionalized pyrrolidinium salts[15] without interference of α-deprotonation (Scheme 1).

Scheme 1. Screening of Conditions for Aminium Radical Cation Cyclization of **1a**



Initial studies focused on the choice of the oxidant[16] and the establishment of suitable reaction conditions. The results are summarized in Table 1. Treatment of the 5,5-diphenyl-4-pentenylamine compound **1a** with tris(*p*-bromophenyl)aminium hexafluorophosphate (**2a**)[17] at −20 °C in 50 mM acetonitrile solution under a nitrogen atmosphere gave the pyrrolidinium salt **3aa** in a moderate 45% yield accompanied by 40% **1a·HPF$_6$** (entry 1). Addition of 2 equiv of K_2CO_3 and 10 equiv of water improved the yield of **3aa** to 88% (entry 2). Treatment with **2b** under otherwise identical conditions yielded the chloropyrrolidinium salt **3ab** (entry 3). Furthermore, 7% of **3aa** and 15% of **1a·HSbCl$_6$** were detected by NMR in the crude reaction mixture. Schmittel's $[Fe(phen)_3](PF_6)_3$ (**2c**)[18] provided **3aa** in 49% isolated yield (entry 4). The moderate yield is basically due to the extremely difficult separation of the salt **3aa** and the reduced iron(II) complex salt. Nitrosyl hexafluorophosphate **2d** oxidized **1a** completely, but benzophenone was the only component to be characterized in the salt product mixture (entry 5). Attempted oxidation of **1a** with ceric ammonium nitrate (CAN) (**2e**)[19] in MeOH or MeCN returned 88% or 48% of the amine, respectively (entry 6).

Table 1. Oxidant Dependence of the Reactivity of Amine **1a**

			products (%)			
entry	**2**	base	**3aa**	**3ab**	**1a**·HX	other
1	**a**[a]		45		40	
2	**a**[a]	K_2CO_3	88			
3	**b**[a]	K_2CO_3	7	44	15	
4	**c**[a]		49			
5	**d**[b]	K_2CO_3				23 (Ph_2CO)
6	**e**[b,c]	K_2CO_3				

[a] Conditions: 50 mM MeCN, −20 °C, 10 equiv of H_2O (2 equiv of base) under N_2. [b] 1 equiv of base. [c] In MeOH at 0 °C according to ref 19c: 88% of **1a** recovered. In MeCN, 48% of **1a** recovered.

Having established that the stable triarylaminium salt **2a** with added base serves as a convenient SET oxidant for cyclization of tertiary pent-4-enylamines **1**, we investigated the scope and limitations of the method (Scheme 2, Table 2). Variation of the amine substituents showed that *N*,*N*-dialkyl-, *N*,*N*-diallyl-, or *N*,*N*-dibenzyl-substituted amines **1b−d** undergo oxidative cyclization to hydroxypyrrolidinium salts **3ba−3da** in high yield in the presence of water (entries 1−3). The reaction is applicable to spirocyclization (entry 1), and the common *N*-allyl or *N*-benzyl amine protecting

Scheme 2. Oxidative Cyclizations of Tertiary 4-Pentenylamines **1**

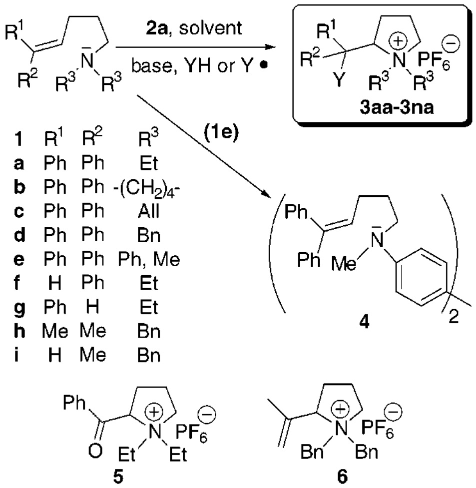


Table 2. Oxidative Cyclizations of Amines **1** to Pyrrolidinium Salts **3** Mediated by **2a**[a]

entry	**1**	Y	**3** (%)	**1**·HX (%)	other (%)
1	**b**	OH	**ba** (74)		
2	**c**	OH	**ca** (82)		
3	**d**	OH	**da** (88)		
4	**e**	OH	**ea** (−)		**4** (46)
5	**f**	OH[b]	**fa** (79)[c]		**5** (2)
6	**f**	OH	**fa** (49)[c]		**5** (18)
7	**g**	OH	**fa** (53)[c]		**5** (20)
8	**h**	HNAc[d]	**ha** (26)		**6** (32)
9	**i**	*d*	**ia** (−)		complex
10	**a**	OMe[b,e]	**ka** (51)	13	
11	**f**	OMe[b,e]	**la** (70)[f]		**3fa** (6), **5** (6)
12	**a**	OEt[b,g]	**ma** (46)	8	**3aa** (10)
13	**a**	LiCl[b,h]	**na** (51)	35	**3aa** (2)

[a] Conditions: 50 mM MeCN, −20 °C, 10 equiv of H_2O, 2 equiv of K_2CO_3, air, unless otherwise stated. [b] Under N_2. [c] 3:1 diastereomeric mixture. [d] 2,6-Di-*tert*-butylpyridine as base. [e] Reaction in MeOH (50 mM). [f] 1:1 diastereomeric mixture. [g] Reaction in EtOH (50 mM). [h] 10 equiv of dried LiCl instead of water.

groups are compatible with the reaction conditions (entries 2 and 3). Neither α-deprotonation-derived nor possible bicyclization products were observed.

In contrast to the reactivity of aliphatic tertiary amines, oxidation of *N*-(5,5-diphenyl-4-pentenyl)-*N*-methylaniline (**1e**) by **2a** yielded a mixture of products from which we were able to isolate the biphenyl derivative **4** in 46% yield (entry 4).

The structure of the alkene acceptor and the presence of air had a notable influence on the reaction outcome. When reacted under nitrogen, (*E*)-5-phenyl-4-pentenylamine (**1f**) gave a 3:1 diastereomeric mixture of the 2-(1-hydroxybenzyl)pyrrolidinium salt **3fa** in 79% yield (entry 5). In addition, the 2-benzoylpyrrolidinium salt **5** was isolated in 2% yield. For the reaction in the presence of air, the yield of **3fa** dropped to 49%, while the amount of **5** increased to 18% (entry 6). The *Z* derivative **1g** provided a similar result in the presence of air (entry 7). Besides alcohol **3fa** (53%), 20% of **5** was isolated. The diastereomeric composition of **3fa** is approximately the same in all cyclization reactions, but we have not been able to assign the relative configuration so far.

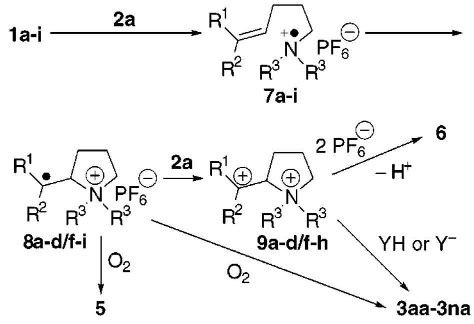
Surprisingly, the 5-methyl-4-hexenylamine species **1h** did not give the alcohol but a separable mixture of (amidomethyl)pyrrolidinium salt **3ha** and 2-isopropenylpyrrolidinium salt **6** in 26 and 32% yields, respectively (entry 8). To ensure complete conversion, the reaction was conducted in the presence of 2,6-di-*tert*-butylpyridine as a homogeneous base. On the other hand, the 4-hexenylamine **1i** led only to an inseparable salt mixture (entry 9).

To broaden the synthetic utility further, we studied the application of trapping reagents other than water. When the oxidative cyclizations of **1a,f** were performed in MeOH or EtOH under N_2, alkoxypyrrolidinium salts **3ka**−**3ma** were obtained in moderate to good unoptimized yields accompanied by some protonated starting material **1a·HPF**$_6$ and **3aa** or **3fa** (entries 10−12). Salts may serve as trapping agents, too, as shown by the formation of the chloropyrrolidinium salt **3na** from **1a** and LiCl. **3na** is identical in its properties with **3ab** obtained with oxidant **2b** (entry 13).

The structure assignment of the products rests on characteristic NMR data and for compounds **3da**, **3ka**, and **6** on X-ray analysis, which will be reported separately.

From these results, the following preliminary mechanistic picture emerges (Scheme 3): Amines **1a**−**i** are oxidized to aminium radical cations **7** by triarylaminium salts **2**. **7a**−**d**,**f**−**i** undergo a 5-exo cyclization to 1,3-radical cations **8a**−**d**,**f**−**i**. This cyclization must be a fast process, since Mariano et al. determined the rate constants for α-deprotonation of related anilinium derivatives by acetate ions to be in the range of 10^5 M^{-1} s^{-1}.[20] Distonic radical cations **8a**−**d**,**f**−**h** can be further oxidized to 1,3-dications **9a**−**d**,**f**−**h**. Nucleophilic trapping or deprotonation finally provide the products **3aa**−**3na** and **6**, respectively.

Scheme 3. Mechanism of the Oxidative Cyclizations of Tertiary Amines **1**



The dichotomy of nucleophilic trapping of the benzylic (**9a**−**g**) vs aliphatic (**9h**) carbenium ions in aqueous acetonitrile may be explained by an equilibrium reaction with excess MeCN that lies to the left with stabilized benzylic species, thus leading to the alcohols **3aa**−**ga**,[21] but to the right with tertiary aliphatic carbenium ion **9h**, providing the product of a Ritter-type reaction. In the presence of air, 1,3-radical cations **8a**−**d,f,g** may be trapped by oxygen in a parallel pathway to give finally the alcohols **3a**−**d,f,g** and ketone **5**.

In conclusion, we have shown for the first time that tertiary amines can be cyclized to pyrrolidinium salts in high yields by applying oxidative SET for N-activation. Depending on the structure of the alkene acceptor, added nucleophiles, and/or oxygen, different products **3** can be obtained. Further studies are clearly warranted to extend the scope of this methodology to other reaction types and substrates.

Acknowledgment. We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for

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(13) For the general reactivity of aminium radical cations, see ref 7 and the following reviews: (a) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550−2589. (b) Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev.* **1978**, *78*, 243−274. (c) Wagner, B. D.; Ruel, G.; Lusztyk, J. *J. Am. Chem. Soc.* **1996**, *118*, 13−19.

(14) (a) Tertiary amines do not cyclize under photolytic conditions but form exciplexes; see: Lewis, F. D.; Bassani, D. M.; Burch, E. L.; Cohen, B. E.; Engleman, J. A.; Reddy, G. D.; Schneider, S.; Jaeger, W.; Gedeck, P.; Gahr, M. *J. Am. Chem. Soc.* **1995**, *117*, 660−669 and references therein. (b) For the use of oxidative PET/deprotonation or desilylation, see the review: Hintz, S.; Heidbreder, A.; Mattay, J. *Top. Curr. Chem.* **1996**, *177*, 77−124. (c) For more recent applications, see: Su, Z.; Mariano, P. S.; Falvey, D. E.; Yoon, U. C.; Oh, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 10676−10686 and references therein.

(15) For a classical Bu$_3$SnH-mediated radical cyclization of phenylselenomethylammonium salts to 3−substituted pyrrolidinium salts, see: Della, E. W.; Smith, P. A. *J. Org. Chem.* **1999**, *64*, 1798−1806.

(16) For a very useful review on SET reagents, see: Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877−910.

(17) Prepared by modification of Shine's procedure: Bandlish, B. K.; Shine, H. J. *J. Org. Chem.* **1977**, *42*, 561−563 (see Supporting Information).

(18) (a) Preparation: Schmittel, M.; Levis, M. *Synlett* **1996**, 315−316. (b) Applications: Schmittel, M.; Burghart, A.; Malisch, W.; Reising, J.; Söllner, R. *J. Org. Chem.* **1998**, *63*, 396−400 and references therein.

(19) (a) Kim, H. J.; Yoon, U. C.; Jung, Y.-S.; Park, N. S.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 860−863. (b) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841−859. (c) Takemoto, Y.; Yamagata, S.; Furuse, S.-i.; Hayase, H.; Echigo, T.; Iwata, C. *Chem. Commun.* **1998**, 651−652.

(20) Zhang, X.; Yeh, S.-R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 4211−4220.

(21) Photosolvolysis of diarylmethylcarbenium ions give also the alcohol, even in the presence of a large excess of MeCN: Bartl, J.; Steenken, S.; Mayr, H.; McClelland, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6918−6928.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1−6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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