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Iron(III)-Promoted Aza-Prins-Cyclization: Direct Synthesis of Six-Membered Azacycles

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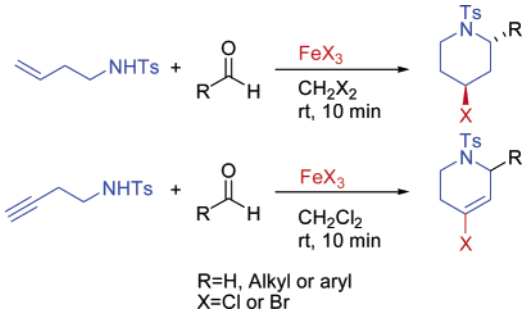
ABSTRACT



A new iron(III) halide-promoted aza-Prins cyclization between γ,δ-unsaturated tosylamines and aldehydes provides six-membered azacycles in good to excellent yields. The process is based on the consecutive generation of γ-unsaturated-iminium ion and further nucleophilic attack by the unsaturated carbon–carbon bond. Homoallyl tosylamine leads to *trans*-2-alkyl-4-halo-1-tosylpiperidine as the major isomer. In addition, the alkyne aza-Prins cyclization between homopropargyl tosylamine and aldehydes gives 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines as the only cyclic products.

The piperidine ring is widely distributed throughout Nature, e.g., in alkaloids,[1] and is an important scaffold for drug discovery, being the core of many pharmaceutically significant compounds.[2,3] The syntheses of these type of compounds have been extensively studied in the development of new drugs containing six-membered-ring heterocycles.[4]

Reactions between *N*-acyliminium ions and nucleophiles, also described as amidoalkylation or Mannich-type condensations, have been frequently used to introduce substituents at the α-carbon of an amine.[5] There are several examples that involve an intramolecular attack of a nucleophilic olefin into an iminium cation for the construction of a heterocyclic ring system.[6] Traditionally, the use of hemiaminals or their derivatives as precursors of *N*-acyliminium intermediates has been a common two-step strategy in these reactions.[6a] Among this type of cyclization is the aza-Prins cyclization,[7] which uses alkenes as intramolecular nucleophile. However, cy-

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(1) (a) Fodor, G. B.; Colasanti, B. *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 23, pp 1−90. (b) Baliah, V.; Jeyarama, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379−423.

(2) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679−3681.

(3) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.

(4) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729 and references therein.

(5) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3187−3856 and references therein.

(6) (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, O., Heathcock, C. H., Eds.; Pergamon: New York, 1991; Vol. 2, pp 1047−1081. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367−4416.

(7) (a) Dobbs, A. P.; Guesné, S. J. J.; Hursthouse, M. B.; Coles, S. J. *Synlett* **2003**, *11*, 1740−1742. (b) Dobbs, A. P.; Guesné, S. J. J.; Martinove, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880−7883. (c) Hanessian, S.; Tremblay, M.; Petersen, F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064−6071 and references therein. (d) Dobbs, A. P.; Guesné, S. J. *Synlett* **2005**, *13*, 2101−2103.

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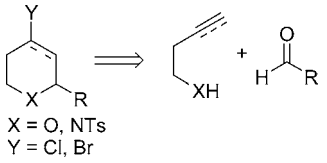
clization reactions of alkynes with weak electrophiles such as iminium ions have received less attention. Intramolecular reactions of alkynes have been reported by Speckamp and co-workers,[6,8] throughout *N*-acyliminium ions. Also, Overman and co-workers discovered that Mannich cyclizations of alkynes are possible in the presence of reactive external nucleophiles throughout formaldiminium ions.[9]

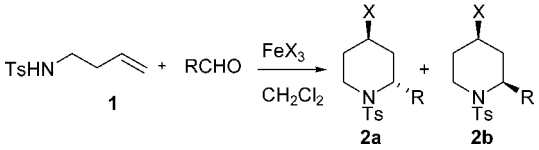
In this paper, we explore the use of iron(III) halides to generate a γ,δ-unsaturated-iminium intermediate which further cyclization, through aza-Prins reaction, leads to six-membered azacycles. The method uses homoallyl and homopropargyl tosylamines and takes into account the similar chemical reactivity of the sulfonamide nitrogen and the alcohol (Scheme 1).[10,11]

Scheme 1. Similar Chemical Reactivity of the Nitrogen in Sulfonamides and the Oxygen in Alcohols



First, to check the catalytic behavior of FeX_3 in the aza-Prins cyclization, we carried out the reaction between *N*-(but-3-enyl)-4-methylbenzenesulfonamide[12] (**1**) and several aldehydes using $FeCl_3$ and $FeBr_3$[13] as promoters.[14] Such Lewis acids showed that the cyclization proceeded in good yields, affording the corresponding *trans*-4-halo-2-alkyl tosylpiperidine **2a** as the major product. Table 1 summarizes the results obtained in this study.[15]

Table 1. Cyclization of Homoallyl Tosyl Amine and Aldehydes with FeX_3 as Promoter



entry	R	X	**2a/2b**	yield (%)
1	*c*-C_6H_{11}	Cl	98:2	68
2	*i*-Bu	Cl	99:1	82
3	*n*-C_7H_{15}	Cl	97:3	88
4	Ph	Cl	90:10[a]	46
5	$PhCH_2$	Cl	83:17[b]	78
6	H	Cl		91
7	*c*-C_6H_{11}	Br	98:2	82
8	*i*-Bu	Br	97:3	96
9	*n*-C_7H_{15}	Br	98:2	90
10	Ph	Br	92:8[a]	82
11	$PhCH_2$	Br	86:14[b]	94
12	H	Br		90

[a] The stereoisomers were isolated by silica chromatography. [b] The stereoisomers were isolated by HPLC, using a semipreparative column.

The aza-Prins cyclization works well with either aliphatic or aromatic aldehydes. In all the cases, the *trans*-diastereomer was obtained as the major product. The *trans* stereochemistry, was confirmed by nOe experiments of 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans[16] and X-ray analysis of **2a** (R = *i*-Bu, X = Cl and R = $PhCH_2$, X = Cl) (Figure 1).

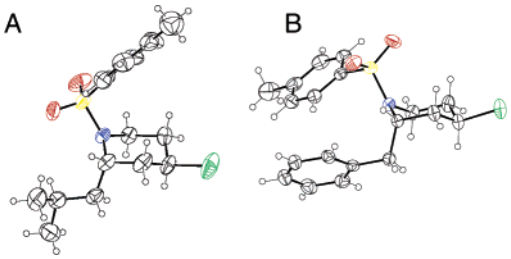
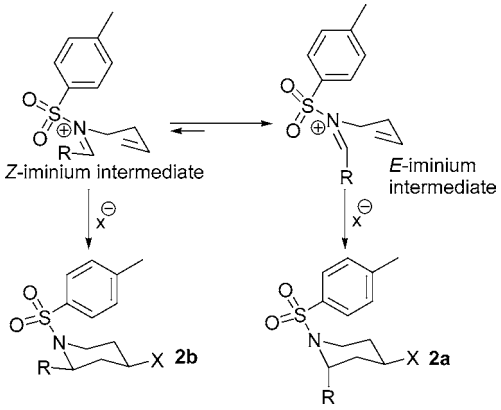


Figure 1. X-ray crystallographic structures of 4-chloro-2-isobutyl-1-tosylpiperidine (A) and 2-benzyl-4-chloro-1-tosylpiperidine (B).

To account for the stereochemical course of the reaction, ab initio theoretical calculations at the B3LYP/6-31G(d) level were performed for some cases of **2a** and **2b**, and their *N*-sulfonyl iminium intermediates (Scheme 2 and Table 2).

Scheme 2. Proposed Intermediates in the Aza-Prins Cyclization to 2-Alkyl-4-halo-1-tosylpiperidines



The calculations showed that the *E*-iminium ion, precursor of *trans* stereoisomers **2a**, is always more stable than the corresponding *Z*-iminium ion, precursor of the *cis*-isomers

(8) (a) Dijkink, J.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, 4043−4046. (b) Dijkink, J.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, 4047−4050. (c) Boer-Terpstra, T.; Dijkink, J.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 939−942.

(9) (a) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612−614. (b) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062−9072. (c) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073−9082. (d) Metais, E.; Overman, L. E.; Rodríguez, M. I.; Stearn, B. A. *J. Org. Chem.* **1997**, *62*, 9210−9216.

(10) (a) Mukai, C.; Sugimoto, Y.-I.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281−6287. (b) Davis, F. A.; Song, M.; Augustine, A. J. *J. Org. Chem.* **2006**, *71*, 2779−2786.

Table 2. Ab Initio Calculations of Some *trans*- and *cis*-2-Alkyl-4-chloro-1-tosylpiperidine and Its *N*-Sulfonyliminium Intermediate

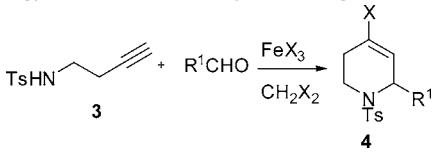
entry	R	$E_{E-iminium}-E_{Z-iminium}$ (kcal/mol)	$E_{trans}-E_{cis}$ (kcal/mol)
1	Me	−0.78	−1.25
2	Et	−1.77	−2.12
3	*i*-Pr	−1.25	−0.41
4	*s*-Bu	−1.56	−0.74
5	CH_2Ph	+0.37	−2.12

2b, when R is an alkyl group (entries 1−4). However, the *Z*-iminium ion becomes a more stable intermediate when R bears an aromatic ring (entry 5). This fact could explain the increase of *cis*-isomer when aromatic aldehydes are being used (Table 1, entries 4, 5, 10, and 11). Interestingly, all the *trans*-compounds are also more stable than their corresponding *cis*-isomers.

In both *cis*- (**2b**) and *trans*-isomers (**2a**) (R = alkyl, entries 1−4), the most stable conformer has the *N*-tosyl group *endo* over the piperidine ring like a "sunshade". This conformer matches with the X-ray crystallographic structure found (Figure 1A). The *N*-tosyl group displays an *exo* disposition with respect to the piperidine ring if R has an aromatic ring (R = CH_2Ph, entry 5) (Figure 1B).

With these results in hand, we extended our studies using homopropargyl tosylamine as the unsaturated amine. We found the corresponding 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines **4** was obtained in good yields (Table 3).

Table 3. Synthesis of 2-Alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines from *N*-Tosyl Homopropargyl Amine and Aldehydes, Using FeX_3 as Catalyst

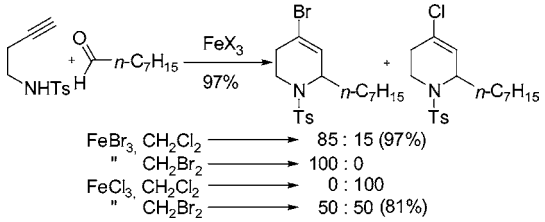


entry	R^1	X	yield (%)
1	*c*-C_6H_{11}	Cl	74
2	*i*-Bu	Cl	85
3	*n*-C_7H_{15}	Cl	91
4	Ph	Cl	29
5	$PhCH_2$	Cl	63
6	H	Cl	83
7	*c*-C_6H_{11}	Br	84
8	*i*-Bu	Br	85
9	*n*-C_7H_{15}	Br	90
10	Ph	Br	38
11	$PhCH_2$	Br	67
12	H	Br	96

The *N*-(but-3-ynyl)-4-methylbenzenesulfonamide **3** was readily prepared from 3-aminopropan-1-ol in three steps, using the Ohira methodology.[17] With the exception of benzaldehyde, the alkyne aza-Prins methodology tolerates a wide range of aldehydes.[15] In all the cases, the desired six-membered ring is obtained in 63−96% yield. Other aldehydes containing aromatic rings although located at a distal position (entries 5 and 11) relative to the carbonyl group proceeded satisfactorily.

From the different solvents screened (THF, CH_3CN, EtOAc, $CHCl_3$, CCl_4, CH_3NO_2, CH_2Cl_2, and 1,2-dichloroethane) we found the best conditions using CH_2Cl_2 and 1,2-dichloroethane. A similar solvent effect to the oxa-alkyne Prins cyclization was observed. When $FeBr_3$ was used as catalyst and the reaction run with CH_2Cl_2 as solvent, the corresponding chlorovinyl derivative was obtained in a mixture with the bromovinyl compound (Scheme III).[11a]

Scheme 3. Participation of the Solvent as the Source of the Halogen in the Alkyne Aza-Prins Cyclization



Several hypotheses could be considered: (a) some halide exchange between the halogenated solvent and the metal,[18] (b) the capture of the solvent halogen by the vinyl cation intermediate,[19] and (c) the combination of both a and b. From the synthetic point of view, it is clear that for each halide the corresponding halogenated solvent must be used. In addition, we did not find any mixture of halogenated products

(11) For the use of iron(III) halides in oxa-Prins cyclizations from our laboratory, see: (a) Miranda, P. O.; Diaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *5*, 1979−1982. (b) Miranda, P. O.; Diaz, D. D.; Padrón, J. I.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57−62.

(12) The *N*-(but-3-enyl)-4-methylbenzenesulfonamide was prepared from 3-bromoprop-1-ene with 4-methylbenzenesulfonamide in 67% yield according to: Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172−4178.

(13) $FeCl_3$ and $FeBr_3$ were purchased from the Aldrich Chemical Co.

(14) To the best of our knowledge, this is the first report on the use of Fe(III) halides promoting this kind of reaction.

(15) **Typical experimental procedure for a ferric halide promoted aza-Prins cyclization**: To a solution of homoallyl tosylamine or homopropargyl tosylamine (1 equiv) and aldehyde (1.5 equiv) in dry CH_2Cl_2 was added anhydrous FeX_3 (1.5 equiv) in one portion. The reaction was concluded in approximately 10 min, quenched by addition of water and extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

(16) See the Supporting Information.

(17) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564.

(18) For a precedent about the halogen transfer from halogenated solvents to a metal, see: Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299−5317.

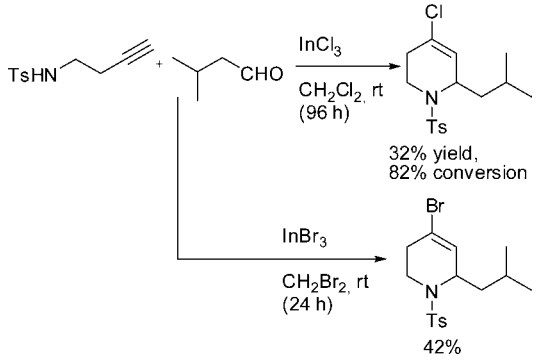
(19) Only a few examples of halogen abstraction by vinyl cations from chlorinated solvents are known: (a) Cook, G. C.; Hayashi, R. *Org. Lett.* **2006**, *8*, 1045−1048. (b) Sun, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13512−13513. (c) Balog, A.; Geib, S. V.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345−352 and references therein.

(**2**, X = Cl or Br) when the aza-Prins cyclization was performed over homoallyl tosylamine.

To improve yields, the amount of anhydrous ferric chloride was also varied from substoichiometric (0.1 equiv) to 2 equiv. We found that the highest values were obtained when 1.5 equiv was used.

To check the advantage of iron over other typical metal halides used in the aza-Prins cyclization, we performed a few runs using indium halides as catalysts (Scheme 4).[20] We

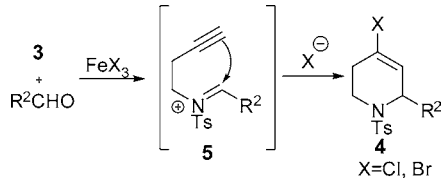
Scheme 4. Alkyne Aza-Prins Cyclization with In(III) Halides as Promoter



found that both $InCl_3$ and $InBr_3$ also induced the cyclization of homopropargyl tosylamine and aldehydes to the corresponding tetrahydropyridines. However, the reactions are slower and the obtained yields are lower.

A plausible mechanism for this new alkyne aza-Prins cyclization is outlined in Scheme 5. The reaction of the

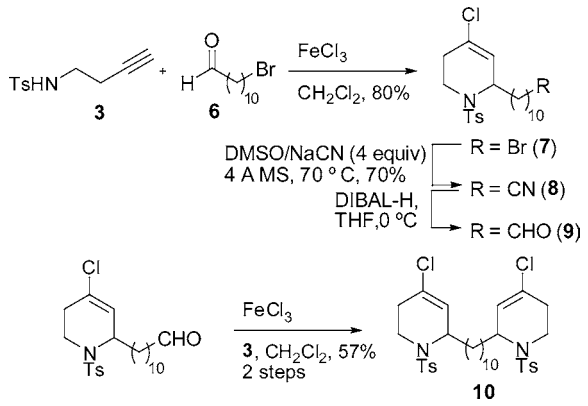
Scheme 5. Plausible Mechanism of the Alkyne Aza-Prins Cyclization



homopropargyl tosylamine and an aldehyde promoted by ferric halide generates the *N*-sulfonyl iminium ion **5**. This intermediate evolves to the corresponding tetrahydropyridine **4**.[21]

Finally, to explore the synthetic scope of this method we decided to perform the synthesis of the dimer 2-alkyl-4-chloro-1-tosyl-1,2,5,6-tetrahydropyridine from the more elaborated and noncommercial aldehyde **9** (Scheme 6). The aza-

Scheme 6. Synthesis of a 2-Alkyl-4-chloro-1-tosyl-1,2,5,6-tetrahydropyridine Dimer-Type



Prins cyclization with the corresponding homopropargyl tosylamine (**3**) and the aldehyde **9** led the unprecedented dimer **10**, showing that this new methodology could be applied to the synthesis of complex molecules in a highly efficient manner.

In conclusion, we have reported on a novel use of iron(III) halides as efficient catalysts for aza-Prins cyclizations. The coupling between homoallyl tosyl- and homopropargyl tosylamines provides in good yields *trans*-2-alkyl-4-halo-1-tosylpiperidine and 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines, respectively. The reaction proceeds satisfactorily with aromatic and aliphatic substrates, as well as with enolizable and nonenolizable aldehydes. It is noteworthy that the carbon−carbon bond formation is very rapid even at 0 °C, usually being completed within 10 min.[22] The method is direct, generating *N*-sulfonyliminium intermediates in situ. Ab initio theoretical calculations support the proposed mechanism. Efforts in the application of the developed methodology to nonterminal olefins and alkynes are currently underway in our laboratory. In addition, the catalytic and asymmetric version is under development and the results will be reported in due course.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For the use of InX_3 in silyl aza-Prins type reactions, see refs 7a and 7b. Examples of the use of InX_3 in the Prins reaction are known. (a) Lee, C.-H. A.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 1641−1644. (b) Chan, K.-P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491−4494. (c) Meiler, K.; Brimble, M. A. *Org. Lett.* **2005**, *7*, 3497−3500. (d) Chan, K.-P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387−8390.

(21) On the basis of our previous results, we cannot discard the formation of a vinylic carbocation as a possible intermediate.

(22) The reaction has been scaled up to 1 g with no difficulty.